



PHARMACOLOGY *for* MEDICAL GRADUATES

REVISED AND
UPDATED EDITION

FOURTH EDITION

Tara V Shanbhag | Smita Shenoy



As per the new competency
based curriculum

PHARMACOLOGY for Medical Graduates

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(REVISED AND UPDATED EDITION)

PHARMACOLOGY for Medical Graduates

TARA V SHANBHAG MD

Professor and Head, Department of Pharmacology
Srinivas Institute of Medical Sciences and Research Centre
Mukka, Surathkal, Mangalore
Karnataka, India

*Formerly, Professor, Department of Pharmacology
Kasturba Medical College, Manipal, Manipal Academy of Higher Education
Manipal, Karnataka, India*

SMITA SHENOY MD

Additional Professor, Department of Pharmacology
Kasturba Medical College, Manipal, Manipal Academy of Higher Education
Manipal, Karnataka, India





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Content Strategist - Education Solutions: Arvind Koul

Content Project Manager: Goldy Bhatnagar and Shubham Dixit

Production Executive: Dhan Singh

Sr Graphic Designer: Milind Majgaonkar

FOREWORD TO THE FIRST EDITION

It is common knowledge that books play a major complementary and contributing role in any educational process. While they are envisioned to facilitate self-learning beyond classroom exercises, not all of them promote learning; some, indeed, hinder it.

To be useful and worthwhile, a book has to be so designed as to present an appropriate body of knowledge in a style that suits students in a particular stage of learning: undergraduate, postgraduate, or postdoctoral.

Accordingly, a book in pharmacology for MBBS phase-II students would have a body of knowledge that relates with the study-course objectives and contains 'must know' and 'nice to know' levels of factual, conceptual and applied aspects of the subject. It has a presentation style that offers an integrated composite picture of the subject interspersed with lucid explanations, cogent reasoning and logical networking of information. Contents will enable students to grasp topics in proper perspective and trigger students' higher mental skills like critical thinking, logical reasoning, etc. Proficiency so acquired would enable the students to not only clear qualifying tests but also to wisely manage drug issues in future.

Designing such a book is a challenging task, especially if it is to be concise and comprehensive in scope. Such a version demands wise sifting, prudent pruning and meaningful condensing of the enormous and variegated knowledge base of pharmacology.

Commendably, Dr (Mrs) Tara Shanbhag has accomplished this in her very first venture. A fairly large number of charts, diagrams and other forms of illustrations in the text amply demonstrate this. No wonder, she has received 'Good Teacher' award time and again.

A well written concise book as this one, serves twice as a preparatory tool: at the start of the study-course it provides a road-map of the subject to be learnt and thus tunes the students for deeper learning; and at the course-end (and examination time) it helps in rapid review and recapitulation of what is learnt.

I am confident that this well thought out and well planned book, Preparatory Manual of Pharmacology for Undergraduates by Dr Tara V Shanbhag will be of tremendous use to the students.

With pleasure, I compliment Dr (Mrs) Tara V Shanbhag, an erstwhile postgraduate student of mine, for such a fine piece of work.

Professor DR Kulkarni

Formerly: Head, Department of Medical Education, BM Patil Medical College, Bijapur;
Director of PG Studies, Head, Department of Pharmacology, KMC, Manipal;
Principal, Dr. Patil Medical College, Kolhapur;
Head, Department of Pharmacology, JNMC, Belgaum;
President, Pharmacological Society of India (1995)

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PREFACE TO THE FOURTH EDITION

Pharmacology is a vast subject and one of the fast-growing branches of medical science and requires addition of latest information from time to time. The present fourth edition includes significant expansion and revision of the third edition. Some new topics like drug dosage forms and calculation of dosage of drugs have been included. The cardiovascular drug summary table also have been included for quick revision. The style has been retained in the form of simple diagrams, self-explanatory flowcharts, tables and student-friendly mnemonics. The textual presentation in tabular format helps in quick reading and recall. Definitions and treatment schedules have been incorporated as per various guidelines.

This extensively revised and updated edition will be useful not only for the students of medicine but also for the practicing doctors as well. This book will also help postgraduates of pharmacology and other clinical subjects for quick revision of pharmacology and therapeutics.

We are extremely thankful to our students and colleagues, who had given us valuable feedback for this edition.

We hope this edition will meet the requirements of the undergraduate medical students and serves as a better learning tool. We would sincerely appreciate critical appraisal of this manual and suggestions for further improvement in future.

Tara V Shanbhag
Smita Shenoy

PREFACE TO THE FIRST EDITION

Pharmacology is a vast subject with many crucial aspects related to drugs, their composition, uses, effects, interactions, etc. which make the subject complicated and difficult to comprehend.

During the course of interaction with my students as well as those of other universities where I went as an examiner, I realized the difficulties faced by them while preparing for their exams due to vastness of the subject. This motivated me to write a preparatory manual that condenses this vital subject into essential elements and yet covers the undergraduate syllabus.

The present book thus is a concise exam-oriented preparatory manual. The text is presented in a simple, precise and point-wise manner. This style of presentation would not only make it easier for the students to understand the subject in a better manner, but would also help them to quickly review and revise the subject before examination. Further, to make learning simpler and comprehension easier for the students, numerous tables, flowcharts and line diagrams have been included.

A large number of people have helped me make this book possible. For this, I thank my postgraduate students and colleagues.

I am grateful to Professor DR Kulkarni for his guidance and suggestions and for writing the Foreword.

I would appreciate critical appraisal of this manual and suggestions for improvement.

Tara V Shanbhag

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COMPETENCY MAP

Code	Competency	Core Y/N	Chapter No.	Page No.
PHARMACOLOGY				
Topic: Pharmacology				
PH1.1	Define and describe the principles of pharmacology and pharmacotherapeutics.	Y	1	1
PH1.2	Describe the basis of Evidence based medicine and Therapeutic drug monitoring.	Y	1	21
PH1.3	Enumerate and identify drug formulations and drug delivery systems.	Y	1, 12	8, 495
PH1.4	Describe absorption, distribution, metabolism & excretion of drugs.	Y	1	8–18
PH1.5	Describe general principles of mechanism of drug action.	Y	1	23–27
PH1.6	Describe principles of Pharmacovigilance & ADR reporting systems.	Y	1	41
PH1.7	Define, identify and describe the management of adverse drug reactions (ADR).	Y	1	37–41
PH1.8	Identify and describe the management of drug interactions.	Y	1	35
PH1.9	Describe nomenclature of drugs i.e. generic, branded drugs.	Y	1	2
PH1.10	Describe parts of a correct, complete and legible generic prescription. Identify errors in prescription and correct appropriately.	Y	-	-
PH1.11	Describe various routes of drug administration, eg., oral, SC, IV, IM, SL.	Y	1	3–8
PH1.12	Calculate the dosage of drugs using appropriate formulae for an individual patient, including children, elderly and patient with renal dysfunction.	Y	12	498–503
PH1.13	Describe mechanism of action, types, doses, side effects, indications and contraindications of adrenergic and anti-adrenergic drugs.	Y	2	75–97
PH1.14	Describe mechanism of action, types, doses, side effects, indications and contraindications of cholinergic and anticholinergic drugs.	Y	2	46–68
PH1.15	Describe mechanism/s of action, types, doses, side effects, indications and contraindications of skeletal muscle relaxants.	Y	2	69–75
PH1.16	Describe mechanism/s of action, types, doses, side effects, indications and contraindications of the drugs which act by modulating autacoids, including: anti-histaminics, 5-HT modulating drugs, NSAIDs, drugs for gout, anti-rheumatic drugs, drugs for migraine.	Y	6	230–254
PH1.17	Describe the mechanism/s of action, types, doses, side effects, indications and contraindications of local anesthetics.	Y	5	181–189

(Continued)

Code	Competency	Core Y/N	Chapter No.	Page No.
PH1.18	Describe the mechanism/s of action, types, doses, side effects, indications and contraindications of general anaesthetics, and pre- anesthetic medications.	Y	5	173–181
PH1.19	Describe the mechanism/s of action, types, doses, side effects, indications and contraindications of the drugs which act on CNS, (including anxiolytics, sedatives & hypnotics, anti-psychotic, anti- depressant drugs, anti-maniacs, opioid agonists and antagonists, drugs used for neurodegenerative disorders, anti-epileptics drugs).	Y	5	164–173, 192–229
PH1.20	Describe the effects of acute and chronic ethanol intake.	Y	5	189–191
PH1.21	Describe the symptoms and management of methanol and ethanol poisonings.	Y	5	191
PH1.22	Describe drugs of abuse (dependence, addiction, stimulants, depressants, psychedelics, drugs used for criminal offences).	Y	1, 5	39, 217
PH1.23	Describe the process and mechanism of drug deaddiction.	Y	1, 5	39, 190–191, 204–205
PH1.24	Describe the mechanism/s of action, types, doses, side effects, indications and contraindications of the drugs affecting renal systems including diuretics, antidiuretics- vasopressin and analogues.	Y	4	151–163
PH1.25	Describe the mechanism/s of action, types, doses, side effects, indications and contraindications of the drugs acting on blood, like anticoagulants, antiplatelets, fibrinolytics, plasma expanders.	Y	3, 8	285–296, 142–143
PH1.26	Describe mechanisms of action, types, doses, side effects, indications and contraindications of the drugs modulating the renin- angiotensin and aldosterone system.	Y	3, 4	98–104, 158–159
PH1.27	Describe the mechanisms of action, types, doses, side effects, indications and contraindications of antihypertensive drugs and drugs used in shock.	Y	3	98–111
PH1.28	Describe the mechanisms of action, types, doses, side effects, indications and contraindications of the drugs used in ischemic heart disease (stable, unstable angina and myocardial infarction), peripheral vascular disease.	Y	3	112–122
PH1.29	Describe the mechanisms of action, types, doses, side effects, indications and contraindications of the drugs used in congestive heart failure.	Y	3	122–131
PH1.30	Describe the mechanisms of action, types, doses, side effects, indications and contraindications of the antiarrhythmics.	N	3	131–138
PH1.31	Describe the mechanisms of action, types, doses, side effects, indications and contraindications of the drugs used in the management of dyslipidemias.	Y	3	138–142
PH1.32	Describe the mechanism/s of action, types, doses, side effects, indications and contraindications of drugs used in bronchial asthma and COPD.	Y	6	256–262
PH1.33	Describe the mechanism of action, types, doses, side effects, indications and contraindications of the drugs used in cough (antitussives, expectorants/ mucolytics).	Y	6	254–256

Code	Competency	Core Y/N	Chapter No.	Page No.
PH1.34	Describe the mechanism/s of action, types, doses, side effects, indications and contraindications of the drugs used as below: 1. Acid-peptic disease and GERD 2. Antiemetics and prokinetics 3. Antidiarrhoeals 4. Laxatives 5. Inflammatory Bowel Disease 6. Irritable Bowel Disorders, biliary and pancreatic diseases.	Y	7	277–284, 263–270, 270–272, 274–276, 272–273
PH1.35	Describe the mechanism/s of action, types, doses, side effects, indications and contraindications of drugs used in hematological disorders like: 1. Drugs used in anemias 2. Colony Stimulating factors.	Y	8	297–302, 302
PH1.36	Describe the mechanism of action, types, doses, side effects, indications and contraindications of drugs used in endocrine disorders (diabetes mellitus, thyroid disorders and osteoporosis).	Y	9	341–354, 309–315, 354–361
PH1.37	Describe the mechanisms of action, types, doses, side effects, indications and contraindications of the drugs used as sex hormones, their analogues and anterior Pituitary hormones.	Y	9	316–326, 304–309
PH1.38	Describe the mechanism of action, types, doses, side effects, indications and contraindications of corticosteroids.	Y	9	331–341
PH1.39	Describe mechanism of action, types, doses, side effects, indications and contraindications the drugs used for contraception.	Y	9	326–331
PH1.40	Describe mechanism of action, types, doses, side effects, indications and contraindications of 1. Drugs used in the treatment of infertility, and 2. Drugs used in erectile dysfunction.	Y	9, 2	322, 91
PH1.41	Describe the mechanisms of action, types, doses, side effects, indications and contraindications of uterine relaxants and stimulants.	Y	10	362–366
PH1.42	Describe general principles of chemotherapy.	Y	11	367–375
PH1.43	Describe and discuss the rational use of antimicrobials including antibiotic stewardship program.	Y	-	-
PH1.44	Describe the first line antitubercular drugs, their mechanisms of action, side effects and doses.	Y	11	412–417
PH1.45	Describe the drugs used in MDR and XDR Tuberculosis.	Y	11	418
PH1.46	Describe the mechanisms of action, types, doses, side effects, indications and contraindications of antileprotic drugs.	Y	11	419–422
PH1.47	Describe the mechanisms of action, types, doses, side effects, indications and contraindications of the drugs used in malaria, KALA-AZAR, amebiasis and intestinal helminthiasis.	Y	11	438–448, 453, 448–452, 454–458
PH1.48	Describe the mechanisms of action, types, doses, side effects, indications and contraindications of the drugs used in UTI/ STD and viral diseases including HIV.	Y	11	409–410, 430–438

(Continued)

Code	Competency	Core Y/N	Chapter No.	Page No.
PH1.49	Describe mechanism of action, classes, side effects, indications and contraindications of anticancer drugs.	Y	11	459–469
PH1.50	Describe mechanisms of action, types, doses, side effects, indications and contraindications of immunomodulators and management of organ transplant rejection.	Y	12	472–476
PH1.51	Describe occupational and environmental pesticides, food adulterants, pollutants and insect repellents.	Y	2	60–61
PH1.52	Describe management of common poisoning, insecticides, common sting and bites.	Y	1	41–42, 60–61
PH1.53	Describe heavy metal poisoning and chelating agents.	N	12	470–472
PH1.54	Describe vaccines and their uses.	Y	12	485–487
PH1.55	Describe and discuss the following National Health Programmes including Immunisation, Tuberculosis, Leprosy, Malaria, HIV, Filariasis, Kala Azar, Diarrhoeal diseases, Anaemia & nutritional disorders, Blindness, Non-communicable diseases, cancer and Iodine deficiency.	Y	-	-
PH1.56	Describe basic aspects of Geriatric and Pediatric pharmacology.	Y	-	-
PH1.57	Describe drugs used in skin disorders.	Y	12	487–491
PH1.58	Describe drugs used in Ocular disorders.	Y	12	491–492
PH1.59	Describe and discuss the following: Essential medicines, Fixed dose combinations, Over the counter drugs, Herbal medicines.	Y	1	1, 21–22
PH1.60	Describe and discuss Pharmacogenomics and Pharmacoeconomics.	N	1	43
PH1.61	Describe and discuss dietary supplements and nutraceuticals.	N	-	-
PH1.62	Describe and discuss antiseptics and disinfectants.	Y	12	476–479
PH1.63	Describe Drug Regulations, acts and other legal aspects.	Y	-	-
PH1.64	Describe overview of drug development, Phases of clinical trials and Good Clinical Practice.	Y	1	43–45
Topic: Clinical Pharmacy				
PH2.1	Demonstrate understanding of the use of various dosage forms (oral/local/parenteral; solid/liquid).	Y	12	495–498
PH2.2	Prepare oral rehydration solution from ORS packet and explain its use.	Y		
PH2.3	Demonstrate the appropriate setting up of an intravenous drip in a simulated environment.	Y		
PH2.4	Demonstrate the correct method of calculation of drug dosage in patients including those used in special situations.	Y	12	498–503

General Pharmacology

Introduction (Definitions and Sources of Drugs) PH1.1, PH1.59

- **Pharmacology:** It is the science that deals with the effects of drugs on living systems.
- **Drug:** World Health Organization (WHO) defines drug as '*any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient*'.
- **Pharmacokinetics:** It means the movement of drug within the body; it includes the processes of absorption (A), distribution (D), metabolism (M) and excretion (E). It means 'what the body does to the drug'.
- **Pharmacodynamics:** It is the study of drugs – their mechanism of action, pharmacological actions and their adverse effects. It covers all the aspects relating to 'what the drug does to the body'.
- **Pharmacy:** It is the branch of science that deals with the preparation, preservation, standardization, compounding, dispensing and proper utilization of drugs.
- **Therapeutics:** It is the aspect of medicine concerned with the treatment of diseases.
- **Chemotherapy:** It deals with treatment of infectious diseases/cancer with chemical compounds that cause relatively selective damage to the infecting organism/cancer cells.
- **Toxicology:** It is the study of poisons, their actions, detection, prevention and treatment of poisoning.
- **Clinical pharmacology:** It is the systematic study of a drug in man, both in healthy volunteers and in patients. It includes the evaluation of pharmacokinetic and pharmacodynamic data, safety, efficacy and adverse effects of a drug by comparative clinical trials.
- **Essential medicines:** According to WHO, essential medicines are '*those that satisfy the healthcare needs of majority of the population*'. They should be of assured quality, available at all times, in adequate quantities and in appropriate dosage forms. They should be selected with regard to disease prevalence in a country, evidence on safety and efficacy, and comparative cost-effectiveness. The examples are iron and folic acid preparations for anaemia of pregnancy, antitubercular drugs like isoniazid, rifampicin, pyrazinamide, ethambutol, etc.
- **Orphan drugs:** Drugs that are used for diagnosis, treatment or prevention of rare diseases. The expenses incurred during the development, manufacture and marketing of drug cannot be recovered by the pharmaceutical company from selling the drug, e.g. digoxin antibody (for digoxin toxicity), fomepizole (for methyl alcohol poisoning), etc.
- **Over-the-counter drugs (OTC drugs, nonprescription drugs):** These drugs can be sold to a patient without the need for a doctor's prescription, e.g. paracetamol, antacids, etc.
- **Prescription drugs:** These are drugs which can be obtained only upon producing the prescription of a registered medical practitioner, e.g. antibiotics, antipsychotics, etc.

SOURCES OF DRUG INFORMATION

Pharmacopoeia: It is a book which contains a list of established and officially approved drugs with description of their physical and chemical characteristics and tests for their identification, purity, methods of storage, etc. Some of the pharmacopoeias are the Indian Pharmacopoeia (IP), the British Pharmacopoeia (BP), and the United States Pharmacopoeia (USP).

Other sources of drug information are National Formulary (NF), Martindale – the Extra Pharmacopoeia, Physician’s Desk Reference (PDR), American Medical Association Drug Evaluation, textbooks and journals of pharmacology and therapeutics, drug bulletins, databases like Micromedex, Medline, Cochrane Library, etc. Information can also be obtained from pharmaceutical companies through their medical representatives, meetings and drug advertisements in journals.

Formulary: It provides information about the available drugs in a country – their use, dose, dosage forms, adverse effects, contraindications, precautions, warnings and guidance on selecting the right drug for a range of conditions.

DRUG NOMENCLATURE

PH1.9

Drugs usually have three types of names, which are as follows:

- 1. Chemical name:** It denotes the chemical structure of a drug, e.g. acetylsalicylic acid is the chemical name of aspirin and N-acetyl-p-aminophenol is of paracetamol. It is not suitable for use in a prescription.
- 2. Nonproprietary name:** It is assigned by a competent scientific body/authority, e.g. the United States Adopted Name (USAN) council. WHO* along with its member countries select and recommend the International Nonproprietary Name (INN) for a drug. So, it is uniform throughout the world and denotes the active pharmaceutical ingredient. Few older drugs have more than one nonproprietary name, e.g. the opioid, pethidine and meperidine. The INN is commonly used as generic name. Ideally, generic names should be used in prescriptions because it is economical and generally uniform all over the world than the branded counterparts. Examples are aspirin and paracetamol are generic names.
- 3. Proprietary name (brand name):** It is given by the drug manufacturers. Brand names are short and easy to recall. Drugs sold under brand name are expensive as compared to their generic version. A drug usually has many brand names – it may have different names within a country and in different countries. Brand names can also be used in prescriptions. Disprin is a brand name of aspirin; Crocin for paracetamol.

Chemical name	Nonproprietary name	Proprietary name/brand name
Acetylsalicylic acid	Aspirin	• Disprin • Ecosprin
N-acetyl-p-aminophenol (Acetaminophen)	Paracetamol	• Crocin • Metacin • Tylenol

*S Kopp-Kubel. International Nonproprietary Names (INN) for pharmaceutical substances. *Bull World Health Organ* 1995;73(3):275–279.

SOURCES OF DRUGS

They are natural, semisynthetic and synthetic. Natural sources are plants, animals, minerals, microorganisms, etc. Semisynthetic drugs are obtained from natural sources and are later chemically modified. Synthetic drugs are produced artificially.

The different sources of drugs:

1. *Plants:*

- Alkaloids are nitrogen containing compounds, e.g. morphine, atropine, quinine, reserpine, ephedrine.
- Glycosides contain sugar group in combination with nonsugar through ether linkage, e.g. digoxin, digitoxin.
- Volatile oils have aroma. They are useful for relieving pain (clove oil), as carminative (eucalyptus oil), flavouring agent (peppermint oil), etc.
- Resins are sticky organic compounds obtained from plants as exudate, e.g. tincture benzoin (antiseptic).

2. *Animals:* Insulin, heparin, antisera.

3. *Minerals:* Ferrous sulphate, magnesium sulphate.

4. *Microorganisms:* Penicillin G, streptomycin, griseofulvin (antimicrobial agents), streptokinase (fibrinolytic).

5. *Semisynthetic:* Hydromorphone, hydrocodone.

6. *Synthetic:* Most of the drugs used today are synthetic, e.g. aspirin, paracetamol.

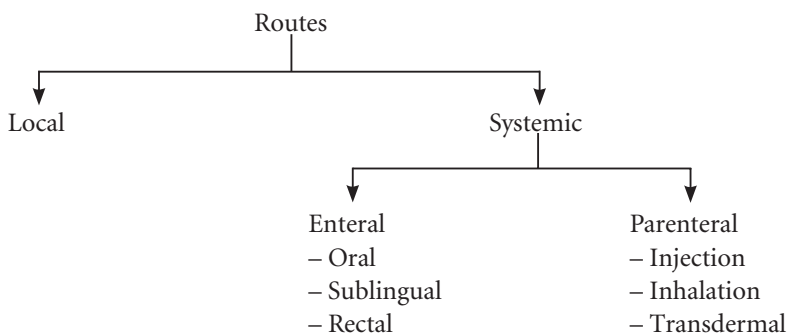
Drugs are also produced by genetic engineering (DNA recombinant technology), e.g. human insulin, human growth hormone and hepatitis B vaccine.

Routes of Drug Administration

PH1.11

Most of the drugs can be administered by different routes. Drug- and patient-related factors determine the selection of routes for drug administration. These factors are

- Characteristics of the drug.
- Emergency/routine use.
- Condition of the patient (unconscious, vomiting and diarrhoea).
- Age of the patient.
- Associated diseases.
- Patient's/doctor's choice (sometimes).



Routes of drug administration

LOCAL ROUTES

It is the simplest mode of administration of a drug at the site where the desired action is required. Systemic side effects are minimal.

1. **Topical:** Drug is applied to the skin or mucous membrane at various sites for localized action.
 - a. *Oral cavity:* As suspension, e.g. nystatin; as a troche, e.g. clotrimazole (for oral candidiasis); as a cream, e.g. acyclovir (for herpes labialis); as ointment, e.g. 5% lignocaine hydrochloride (for topical anaesthesia); as a spray, e.g. 10% lignocaine hydrochloride (for topical anaesthesia).
 - b. *GI tract:* As tablet which is not absorbed, e.g. neomycin (for sterilization of gut before surgery).
 - c. *Rectum and anal canal:*
 - 1) As an enema (administration of drug into the rectum in liquid form):
 - Evacuant enema (for evacuation of bowel): For example, soap water enema – soap acts as a lubricant and water stimulates rectum.
 - Retention enema: For example, methylprednisolone in ulcerative colitis.
 - 2) As a suppository (administration of the drug in a solid form into the rectum), e.g. bisacodyl suppository for evacuation of bowel.
 - d. *Eye, ear and nose:* As drops, ointment and spray (for infection, allergic conditions, etc.), e.g. gentamicin – eye and ear drops.
 - e. *Bronchi:* As inhalation, e.g. salbutamol, ipratropium bromide, etc. (for bronchial asthma and chronic obstructive pulmonary disease).
 - f. *Vagina:* As tablet, cream, pessary, etc. (for vaginal candidiasis).
 - g. *Urethra:* As jelly, e.g. lignocaine.
 - h. *Skin:* As ointment, cream, lotion, powder, e.g. clotrimazole (antifungal) for cutaneous candidiasis.
2. **Intra-arterial route:** This route is rarely employed. It is mainly used during diagnostic studies, such as coronary angiography and for the administration of some anticancer drugs, e.g. for treatment of malignancy involving limbs.
3. Administration of the drug into **deep tissues** by injection, e.g. administration of triamcinolone directly into the joint space in rheumatoid arthritis.

SYSTEMIC ROUTES

Drugs administered by this route enter the blood and produce systemic effects.

Enteral Routes

They include oral, sublingual and rectal routes.

Oral Route. It is the most common and acceptable route for drug administration. Dosage forms are tablet, capsule, powder, syrup, linctus, mixture, suspension, etc., e.g. paracetamol tablet for fever, omeprazole capsule for peptic ulcer are given orally. Tablets could be coated (covered with a thin film of another substance) or uncoated. They are also available as chewable (albendazole), dispersible (aspirin), mouth dissolving (ondansetron) and sustained release forms. Capsules have a soft or hard shell.

Advantages

- Safer.
- Cheaper.
- Painless.

- Convenient for repeated and prolonged use.
- Can be self-administered.

Disadvantages

- It is **not** suitable for/in:
 - unpalatable and highly irritant drugs
 - unabsorbable drugs (e.g. aminoglycosides)
 - drugs that are destroyed by digestive juices (e.g. insulin)
 - drugs with extensive first-pass metabolism (e.g. lignocaine)
 - unconscious patients
 - uncooperative and unreliable patients
 - patients with severe vomiting and diarrhoea
 - emergency as onset of action of orally administered drugs is slow

Sublingual Route. The preparation is kept under the tongue. The drug is absorbed through the buccal mucous membrane and enters systemic circulation directly, e.g. nitroglycerin (for acute attack of angina) and buprenorphine.

Advantages

- Quick onset of action of the drug.
- Action can be terminated by spitting out the tablet.
- Bypasses the first-pass metabolism.
- Self-administration is possible.

Disadvantages

- It is not suitable for:
 - irritant and lipid-insoluble drugs
 - drugs with bad taste

Rectal Route. Drugs can be given in the form of solid or liquid.

1. **Suppository:** It can be used for local (topical) effect (see p. 4) as well as systemic effect, e.g. indomethacin for rheumatoid arthritis.
2. **Enema:** Retention enema can be used for local effect (see p. 4) as well as systemic effect. The drug is absorbed through rectal mucous membrane and produces systemic effect, e.g. diazepam for status epilepticus in children methylprednisolone enema in ulcerative colitis.

Parenteral Routes

Routes of administration other than enteral route are called parenteral routes.

Advantages

- Onset of action of drugs is faster, hence suitable for emergency.
- Useful in:
 - unconscious patient
 - uncooperative and unreliable patient
 - patients with vomiting and diarrhoea
- Suitable for:
 - irritant drugs
 - drugs with high first-pass metabolism
 - drugs not absorbed orally
 - drugs destroyed by digestive juices

Disadvantages

- Require aseptic conditions.
- Preparation should be sterile, and is expensive.
- Require invasive techniques, which are painful.
- Cannot be usually self-administered.
- Can cause local tissue injury to nerves, vessels, etc.

Inhalation. Volatile liquids and gases are given by inhalation for systemic effects, e.g. general anaesthetics.

Advantages

- Quick onset of action.
- Dose required is very less, so systemic toxicity is minimized.
- Amount of drug administered can be regulated.

Disadvantages

- Local irritation may cause increased respiratory secretion and bronchospasm.

Injections (Fig. 1.1)

Intradermal Route. The drug is injected into the layers of skin, e.g. BCG vaccination and drug sensitivity tests. It is painful and a small amount of the drug can be administered.

Subcutaneous (s.c.) Route. The drug is injected into the subcutaneous tissue of the thigh, abdomen, arm, e.g. adrenaline, insulin, etc.

Advantages

- Self-administration of drug is possible, e.g. insulin.
- Depot preparations can be inserted into the subcutaneous tissue, e.g. norplant for contraception.

Disadvantages

- It is suitable only for nonirritant drugs.
- Drug absorption is slow, hence not suitable for emergency.

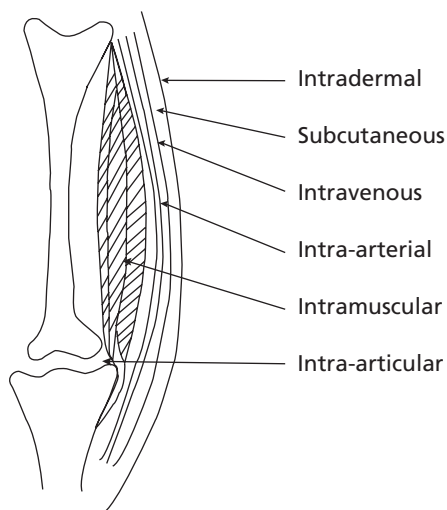


Fig. 1.1 Injectable routes of drug administration.

Intramuscular (i.m.) Route. Drugs are injected into large muscles, such as deltoid, gluteus maximus and vastus lateralis, e.g. paracetamol, diclofenac, etc. A volume of 5–10 mL can be given at a time.

Advantages

- Absorption is more rapid as compared to oral route.
- Mild irritants, depot injections, soluble substances and suspensions can be given by this route.

Disadvantages

- Aseptic conditions are needed.
- Intramuscular (i.m.) injections are painful and may cause abscess.
- Self-administration is not possible.
- There may be injury to nerves.

Intravenous (i.v.) Route. Drugs are injected directly into the blood stream through a vein. Drugs are administered as

1. **Bolus:** Single, relatively large dose of a drug injected rapidly or slowly into a vein, e.g. i.v. ranitidine in bleeding peptic ulcer.
2. **Slow intravenous injection:** For example, i.v. morphine in myocardial infarction.
3. **Intravenous infusion:** For example, dopamine infusion in cardiogenic shock; mannitol infusion in cerebral oedema; fluids infused intravenously in dehydration.

Advantages

- Bioavailability is 100%.
- Quick onset of action, so it is the route of choice in emergency, e.g. intravenous diazepam to control convulsions in status epilepticus.
- Large volume of fluid can be administered, e.g. intravenous fluids in patients with severe dehydration.
- Highly irritant drugs, e.g. anticancer drugs can be given because they get diluted in blood.
- Hypertonic solution can be infused by intravenous route, e.g. 20% mannitol in cerebral oedema.
- By i.v. infusion, a constant plasma level of the drug can be maintained, e.g. dopamine infusion in cardiogenic shock.

Disadvantages

- Local irritation may cause phlebitis.
- Self-administration is usually not possible.
- Strict aseptic conditions are needed.
- Extravasation of some drugs (e.g. noradrenaline) can cause injury, necrosis and sloughing of tissues.
- Depot preparations cannot be given by i.v. route.

Precautions

- Drug should usually be injected slowly.
- Before injecting, make sure that the tip of the needle is in the vein.

Intrathecal Route. Drug is injected into the subarachnoid space, e.g. lignocaine (spinal anaesthesia), antibiotics (amphotericin B), etc.

Transdermal Route (Transdermal Therapeutic System). The drug is administered in the form of a patch or ointment that delivers the drug into the circulation for systemic effect (Fig. 1.2), e.g. scopolamine patch for sialorrhoea and motion sickness, nitroglycerin

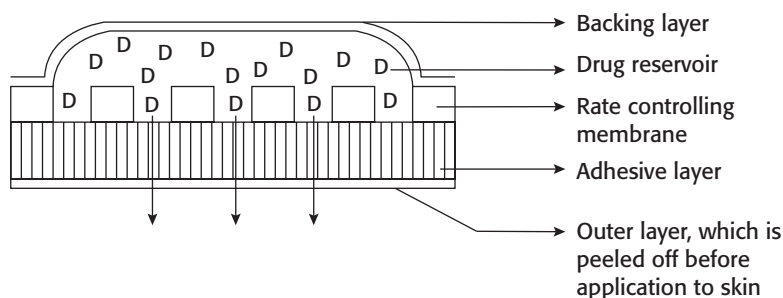


Fig. 1.2 Transdermal drug delivery system.

patch/ointment for prophylaxis of angina, oestrogen patch for hormone replacement therapy (HRT), clonidine patch for hypertension, fentanyl patch for terminal stages of cancer pain and chronic pain, nicotine patch for tobacco deaddiction, etc.

Advantages

- Self-administration is possible.
- Patient compliance is better.
- Duration of action is prolonged.
- Systemic side effects are reduced.
- Provides a constant plasma concentration of the drug.
- First-pass metabolism is bypassed.

Disadvantages

- Expensive.
- Local irritation may cause dermatitis and itching.
- Patch may fall off unnoticed.

SPECIAL DRUG DELIVERY SYSTEMS

PH1.3

They have been developed to prolong duration of drug action, for targeted delivery of drugs or to improve patient compliance.

1. **Ocusert:** It is kept beneath the lower eyelid in glaucoma. It releases the drug slowly for a week following a single application, e.g. pilocarpine ocusert.
2. **Progestasert:** It is an intrauterine contraceptive device that releases progesterone slowly for a period of one year.
3. **Liposomes:** They are minute vesicles made of phospholipids into which the drug is incorporated. They help in targeted delivery of drugs, e.g. liposomal formulation of amphotericin B for fungal infections.
4. **Monoclonal antibodies:** They are immunoglobulins, produced by cell culture, selected to react with a specific antigen. They are useful for targeted delivery of drugs, e.g. delivery of anticancer drugs using monoclonal antibodies.
5. **Drug-eluting stents:** e.g. paclitaxel releasing stents used in coronary angioplasty.
6. **Computerized, miniature pumps,** e.g. insulin pump for continuous subcutaneous delivery of insulin

Pharmacokinetics

PH1.4

Pharmacokinetics is derived from two words: *Pharmacon* meaning drug and *kinesis* meaning movement. In short, it is 'what the body does to the drug'. It includes

absorption (A), distribution (D), metabolism (M) and excretion (E). All these processes involve movement of the drug molecule through various biological membranes.

All biological membranes are made up of a lipid bilayer. Drugs cross various biological membranes by the following mechanisms:

1. **Passive diffusion:** It is a bidirectional process. The drug molecules move from a region of higher to lower concentration until equilibrium is attained. The rate of diffusion is directly proportional to the concentration gradient across the membrane. Lipid-soluble drugs are transported across the membrane by passive diffusion. It does not require energy and is the process by which majority of the drugs are absorbed.
2. **Active transport:** Drug molecules move from a region of lower to higher concentration against the concentration gradient. It requires energy, e.g. transport of sympathomimetic amines into neural tissue, transport of choline into cholinergic neurons and absorption of levodopa from the intestine. In primary active transport, energy is obtained by hydrolysis of ATP. In secondary active transport, energy is derived from transport of another substrate (either symport or antiport).
3. **Facilitated diffusion:** This is a type of carrier-mediated transport and does not require energy. The drug attaches to a carrier in the membrane, which facilitates its diffusion across the membrane. The transport of molecules is from the region of higher to lower concentration, e.g. transport of glucose across muscle cell membrane by a transporter GLUT 4.
4. **Filtration:** Filtration depends on the molecular size and weight of the drug. If drug molecules are smaller than the pores, they are filtered easily through the membrane.
5. **Endocytosis:** The drug is taken up by the cell through vesicle formation. Absorption of vitamin B₁₂–intrinsic factor complex in the gut is by endocytosis.

DRUG ABSORPTION

PH1.4

Movement of a drug from the site of administration into the blood stream is known as absorption.

Factors Influencing Drug Absorption

1. Physicochemical properties of the drug:

- a. *Physical state:* Liquid form of the drug is better absorbed than solid formulations.
- b. *Lipid-soluble and unionized form* of the drug is better absorbed than water-soluble and ionized form.
- c. *Particle size:* Drugs with smaller particle size are absorbed better than larger ones, e.g. microfine aspirin, digoxin and griseofulvin are well absorbed from the gut and produce better effects. Some of the anthelmintics have larger particle size. They are poorly absorbed through gastrointestinal (GI) tract, hence they produce better effect on gut helminths.
- d. *Disintegration time:* It is the time taken for the formulation (tablet or capsule) to break up into small particles and its variation may affect the bioavailability.
- e. *Dissolution time:* It is the time taken for the particles to go into solution. Shorter the time, better is the absorption.
- f. *Formulations:* Pharmacologically inert substances like lactose, starch, calcium sulphate, gum, etc. are added to formulations as binding agents. These are not totally inert and may affect the absorption of drugs, e.g. calcium reduces the absorption of tetracyclines.

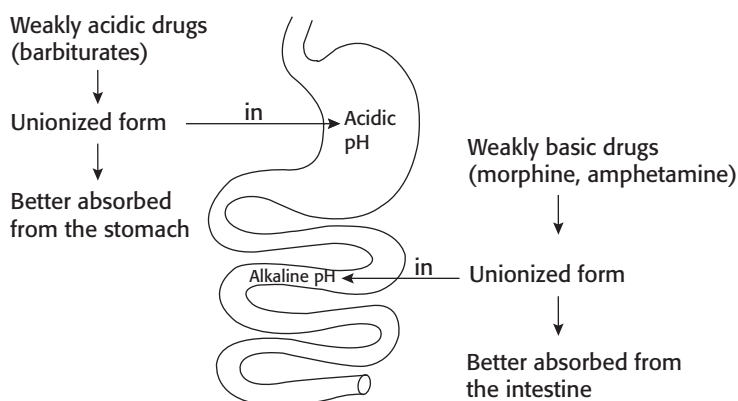


Fig. 1.3 Effect of pH and ionization on drug absorption.

2. **Route of drug administration:** A drug administered by intravenous route bypasses the process of absorption as it directly enters the circulation. Some drugs are highly polar compounds, ionize in solution and are not absorbed through GI tract, hence are given parenterally, e.g. gentamicin. Drugs like insulin are administered parenterally because they are degraded in the GI tract on oral administration.
3. **pH and ionization:** Strongly acidic (heparin) and strongly basic (aminoglycosides) drugs usually remain ionized at all pH, hence they are poorly absorbed ([Fig. 1.3](#)).
4. **Food:** Presence of food in the stomach can affect the absorption of some drugs. Food decreases the absorption of rifampicin, levodopa, etc., hence they should be taken on an empty stomach for better effect. Milk and milk products decrease the absorption of tetracyclines. Fatty meal increases the absorption of griseofulvin.
5. **Presence of other drugs:** Concurrent administration of two or more drugs may affect their absorption, e.g. ascorbic acid increases the absorption of oral iron. Antacids reduce the absorption of tetracyclines.
6. **Area of the absorbing surface:** Normally, drugs are better absorbed in small intestine because of a larger surface area. Resection of the gut decreases absorption of drugs due to a reduced surface area.
7. **Gastrointestinal and other diseases:** In gastroenteritis, there is increased peristaltic movement that decreases drug absorption. In achlorhydria, absorption of iron from the gut is reduced. In congestive cardiac failure, there is GI mucosal oedema that reduces absorption of drugs.

BIOAVAILABILITY

It is the fraction of a drug that reaches systemic circulation from a given dose. Intravenous route of drug administration gives 100% bioavailability as it directly enters the circulation. The term bioavailability is used commonly for drugs given by oral route.

If two formulations of the same drug produce equal bioavailability, they are said to be bioequivalent. If formulations differ in their bioavailability, they are said to be bioinequivalent.

Factors Affecting Bioavailability. *The factors which affect drug absorption (physico-chemical properties of the drug, route of drug administration, pH and ionization, food,*

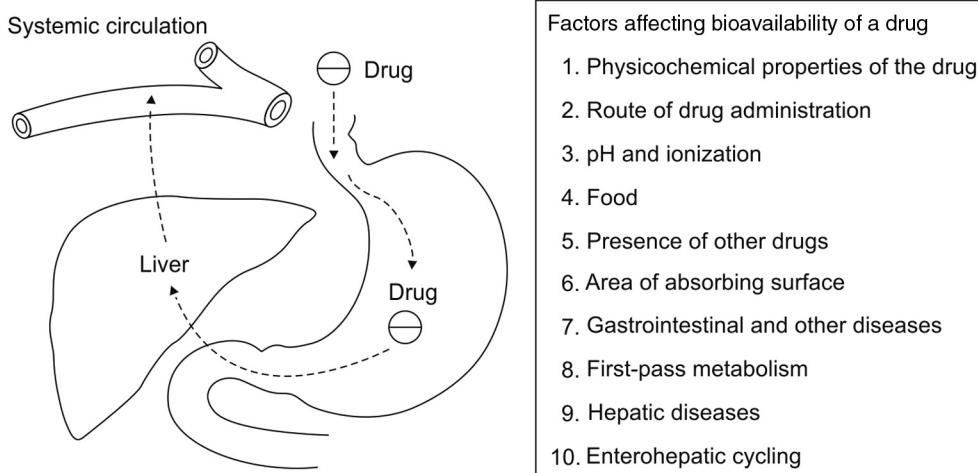


Fig. 1.4 First-pass metabolism.

presence of other drugs, area of absorbing surface, GI and other diseases) also affect bioavailability of a drug. Other factors that affect the bioavailability of a drug are discussed as follows:

- 1. First-pass metabolism (First-pass effect, presystemic elimination):** When drugs are administered orally, they have to pass via gut wall → portal vein → liver → systemic circulation (Fig. 1.4). During this passage, certain drugs get metabolized and are removed or inactivated before they reach the systemic circulation. This process is known as first-pass metabolism. The net result is a decreased bioavailability of the drug and diminished therapeutic response, e.g. drugs like lignocaine (liver), isoprenaline (gut wall), etc.

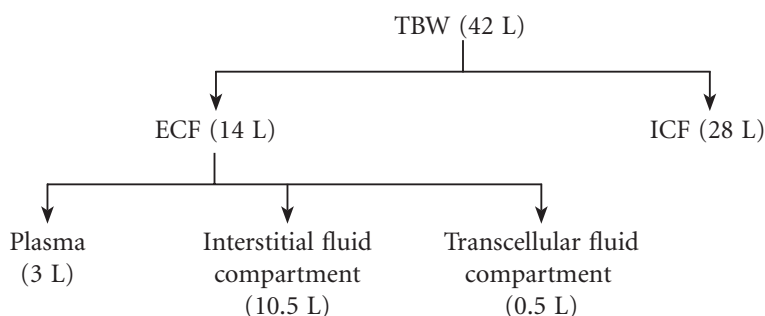
Consequences of high first-pass metabolism:

- 1) Drugs which undergo extensive first-pass metabolism are administered parenterally, e.g. lignocaine is administered intravenously in ventricular arrhythmias.
- 2) Dose of a drug required for oral administration is more than that given by other systemic routes, e.g. nitroglycerin.
- 2. Hepatic diseases:** They result in a decrease in drug metabolism, thus increasing the bioavailability of drugs that undergo high first-pass metabolism, e.g. propranolol and lignocaine.
- 3. Enterohepatic cycling:** Some drugs are excreted via bile but after reaching the intestine they are reabsorbed → liver → bile → intestine and the cycle is repeated – such recycling is called enterohepatic circulation and it increases bioavailability as well as the duration of action of the drug, e.g. morphine and doxycycline.

DRUG DISTRIBUTION

PH1.4

Distribution is defined as the reversible transfer of drugs between body-fluid compartments. After absorption, a drug enters the systemic circulation and is distributed in the body fluids. Various body-fluid compartments for a 70-kg person can be depicted as follows:



ECF, extracellular fluid; ICF, intracellular fluid; TBW, total body water.

Apparent Volume of Distribution

Apparent volume of distribution (aV_d) is defined as the hypothetical volume of body fluid into which a drug is uniformly distributed at a concentration equal to that in plasma, assuming the body to be a single compartment.

$$aV_d = \frac{\text{Total administered amount of drug}}{\text{Concentration of the drug in plasma}}$$

- Drugs with high molecular weight (e.g. heparin) or extensively bound to plasma protein (e.g. warfarin) are largely restricted to the vascular compartment, hence their aV_d is low.
- If aV_d of a drug is about 14–16 L (0.25 mL/kg in a person weighing 70 kg), it indicates that the drug is distributed in the ECF, e.g. gentamicin, streptomycin, etc.
- Small water-soluble molecules like ethanol are distributed in total body water – aV_d is approximately 42 L.
- Drugs which accumulate in tissues have a volume of distribution which exceeds total body water, e.g. chloroquine (13,000 L) and digoxin (500 L). Haemodialysis is not useful for removal of drugs with large aV_d in case of overdose.
- In congestive cardiac failure, V_d of some drugs can increase due to an increase in ECF volume (e.g. alcohol) or decrease because of reduced perfusion of tissues.
- In uraemia, the total body water can increase which increases V_d of small water-soluble drugs. Toxins which accumulate can displace drugs from plasma protein binding sites resulting in increased concentration of free form of drug which can leave the vascular compartment leading to an increase in V_d .
- Fat:lean body mass ratio – highly lipid-soluble drugs get distributed to the adipose tissue. If the ratio is high, the volume of distribution for such a drug will be higher; fat acts as a reservoir for such drugs.

Redistribution (see p. 178)

Highly lipid-soluble drug, such as thiopentone, on intravenous administration, immediately gets distributed to the areas of high blood flow, such as brain, and causes general anaesthesia. Immediately within few minutes, it diffuses across the blood–brain barrier (BBB) into blood and then to the less perfused tissues, such as muscle and adipose tissue. This is called redistribution, which results in termination of drug action. Thiopentone has a very short duration of action (5–10 minutes) and is used for induction of general anaesthesia.

Drug Reservoirs or Tissue Storage

Some drugs are concentrated or accumulated in tissues or some organs of the body, which can lead to toxicity on chronic use, e.g. tetracyclines – bones and teeth; thiopentone and DDT – adipose tissue; chloroquine – liver and retina; digoxin – heart, etc.

Blood–Brain Barrier

The capillary boundary that is present between blood and brain is called blood–brain barrier (BBB). In the brain capillaries, the endothelial cells are joined by tight junctions. Only the lipid-soluble and unionized form of drugs can pass through BBB and reach the brain, e.g. barbiturates, diazepam, volatile anaesthetics, amphetamine, etc. Lipid-insoluble and ionized particles do not cross the BBB, e.g. dopamine and aminoglycosides.

Pathological states like meningitis and encephalitis increase the permeability of the BBB and allow the normally impermeable substances to enter the brain, e.g. penicillin G in normal conditions has poor penetration through BBB, but its penetrability increases during meningitis and encephalitis.

Placental Barrier

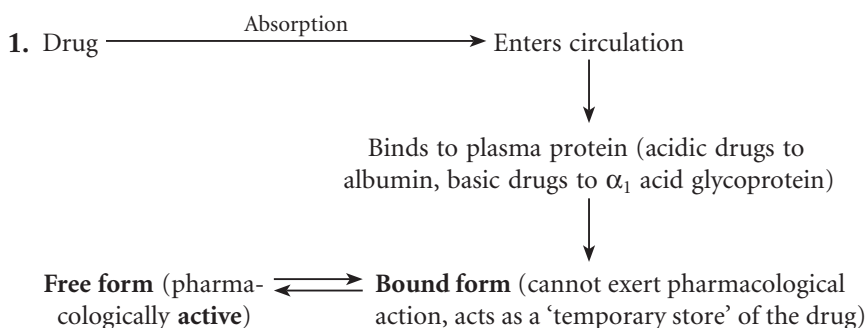
Drugs administered to a pregnant woman can cross placenta and reach the fetus. Passage across placenta is affected by lipid solubility, degree of plasma protein binding, presence of transporters, etc. Quaternary ammonium compounds, e.g. d-tubocurarine (d-TC) and substances with high molecular weight like insulin cannot cross the placental barrier.

PLASMA PROTEIN BINDING

PH1.4

Many drugs bind to plasma proteins like albumin, α_1 acid glycoprotein, etc.

Clinical importance of plasma protein binding



- Drugs that are highly bound to plasma proteins have a low volume of **distribution**.
- Plasma protein binding delays the **metabolism** of drugs.
- Bound form is not available for filtration at the glomeruli. Hence, **excretion** of highly plasma protein bound drugs by **filtration** is delayed.
- Highly protein bound drugs have a longer duration of action, e.g. sulphadiazine is less plasma protein bound and has a duration of action of 6 hours, whereas sulphadoxine is highly plasma protein bound and has a duration of action of 1 week.
- In case of poisoning, highly plasma protein bound drugs are difficult to be removed by haemodialysis.
- In disease states like anaemia, renal failure, chronic liver diseases, etc. plasma albumin levels are low (hypoalbuminaemia). So, there will be a decrease in bound form and an increase in free form of the drug, which can lead to drug toxicity.
- Plasma protein binding can cause displacement interactions. More than one drug can bind to the same site on plasma protein. The drug with higher affinity will displace the one having lower affinity and may result in a sudden increase in the free concentration of the drug with lower affinity.

BIOTRANSFORMATION (Drug Metabolism)

PH1.4

Chemical alteration of the drug in a living organism is called biotransformation. The metabolism of a drug usually converts lipid-soluble and unionized compounds into water-soluble and ionized compounds, hence not reabsorbed in the renal tubules and are excreted. If the parent drug is highly polar (ionized), then it may not get metabolized and is excreted as such.

Sites: Liver is the main site for drug metabolism; other sites are GI tract, kidney, lungs, blood, skin and placenta.

The end result of drug metabolism is inactivation, but sometimes a compound with pharmacological activity may be formed as shown below:

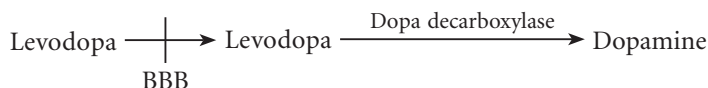
1. **Active drug to inactive metabolite:** This is the most common type of metabolic transformation.
Phenobarbitone $\longrightarrow$ Hydroxyphenobarbitone
Phenytoin $\longrightarrow$ *p*-Hydroxyphenytoin
2. **Active drug to active metabolite**
Codeine $\longrightarrow$ Morphine
Diazepam $\longrightarrow$ Oxazepam
3. **Inactive drug (prodrug) to active metabolite**
Levodopa $\longrightarrow$ Dopamine
Prednisone $\longrightarrow$ Prednisolone

Prodrug

It is an inactive form of a drug, which is converted to an active form after metabolism.

Uses of Prodrugs (Advantages)

1. **To improve bioavailability:** Parkinsonism is due to deficiency of dopamine. Dopamine itself cannot be used since it does not cross BBB. So, it is given in the form of a prodrug, levodopa. Levodopa crosses the BBB and is then converted into dopamine.



2. **To prolong the duration of action:** Phenothiazines have a short duration of action, whereas esters of phenothiazine (fluphenazine) have a longer duration of action.
3. **To improve taste:** Clindamycin has a bitter taste, so clindamycin palmitate suspension has been developed for paediatric use to improve the taste.
4. **To provide site-specific drug delivery:**



Pathways of Drug Metabolism. Drug metabolic reactions are grouped into two phases. They are Phase I or nonsynthetic reactions and Phase II or synthetic reactions.

Phase I Reactions (Table 1.1). Oxidation: Addition of oxygen or removal of hydrogen is called oxidation. It is the most important and common metabolic reaction.

- Oxidation reactions are mainly carried out by cytochrome P450, cytochrome P450 reductase, molecular O_2 and NADPH.
- There are several cytochrome P450 isoenzymes.

Table 1.1 ■ Phase I reactions

Oxidation	Addition of oxygen/removal of hydrogen	Phenytoin, phenobarbitone, pento-barbitone, propranolol
Reduction	Removal of oxygen/addition of hydrogen	Chloramphenicol, methadone
Hydrolysis	Break down of compound by addition of water	Esters – procaine, succinylcholine Amides – lignocaine, procainamide
Cyclization	Conversion of straight chain compound into ring structure	Proguanil
Decyclization	Breaking up of the ring structure of the drug	Phenobarbitone, phenytoin

- They are numbered as 1,2,3,4... (to denote families) and each as A, B, C, D (subfamilies).
- More than 50% of drugs undergo biotransformation reactions by CYP3A4/5. Other enzymes include CYP2D6, CYP2C9, CYP2E1, CYP2C19, etc.

Reduction: Removal of oxygen or addition of hydrogen is known as reduction.

Hydrolysis: Breakdown of the compound by addition of water is called hydrolysis. This is common among esters and amides.

Cyclization: Conversion of a straight chain compound into ring structure.

Decyclization: Breaking up of the ring structure of the drug.

At the end of phase I, the metabolite may be active or inactive.

Phase II Reactions (Table 1.2). Phase II consists of conjugation reactions. If the phase I metabolite is polar, it is excreted in urine or bile. However, many metabolites are lipophilic and undergo subsequent conjugation with an endogenous substrate, such as glucuronic acid, sulphuric acid, acetic acid or amino acid. These conjugates are polar, usually water-soluble and inactive.

Not all drugs undergo phase I and phase II reactions in that order. In case of isoniazid (INH), phase II reaction precedes phase I reaction (Fig. 1.5).

Table 1.2 ■ Phase II reactions

Conjugation reaction	Enzyme	Examples
Glucuronidation	UDP glucuronosyl transferase	• Aspirin • Morphine
Acetylation	N-acetyltransferase	• Isoniazid • Dapsone
Sulphation	Sulphotransferase	• Paracetamol • Methyldopa
Methylation	Transmethylase	• Adrenaline • Dopamine
Glutathione conjugation	Glutathione transferase	• Paracetamol
Glycine conjugation	Acyl CoA glycine transferase	• Salicylates

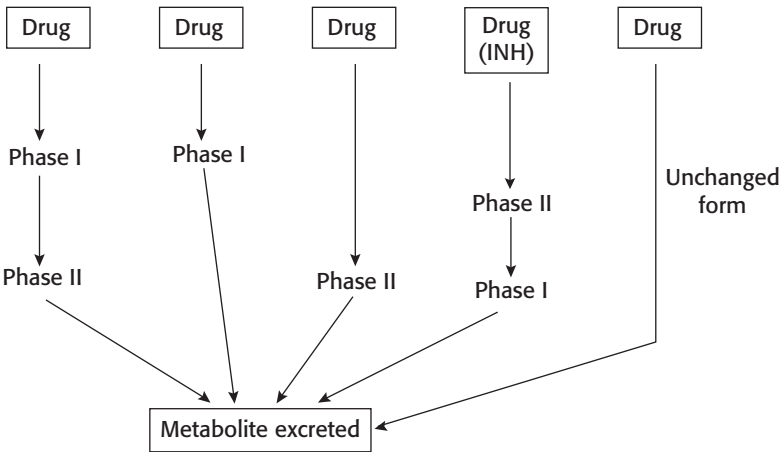


Fig. 1.5 Phases of biotransformation.

Table 1.3 ■ Microsomal and nonmicrosomal enzymes

Microsomal enzymes	Nonmicrosomal enzymes
Location Smooth endoplasmic reticulum of cells, liver, kidney, lungs, e.g. cytochrome P450, monooxygenase, glucuronyl transferase	Cytoplasm, mitochondria, plasma, e.g. conjugases, esterases, amidases, flavoprotein oxidases
Reactions Most of the phase I reactions, Glucuronide conjugation Inducible	Oxidation, reduction (few), hydrolysis. All conjugations except glucuronide conjugation Not inducible – may show genetic polymorphism

Drug-Metabolizing Enzymes

They are broadly divided into two groups – microsomal and nonmicrosomal enzyme systems (Table 1.3).

Hofmann Elimination

Drugs can be inactivated without the need of enzymes – this is known as Hofmann elimination. Atracurium, a skeletal muscle relaxant, undergoes Hofmann elimination.

Factors Affecting Drug Metabolism

- 1. **Age:** Neonates and elderly metabolize some drugs to a lesser extent than adults. In these cases, it is due to diminished amount/activity of hepatic microsomal enzymes. Neonates conjugate chloramphenicol more slowly, hence develop toxicity – grey baby syndrome. Increased incidence of toxicity with propranolol and lignocaine in elderly is due to their decreased hepatic metabolism.
- 2. **Diet:** Poor nutrition can decrease enzyme function.
- 3. **Diseases:** Chronic diseases of liver may affect hepatic metabolism of some drugs, e.g. increased duration of action of diazepam, in patients with cirrhosis, due to its impaired metabolism.

4. **Genetic factors (pharmacogenetics):** These factors also influence drug metabolism. The study of genetically determined variation in drug response is called pharmacogenetics
 - a. **Slow and fast acetylators of isoniazid:** There is an increased incidence of peripheral neuritis with isoniazid in slow acetylators. The fast acetylators require a larger dose of the drug to produce therapeutic effect.
 - b. **Succinylcholine apnoea:** Succinylcholine, a neuromuscular blocker, is metabolized by plasma pseudocholinesterase enzyme. The duration of action of succinylcholine is 3–6 minutes. However, some individuals have atypical pseudocholinesterase that metabolizes the drug very slowly. This results in prolonged succinylcholine apnoea due to paralysis of respiratory muscles, which is dangerous.
 - c. **Glucose-6-phosphate dehydrogenase (G6PD) deficiency and haemolytic anaemia:** G6PD activity is important to maintain the integrity of the RBCs. A person with G6PD deficiency may develop haemolysis when exposed to certain drugs like sulphonamides, primaquine, salicylates, dapsone, etc.
5. **Simultaneous administration of drugs:** This can result in increased or decreased metabolism of drugs (see enzyme induction or inhibition).

Enzyme Induction. Repeated administration of certain drugs increases the synthesis of microsomal enzymes. This is known as enzyme induction. The drug is referred to as an enzyme inducer, e.g. rifampicin, phenytoin, barbiturates, carbamazepine, griseofulvin, etc.

Clinical Importance of Microsomal Enzyme Induction

1. Enzyme induction may accelerate the metabolism of drugs, thus reducing the duration and intensity of drug action leading to therapeutic failure, e.g. rifampicin and oral contraceptives. Rifampicin induces the drug metabolizing enzyme of oral contraceptives, thus enhancing its metabolism and leading to contraceptive failure.
2. Autoinduction may lead to development of drug tolerance, e.g. carbamazepine enhances its own metabolism.
3. Enzyme induction can lead to drug toxicity, e.g. increased incidence of hepatotoxicity with paracetamol in alcoholics is due to overproduction of toxic metabolite of paracetamol.
4. Prolonged phenytoin therapy may produce osteomalacia due to enhanced metabolism of vitamin D₃.
5. Enzyme inducers, e.g. barbiturates, can precipitate porphyria due to overproduction of porphobilinogen.
6. Enzyme induction can also be beneficial, e.g. phenobarbitone in neonatal jaundice – phenobarbitone induces glucuronyl transferase enzyme, hence bilirubin is conjugated and jaundice is resolved.

Enzyme Inhibition. Certain drugs, e.g. chloramphenicol, ciprofloxacin, erythromycin, etc. inhibit the activity of drug metabolizing enzymes and are known as enzyme inhibitors. Inhibition of metabolism of one drug by another can occur when both are metabolized by the same enzyme. Enzyme inhibition is a rapid process as compared to enzyme induction.

Clinical Relevance of Enzyme Inhibition. Enzyme inhibition can result in drug toxicity, e.g. increased incidence of bleeding with warfarin, due to concomitant administration of erythromycin or chloramphenicol, etc. These drugs inhibit drug metabolizing enzyme of warfarin resulting in increased plasma concentration of warfarin and enhanced anticoagulant effect (bleeding). Toxicity following inhibition of metabolism is significant for those

drugs which have saturation kinetics of metabolism. Enzyme inhibition can be beneficial, e.g. boosted protease inhibitor regimen used for treatment of HIV infection (see p. 436).

DRUG EXCRETION

PH1.4

Removal of the drug and its metabolite from the body is known as drug excretion. The main channel of excretion of drugs is the kidney; others include lungs, bile, faeces, sweat, saliva, tears, milk, etc.

1. **Kidney:** The processes involved in the excretion of drugs via kidney are glomerular filtration, passive tubular reabsorption and active tubular secretion. Glomerular filtration and active tubular secretion facilitate drug excretion, whereas tubular reabsorption decreases drug excretion.

Rate of renal excretion = (Rate of filtration + Rate of secretion) – Rate of reabsorption

- 1) *Glomerular filtration:* Drugs with small molecular size are more readily filtered. The extent of filtration is directly proportional to the glomerular filtration rate (GFR) and to the fraction of the unbound drug in plasma.
 - 2) *Passive tubular reabsorption:* The main factor affecting passive reabsorption is the pH of renal tubular fluid and the degree of ionization. Strongly acidic and strongly basic drugs remain in ionized form at any pH of urine, hence are excreted in urine.
 - a) Weakly acidic drugs (e.g. salicylates, barbiturates) in acidic urine remain mainly in 'unionized' form, so they are reabsorbed into the circulation. If the pH of urine is made alkaline by sodium bicarbonate, the weakly acidic drugs get 'ionized' and are excreted easily.
 - b) Similarly, weakly basic drugs (e.g. morphine, amphetamine, etc.) in alkaline urine remain in 'unionized' form, hence are reabsorbed. If the pH of urine is made acidic by vitamin C (ascorbic acid), these weakly basic drugs get 'ionized' and are excreted easily.
 - 3) *Active tubular secretion:* It is a carrier-mediated active transport which requires energy. Active secretion is unaffected by changes in the pH of urine and protein binding. Most of the acidic drugs (e.g. penicillin, diuretics, probenecid, sulphonamides, etc.) and basic drugs (e.g. quinine, procaine, morphine, etc.) are secreted by the renal tubular cells. The carrier system is relatively nonselective and therefore drugs having similar physicochemical properties compete for the same carrier system, e.g. probenecid competitively inhibits the tubular secretion of penicillins, thereby increasing the duration of action as well as the plasma half-life and effectiveness of penicillins in the treatment of diseases, such as gonococcal infections.
2. **Lungs:** Alcohol and volatile general anaesthetics, such as ether, halothane, isoflurane, sevoflurane and ether are excreted via lungs.
 3. **Faeces:** Drugs like purgatives, e.g. senna, cascara, etc. are excreted in faeces
 4. **Bile:** Some drugs are secreted in bile. They are reabsorbed in the gut while a small portion is excreted in faeces, e.g. tetracyclines.
 5. **Skin:** Metals like arsenic and mercury are excreted through skin.
 6. **Saliva:** Certain drugs like potassium iodide, phenytoin, metronidazole and lithium are excreted in saliva. Salivary estimation of lithium may be used for noninvasive monitoring of lithium therapy.
 7. **Milk:** Drugs taken by lactating women may appear in milk. They may or may not adversely affect the breast fed infant. Drugs like penicillins, erythromycin, etc. are safe for use but amiodarone is to be avoided in mothers during breast feeding.

PHARMACOKINETIC PARAMETERS

The important pharmacokinetic parameters are bioavailability, volume of distribution, plasma half-life ($t_{1/2}$) and clearance.

Plasma Half-Life ($t_{1/2}$)

It is the time required for the plasma concentration of a drug to decrease by 50% of its original value (Fig. 1.6A). Plasma half-life of lignocaine is 1 hour and for aspirin it is 4 hours.

Clinical Importance of Plasma Half-Life. It helps to

- determine the duration of drug action.
- determine the frequency of drug administration.
- estimate the time required to reach the steady state. At steady state, the amount of drug administered is equal to the amount of drug eliminated in the dose interval. It takes approximately four to five half-lives to reach the steady state during repeated administration of the drug. A drug is almost completely eliminated in four to five half-lives after single administration.

Clearance

Clearance (CL) of a drug is defined as that volume of plasma from which the drug is removed in unit time.

$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Plasma concentration of the drug}}$$

1. **First-order kinetics:** A constant *fraction* of the drug in the body is eliminated per unit time.

For example, assume drug 'A' with plasma $t_{1/2}$ of 1 hour following first-order kinetics of elimination and having an initial plasma concentration of 100 mcg/mL.

$$100 \text{ mcg/mL} \xrightarrow[\frac{1}{2}]{1 \text{ hour}} 50 \text{ mcg/mL} \xrightarrow[\frac{1}{2}]{1 \text{ hour}} 25 \text{ mcg/mL}$$

If its concentration is increased to 200 mcg/mL, a constant fraction (1/2) gets eliminated in unit time, i.e. after 1 hour, concentration is 100 mcg/mL.

The rate of drug elimination is *directly proportional* to its plasma concentration.

The $t_{1/2}$ of the drugs following first-order kinetics will always remain constant. The drug will be almost completely eliminated in four to five plasma half-lives if administered at a constant rate at each half-life. Most of the drugs follow first-order kinetics.

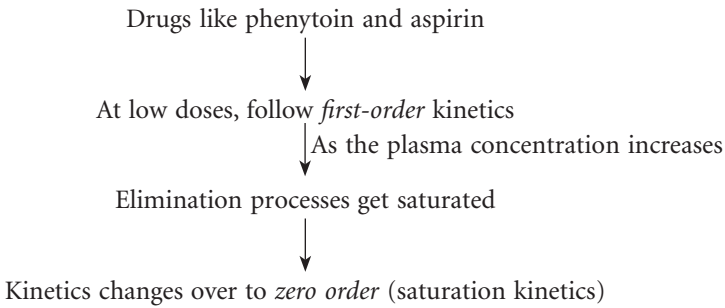
2. **Zero-order kinetics:** A constant *amount* of a drug in the body is eliminated per unit time. For example, ethanol is eliminated from the body at the rate of about 10 mL/h.

Assume a drug 'B' with an initial plasma concentration of 200 mcg/mL and eliminated at a constant amount of 10 mcg per unit time. The concentration will be 190 mcg/mL after 1 hour and 100 mcg/mL after 10 hours. So, half-life is 10 hours.

$$200 \text{ mcg/mL} \xrightarrow[10 \text{ mcg}]{1 \text{ hour}} 190 \text{ mcg/mL} \xrightarrow[10 \text{ mcg}]{1 \text{ hour}} 180 \text{ mcg/mL}$$

If its concentration is increased to 300 mcg/mL, concentration will be 290 mcg/mL after 1 hour (as constant amount 10 mcg per unit time is eliminated) and

150 mcg/mL after 15 hours. The half-life increases to 15 hours. Thus, the $t_{1/2}$ of the drug following zero-order kinetics is never constant. The rate of elimination is *independent* of plasma drug concentration



Note: Phenytoin exhibits *saturation kinetics* and its plasma concentration has to be carefully monitored (therapeutic drug monitoring, TDM) when used in the treatment of epilepsy. Once the kinetics changes to zero order, an increase in dose will result in a marked increase in plasma concentration leading to drug toxicity.

Steady-State Concentration

If constant dose of a drug is given at constant intervals at its $t_{1/2}$, plasma concentration of the drug increases due to its absorption and falls due to elimination in each dosing interval. Finally, the amount of drug eliminated will equal the amount of drug administered in the dosing interval. The drug is said to have reached steady-state or plateau level (Fig. 1.6B). It is attained after approximately four to five half-lives.

Target Level Strategy

The dosage of drug is calculated to achieve the desired plasma steady state concentration of the drug which produces therapeutic effect with minimal side effects.

Loading dose: Initially, a large dose or series of doses of a drug is given with the aim of rapidly attaining the target level in plasma. This is known as loading dose. A loading dose is administered if the time taken to reach steady state is relatively more as

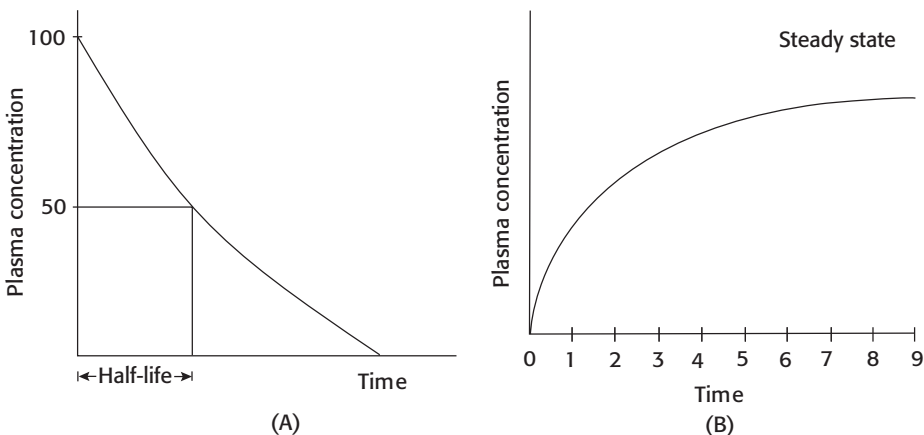


Fig. 1.6 (A) Plasma half-life of a drug after single intravenous injection. (B) Steady state: achieved after approximately four to five half-lives during repeated administration at a constant rate.

compared to the patient's condition, e.g. the half-life of lignocaine is more than 1 hour, so it takes more than 4–6 hours to reach the target concentration at steady state. When a patient has life-threatening ventricular arrhythmias after myocardial infarction, initially a large dose of lignocaine has to be given to achieve desired plasma concentration quickly. Once it is achieved, it is maintained by giving the drug as an intravenous infusion.

Maintenance dose: The dose of a drug which is repeated at fixed intervals or given as a continuous infusion to maintain target level in plasma or steady-state concentration is known as maintenance dose. The dose administered is equal to dose eliminated in a dosing interval.

Therapeutic Drug Monitoring

PH1.2

Monitoring drug therapy by measuring plasma concentration of a drug is known as therapeutic drug monitoring (TDM).

Indications of TDM

1. Drugs with narrow therapeutic index, e.g. lithium, digoxin, phenytoin, aminoglycosides, etc.
2. Drugs showing wide interindividual variations, e.g. tricyclic antidepressants.
3. To ascertain patient compliance.
4. For drugs whose toxicity is increased in the presence of renal failure, e.g. aminoglycosides.
5. In patients who do not respond to therapy without any known reason.

In drug poisoning, estimation of plasma drug concentration is done.

TDM is not required in the following situations:

1. When clinical and biochemical parameters are available to assess response:
 - a. Blood pressure measurement for antihypertensives.
 - b. Blood sugar estimation for antidiabetic agents.
 - c. Prothrombin time, aPTT and International Normalized Ratio (INR) for anti-coagulants.
2. Drugs producing tolerance, e.g. opioids.
3. Drugs whose effect persists longer than the drug itself, e.g. omeprazole.

Fixed-Dose Combinations (FDCs; Fixed-Dose Ratio Combinations)

PH1.59

It is the combination of two or more drugs in a fixed-dose ratio in a single formulation.

Some of the examples of WHO approved FDCs are

- Levodopa + carbidopa for parkinsonism
- Isoniazid + rifampicin + pyrazinamide + ethambutol for tuberculosis.
- Ferrous sulphate + folic acid for anaemia of pregnancy
- Sulphamethoxazole + trimethoprim in cotrimoxazole (antimicrobial agent)
- Amoxicillin + clavulanic acid (antimicrobial agent)
- Oestrogen + progesterone (oral contraceptive)

Advantages and disadvantages of FDCs are explained in [Table 1.4](#), p. 22.

Methods to Prolong the Duration of Drug Action

Prolongation of action of a drug helps

- to reduce the frequency of drug administration.
- to improve patient compliance.
- to minimize fluctuations in plasma concentration.

Table 1.4 ■ Advantages and disadvantages of FDCs

Advantages	Disadvantages
1. Increased patient compliance	1. Inflexible fixed-dose ratio
2. Prevents development of microbial resistance in diseases like TB, AIDS, etc. as missing of single drug is prevented	2. Incompatible pharmacokinetics can interfere with action of the drug
3. Increased efficacy	3. Increased toxicity due to inappropriate combinations. If adverse effect occurs, difficult to identify the component of FDC causing it
4. Reduced side effects	4. The preparation cannot be used if there is a contraindication for use of one component
5. Reduced cost	5. Physician and pharmacist's ignorance of the contents
6. Synergistic effect	

Various methods to prolong the duration of drug action are

1. By retarding drug absorption:

a. For orally administered drugs:

- *Using sustained release/controlled release preparations:* Sustained release preparations consist of drug particles, which have different coatings that dissolve at different intervals of time. It prolongs the duration of action of the drug, reduces the frequency of administration and improves patient compliance, e.g. tab. diclofenac has a duration of action of 12 hours, whereas diclofenac sustained release preparation has a duration of action of 24 hours.

b. For parenterally administered drugs:

- *By decreasing the vascularity of the absorbing surface:* This is achieved by adding a vasoconstrictor to the drug, e.g. adrenaline with local anaesthetics. When adrenaline is added to a local anaesthetic, the vasoconstriction produced by adrenaline will delay the removal of the local anaesthetic from the site of administration and prolongs the duration of its action. It also reduces the systemic toxicity of the local anaesthetic and minimizes bleeding in the operative field.
- *By decreasing the solubility of the drug:* by combining it with a water-insoluble compound, e.g. combining procaine/benzathine with penicillin G.
 - Injection penicillin G has a duration of action of 4–6 hours.
 - Injection procaine penicillin G: It has a duration of action of 12–24 hours.
 - Injection benzathine penicillin G: It has a duration of action of 3–4 weeks.
- *By combining the drug with a protein,* e.g. protamine zinc insulin – the complexed insulin is released slowly from the site of administration, thus prolonging its action.
- *By esterification:* Esters of testosterone, e.g. testosterone propionate and testosterone enanthate are slowly absorbed following intramuscular administration resulting in prolonged action.
- *Injecting the drug in oily solution,* e.g. depot progestins (depot medroxyprogesterone acetate).
- *Pellet implantation:* e.g. norplant for contraception.
- *Transdermal patch* (see p. 7)

2. By increasing the plasma protein binding of the drug, e.g. sulphadiazine is less bound to plasma proteins and has duration of action of 6 hours. Sulphadoxine is highly protein bound and so has duration of action of 1 week.

3. **By inhibiting drug metabolism:** For example, allopurinol + 6-mercaptopurine (6-MP). 6-MP is metabolized by xanthine oxidase. Allopurinol (xanthine oxidase inhibitor) → inhibits metabolism of 6-MP → prolongs action of 6-MP.
4. **By delaying renal excretion of the drug,** e.g. penicillin/cephalosporins with probenecid (see p. 36).

Pharmacodynamics

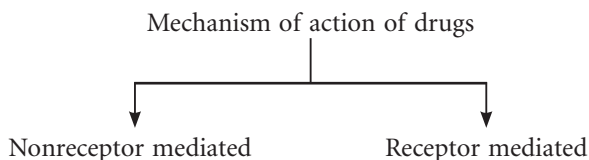
Pharmacodynamics (Greek *pharmakon*: drug; *dynamis*: power). It covers all aspects relating to ‘what the drug does to the body’. It is the study of drugs – their mechanism of action, pharmacological actions and adverse effects.

TYPES OF EFFECTS OF A DRUG

1. **Stimulation:** Some drugs act by increasing the activity of specific organ/system, e.g. adrenaline stimulates the heart resulting in an increase in heart rate and force of contraction.
2. **Depression:** Some drugs act by decreasing the activity of specific organ/system, e.g. alcohol, barbiturates, general anaesthetics, etc. depress the central nervous system.
3. **Irritation:** Certain agents on topical application can cause irritation of the skin and adjacent tissues. When an agent on application to the skin relieves deep seated pain, it is known as counterirritant, e.g. eucalyptus oil, methyl salicylate, etc. They are useful in sprain, joint pain and myalgia. They exert their action by
 - reflexly increasing local circulation in deeper structures.
 - blocking impulse conduction in the spinal cord.
4. **Cytotoxic:** Drugs are selectively toxic for the infecting organism/cancer cells, e.g. antibiotics/anticancer drugs.
5. **Replacement:** When there is a deficiency of endogenous substances, they can be replaced by drugs, e.g. insulin in diabetes mellitus, thyroxine in cretinism and myxoedema, etc.

MECHANISM OF DRUG ACTION

PH1.5



Nonreceptor-Mediated Mechanism of Action of Drugs

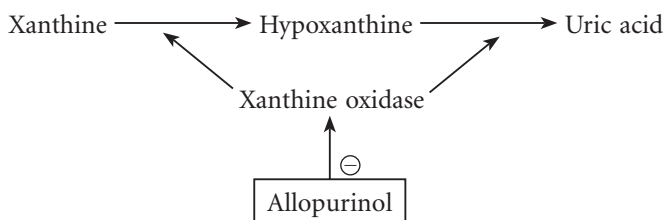
1. **By physical action:**
 - a. **Osmosis:** Some drugs act by exerting an osmotic effect, e.g. 20% mannitol in cerebral oedema and acute congestive glaucoma.
 - b. **Adsorption:** Activated charcoal adsorbs toxins; hence, it is used in the treatment of drug poisoning.
 - c. **Demulcent:** Cough syrup produces a soothing effect in pharyngitis by coating the inflamed mucosa.
 - d. **Radioactivity:** Radioactive isotopes emit rays and destroy the tissues, e.g. ^{131}I in hyperthyroidism.

2. By chemical action:

- Antacids are weak bases – they neutralize gastric acid – useful in peptic ulcer.
- Metals like iron, copper, mercury, etc. are eliminated from the body with the help of chelating agents. These agents trap metals and form water-soluble complexes, which are rapidly excreted from the body, e.g. dimercaprol (BAL) in arsenic poisoning, desferrioxamine in iron poisoning and d-penicillamine in copper poisoning.

3. Through enzymes: Some drugs act by inhibiting the enzyme activity.

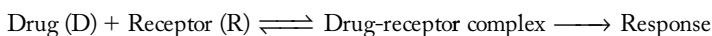
- Angiotensin-converting enzyme (ACE) inhibitors, such as captopril, enalapril, etc. act by inhibiting ACE. They are used in the treatment of hypertension, congestive heart failure, etc.
- Xanthine and hypoxanthine are oxidized to uric acid by the enzyme xanthine oxidase, which is inhibited by allopurinol. Allopurinol (competitive inhibitor) is used in the treatment of chronic gout to reduce the synthesis of uric acid.



- Through ion channels:** Some drugs directly bind to ion channels and alter the flow of ions, e.g. local anaesthetics block sodium channels in neuronal membrane to produce local anaesthesia.
- Through antibody production:** Vaccines produce their effect by stimulating the formation of antibodies, e.g. vaccine against tuberculosis (BCG), oral polio vaccine, etc.
- Transporters:** Some drugs produce their effect by binding to transporters. Selective serotonin reuptake inhibitors (SSRIs) → bind to 5-HT transporter → block 5-HT reuptake into neurons → antidepressant effect.
- Others:** Drugs, like colchicine, bind to tubulin and prevent migration of neurophils (hence useful in acute gout).

Receptor-Mediated Mechanism of Action of Drugs

Receptors are macromolecules, present either on the cell surface, cytoplasm or in the nucleus with which the drug binds and interacts to produce cellular changes.



For example, adrenergic receptors (α and β), cholinergic receptors (muscarinic and nicotinic), opioid receptors, etc.

Affinity: The ability of the drug to get bound to receptor is known as affinity.

Intrinsic activity: The ability of the drug to produce pharmacological action after combining with the receptor is known as intrinsic activity of the drug.

Agonist: A drug that is capable of producing pharmacological action after binding to the receptor is called an agonist.

Agonist has high affinity + high intrinsic activity (e.g. morphine and adrenaline).

Antagonist: A drug that prevents binding of agonist to its receptor or blocks its effect/s is called an antagonist. It does not by itself produce any effect.

Competitive antagonist has high affinity without intrinsic activity (e.g. naloxone and atropine). It produces receptor blockade.

Partial agonist: A drug that binds to the receptor but produces an effect less than that of an agonist is called partial agonist. It inhibits the effect of agonist.

Partial agonist has affinity + less intrinsic activity (e.g. pindolol and buprenorphine).

Inverse agonist: It has full affinity towards the receptor but produces effect opposite to that of an agonist, e.g. benzodiazepines (BZDs) produce antianxiety and anticonvulsant effects by interacting with BZD receptors, but β -carbolines act as inverse agonist at BZD receptor and produce anxiety and convulsions.

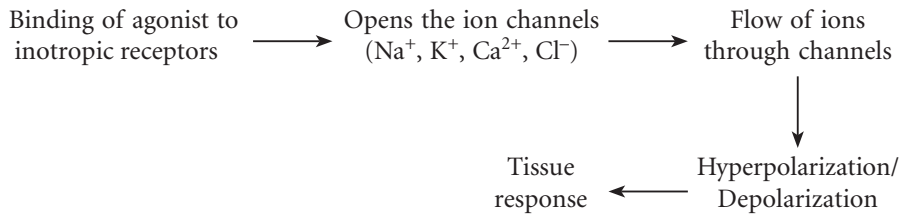
Inverse agonist has affinity + intrinsic activity between 0 and -1 (e.g. β -carboline).

RECEPTOR FAMILIES (Table 1.5)

PH1.5

- 1. Ligand-gated ion channels (inotropic receptors)
- 2. G protein-coupled receptors (GPCRs; metabotropic receptors)
- 3. Enzymatic receptors
- 4. Receptor-regulating gene expression (transcription factors) or the nuclear receptor

Ligand-Gated Ion Channels (Inotropic Receptors). Examples are nicotinic (N_M) acetylcholine receptors at neuromuscular junction, GABA (gamma amino butyric acid) and glutamate receptors in the CNS.



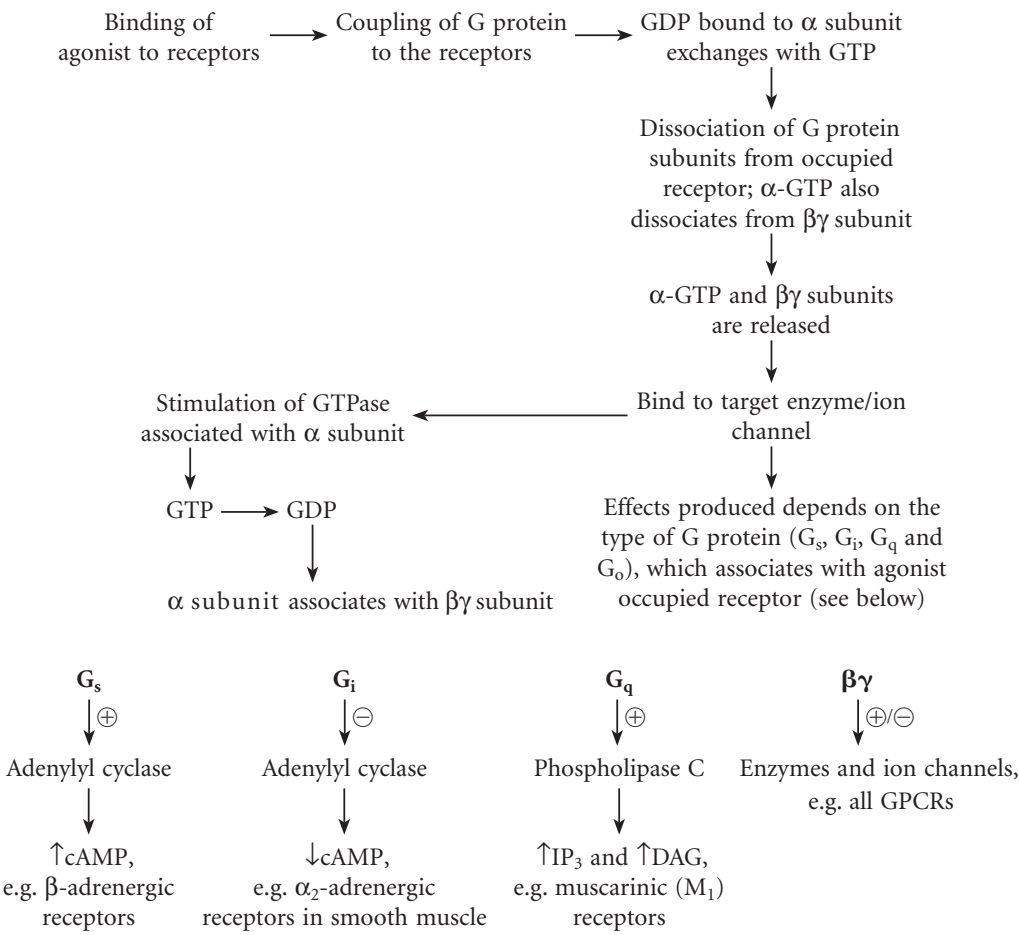
The onset of action of a drug is fastest through this receptor.

G Protein-Coupled Receptors (GPCRs, Metabotropic Receptors). GPCRs are transmembrane receptors which control cell function via adenylyl cyclase, phospholipase C, ion channels, etc. They are coupled to intracellular effectors through G proteins. G proteins are membrane proteins and have three subunits (α , β , γ) with GDP bound to α subunit.

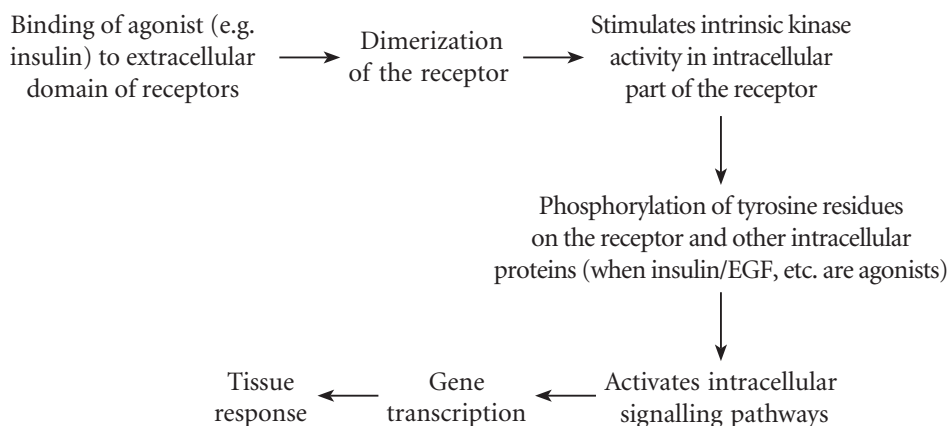
Table 1.5 ■ Characteristics of various receptor families

	Ligand-gated ion channels	G protein-coupled receptors	Enzymatic receptors	Nuclear receptors
Location	Membrane	Membrane	Membrane	Intracellular
Effector	Ion channel	Channel or enzyme	Enzyme	Gene transcription
Examples	Nicotinic, GABA _A receptors	Muscarinic, adrenergic receptors	Insulin epidermal growth factor receptors	Steroid, thyroid hormone receptors
Time required for response	Milliseconds	Seconds	Minutes to hours	Hours

The agonist that binds to the receptor is the first messenger. It results in the formation or recruitment of molecules (second messengers) that initiate the signalling mechanism in a cell. Examples of second messengers are cAMP (generated by adenylyl cyclase), cGMP (generated by guanylyl cyclase), Ca^{2+} , IP_3 -DAG (generated by phospholipase C), nitric oxide, etc.



Transmembrane Enzyme-Linked Receptors. Transmembrane enzyme-linked receptors have enzymatic activity in their intracellular portion. The enzyme is mainly tyrosine kinase, e.g. receptor tyrosine kinases for insulin, epidermal growth factor, etc.).



Transmembrane JAK (Janus kinase)-STAT (signal transducer and activator of transcription) receptors, e.g. receptors for cytokines, growth hormone, etc. These receptors do not have intrinsic enzymatic activity in their intracellular part. On activation, they dimerize followed by their binding to kinases in the cytoplasm, e.g. JAK → phosphorylates tyrosine residues on the receptor → binding of receptor to STAT which gets phosphorylated → dissociation of STAT from receptor → binds to gene to alter transcription.

Nuclear Receptors – Regulate Gene Expression. Examples: receptors for thyroxine, vitamins A and D, sex steroids and glucocorticoids.

Steroids → bind to receptors in cytoplasm → steroid-receptor complex → migrates to nucleus → binds to specific site on the DNA → regulate protein synthesis → response

Regulation of Receptors

Receptors can be regulated by various mechanisms resulting in either their upregulation or downregulation (Table 1.6).

Table 1.6 ■ Regulation of receptors

Receptor downregulation	Receptor upregulation
Prolonged use of agonists ↓ ↓↓ Receptor number and sensitivity ↓ ↓↓ Drug effect For example, chronic use of salbutamol downregulates β_2-adrenoceptors, which may be responsible for decreased effect of salbutamol in asthmatics.	Prolonged use of antagonists ↓ ↑↑ Receptor number and sensitivity; On sudden stoppage of the antagonist ↓ ↑↑ Response to agonist For example, when propranolol is stopped after prolonged use, some patients experience symptoms, such as nervousness, anxiety, palpitation, tachycardia, rise in BP, increased incidence of angina or even myocardial infarction may be precipitated. This is due to upregulation or supersensitivity of β-adrenoceptors to catecholamines. Therefore, propranolol should not be discontinued abruptly.

DOSE-RESPONSE RELATIONSHIP

The pharmacological effect of a drug depends on its concentration at the site of action, which in turn is determined by dose of the drug administered. Such a relationship is called 'dose-response relationship'.

TYPES OF DOSE-RESPONSE CURVES

1. **Graded dose-response:** This curve when plotted on a graph takes the form of a rectangular hyperbola, whereas log dose-response curve (DRC) is sigmoid shaped (Fig. 1.7A and B).
2. **Quantal DRC:** Certain pharmacological effects which cannot be quantified but can only be said to be present or absent (all or none) are called as quantal responses, e.g. a drug causing ovulation (Fig. 1.7C).

Therapeutic Index

Therapeutic index (TI) is an index of drug safety.

$$TI = \frac{\text{Median lethal dose (LD}_{50}\text{) of the drug}}{\text{Median effective dose (ED}_{50}\text{) of the drug}}$$

It is the ratio of median lethal dose to the median effective dose (Fig. 1.8).

1. **LD₅₀:** It is the dose of a drug, which is lethal for 50% of the population.
2. **ED₅₀:** It is the dose of drug, which produces the desired effect in 50% of the population.

Higher the value of therapeutic index, safer is the drug, e.g. penicillin G has a high therapeutic index; digitalis, lithium and phenytoin have narrow therapeutic index.

Drug Potency

The amount of a drug required to produce a desired response is called potency of the drug. Lower the dose required for a given response, more potent is the drug, e.g. analgesic dose of morphine is 10 mg and that of pethidine is 100 mg. Therefore, morphine is ten times more potent than pethidine as an analgesic. DRC of drug A (morphine) and drug B (pethidine, rightward DRC) as analgesic is compared (Fig. 1.9).

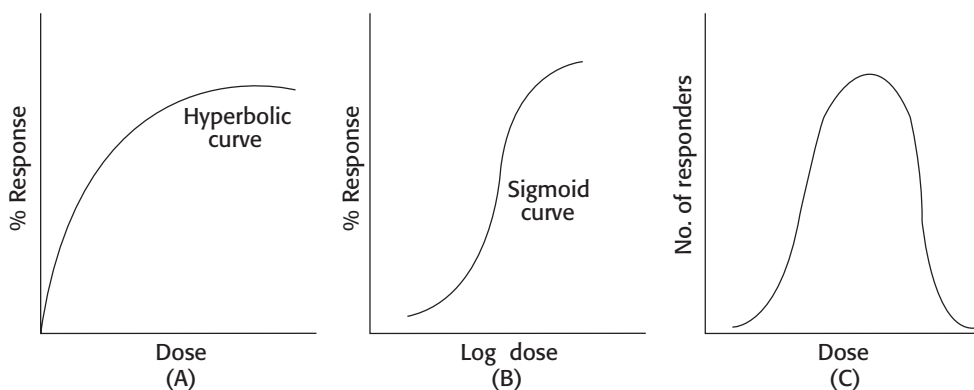


Fig. 1.7 (A) Dose-response curve. (B) Log dose-response curve. (C) Quantal dose-response curve.

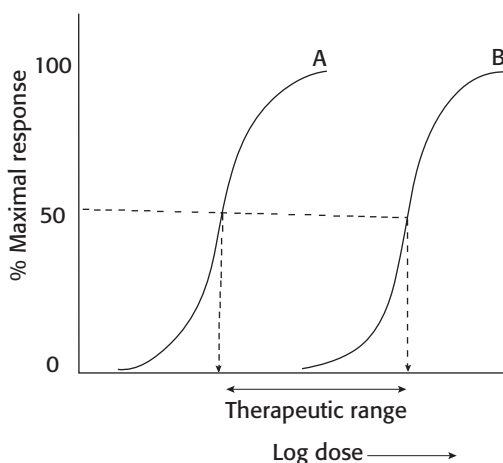


Fig. 1.8 Dose-response curves of therapeutic effect (A) and adverse effect (B).

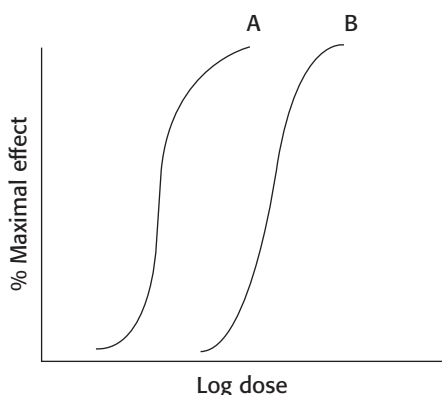


Fig. 1.9 Relative potency of two drugs.

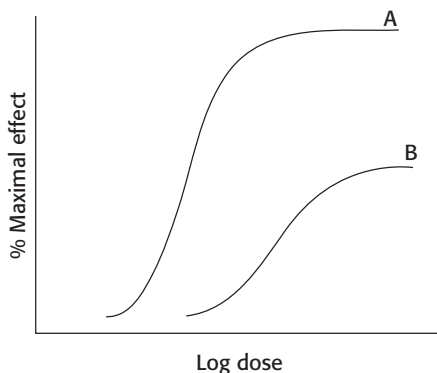


Fig. 1.10 Relative efficacy of two drugs.

Drug Efficacy

It is the maximum effect of a drug, e.g. morphine is more efficacious than aspirin as an analgesic (Fig. 1.10). DRC of drug A (morphine) and drug B (aspirin) as an analgesic is compared.

Therapeutic Range

It is the range of concentration of the drug which produces desired response with minimal toxicity.

COMBINED EFFECT OF DRUGS

A combination of two or more drugs can result in an increase or a decrease in response.

Increased Response

- Additive effect:** The combined effect of two or more drugs is equal to the sum of their individual effect.

Effect of drugs A + B = Effect of drug A + Effect of drug B

For example, combination of ibuprofen and paracetamol as analgesic.

- 2. Potentiation (supra-additive):** The enhancement of action of one drug by another drug which is inactive is called potentiation.

Effect of drugs A + B > Effect of drug A + Effect of drug B

For example, levodopa + carbidopa; acetylcholine + physostigmine.

Carbidopa and physostigmine inhibit breakdown of levodopa and acetylcholine, respectively, thus enhancing their effects.

- 3. Synergism:** When two or more drugs are administered simultaneously, their combined effect is greater than that elicited by either drug alone.

For example, sulphamethoxazole + trimethoprim; pyrimethamine + sulphadoxine.

Decreased Response (Drug Antagonism)

In antagonism, the effect of one drug is decreased or abolished in the presence of another drug.

- 1. Physical antagonism:** The opposing action of two drugs is due to their physical property, e.g. adsorption of alkaloids by activated charcoal – useful in alkaloid poisoning.
- 2. Chemical antagonism:** The opposing action of two drugs is due to their chemical property, e.g. antacids are weak bases; they neutralize gastric acid and are useful in peptic ulcer; chelating agents complex metals and are useful in heavy metal poisoning (dimercaprol in arsenic poisoning).
- 3. Physiological (functional) antagonism:** Here, two drugs act at different receptors or by different mechanisms on the same physiological system and produce opposite effects, e.g. insulin and glucagon on blood sugar; adrenaline and histamine on bronchial smooth muscle – histamine produces bronchoconstriction (via histamine receptors), whereas adrenaline produces bronchodilatation by acting through adrenergic (β_2) receptors – hence, adrenaline helps to reverse bronchospasm in anaphylactic shock.
- 4. Receptor antagonism:** The antagonist binds to the same receptor as the agonist and inhibits its effects. It can be competitive or noncompetitive.
 - a. **Competitive antagonism (equilibrium type):** In competitive antagonism, both agonist and the antagonist bind reversibly to same site on the receptor.
For example,

Acetylcholine $\longrightarrow$ Muscarinic receptors $\longleftarrow$ Atropine

Morphine $\longrightarrow$ Opioid receptors $\longleftarrow$ Naloxone
(Agonists) (Antagonists)

Equilibrium type of competitive antagonism can be overcome (reversible) by increasing concentration of the agonist. The log DRC of the agonist shows a rightward parallel shift in the presence of competitive antagonist (Fig. 1.11).

Nonequilibrium antagonism: The antagonist binds to the same site on the receptor as agonist but binding is irreversible. The antagonist forms strong covalent bond with the receptor, e.g. phenoxybenzamine is an irreversible antagonist of adrenaline at α receptors.

- b. **Noncompetitive antagonism:** The antagonist binds to a different site on the receptor and prevents the agonist from interacting with the receptor. In this type, the antagonistic effect cannot be overcome by increasing the concentration of the agonist. There is a flattening of the DRC in noncompetitive antagonism, e.g. diazepam and bicuculline (Fig. 1.12).

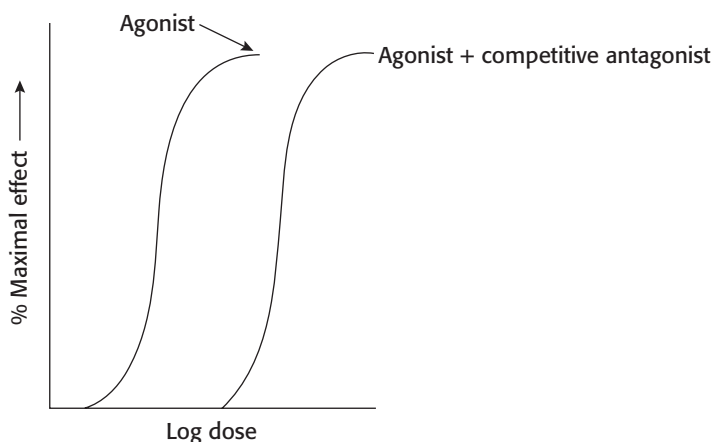


Fig. 1.11 Competitive antagonism. (Adapted from Alfred Gilman Sr. and Louis S. Goodman: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12th edition, McGraw Hill, 2018.)

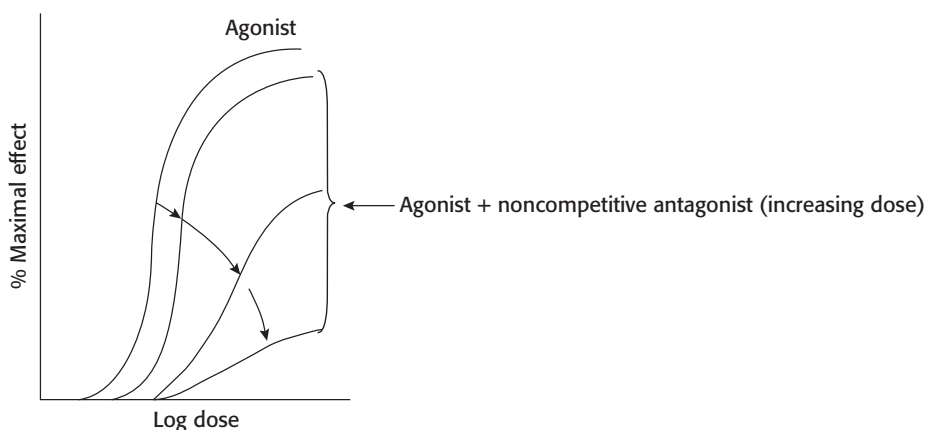


Fig. 1.12 Noncompetitive antagonism. (Adapted from Alfred Gilman Sr. and Louis S. Goodman: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12e.)

Factors Modifying Drug Action

There are a number of factors which can influence drug response. Individuals may often show quantitative variations in drug response but rarely show qualitative variations. The important factors are described in [Table 1.7](#).

DRUG FACTORS

1. **Route of administration:** When a drug is administered by different routes, it commonly exhibits quantitative variations, but sometimes it may also result in qualitative variations in response.
 - a. **Quantitative variation:** Oral dose of drugs are usually larger than intravenous dose (since i.v. route produces 100% bioavailability), e.g. for analgesic effect, intravenous dose of morphine required is 5–10 mg whereas oral dose is 30–60 mg. Onset of drug action following intravenous administration is rapid.

Table 1.7 ■ Factors influencing drug response

Drug factors	Patient factors
• Route of administration • Presence of other drugs • Cumulation	• Age • Body weight • Sex • Environment • Genetic factor • Psychological factor • Pathological state • Tolerance • Drug dependence

b. **Qualitative variation:** The drug may produce an entirely different response when administered by different routes, e.g. magnesium sulphate administered orally produces purgative effect; parenterally, it causes CNS depression and on local application reduces oedema in the inflamed area.

2. **Presence of other drugs:** See addition, potentiation, synergism and antagonism.
3. **Cumulation:** If the elimination of a drug is slow, then repeated administration of such drug will result in its accumulation in the body causing toxicity, e.g. digoxin, emetine and chloroquine.

PATIENT FACTORS

1. **Age:** In neonates, metabolizing function of liver and excretory function of kidney is not fully developed, e.g. chloramphenicol can cause grey baby syndrome when given to neonates as the metabolizing enzymes are not fully developed. In adults, penicillin G is given 6 hourly, but in infants it is given 12 hourly as the excretory function is not completely developed. In the elderly, renal and hepatic functions progressively decline. The incidence of adverse effect of drugs is also relatively more, and hence drug doses have to be reduced accordingly, e.g. dose of aminoglycosides in elderly is less than normal adult dose.
- The dose of a drug for a child can be calculated as follows:

Young's formula:
$$\text{Child dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{adult dose}$$

Dilling's formula:
$$\text{Child dose} = \frac{\text{Age}}{20} \times \text{adult dose}$$

2. **Body weight and body surface:** An average dose of a drug is usually calculated in terms of body weight (mg/kg).

$$\text{Dose} = \frac{\text{Body weight (kg)}}{70} \times \text{Average adult dose}$$

In obese individuals and in patients with dehydration or oedema, dose calculation on the basis of body weight is not very appropriate. A more accurate method

for calculating a dose is on the basis of the body surface area (BSA) of the patient. Nomograms are available to calculate BSA from height and weight of the patient.

Since it is inconvenient to calculate BSA, dose is routinely calculated on body weight basis. Dose of anticancer drugs and a few other drugs are calculated on the basis of BSA.

3. **Sex:** Drugs like β blockers, diuretics and clonidine can cause decreased libido in males.
4. **Diet and environmental factors:** Milk reduces absorption of tetracyclines; fatty meal increases the absorption of griseofulvin (antifungal agent). Cigarette smoke induces hepatic microsomal enzymes and increases metabolism of drugs, such as theophylline. So, the dose of the drug administered may be inadequate in smokers.
5. **Genetic factor:** For example, fast and slow acetylators of isoniazid, prolonged succinylcholine apnoea, primaquine induced haemolysis in G6PD deficiency individuals (see p. 17 under metabolism). Other examples are as follows—

- **Acute porphyria**

Barbiturates may precipitate attacks of acute intermittent porphyria in susceptible individuals by inducing ALA (aminolevulinic acid) synthase enzyme that catalyses the production of porphyrins.

- **Malignant hyperthermia**

In some patients, dangerous rise in body temperature (malignant hyperthermia) may occur especially when halothane–succinylcholine combination is used due to genetic abnormality.

- In person with shallow anterior chamber/and or narrow iridocorneal angle, mydriatics may precipitate acute congestive glaucoma.
 - There is an increased risk of bleeding with coumarin anticoagulants due to reduced activity of metabolizing enzyme, CYP2C9.
6. **Psychological factor:** Personality of the doctor as well as the patient can affect response to a drug. Some patients respond to inert dosage forms (placebo) in conditions like pain, bronchial asthma, anxiety, etc.

Placebo effect: ‘Placebo’ is a Latin term that means ‘I will please’. It is a dummy medicine having no pharmacological activity. The effect produced by placebo is called placebo effect. Sugar tablets and distilled water injection are used as placebos.

- 1) **Uses**

- a) Placebos are used for the relief of subjective symptoms like anxiety, headache, tremors, pain, insomnia, etc.
- b) Placebos are used in clinical trials in order to minimize bias.

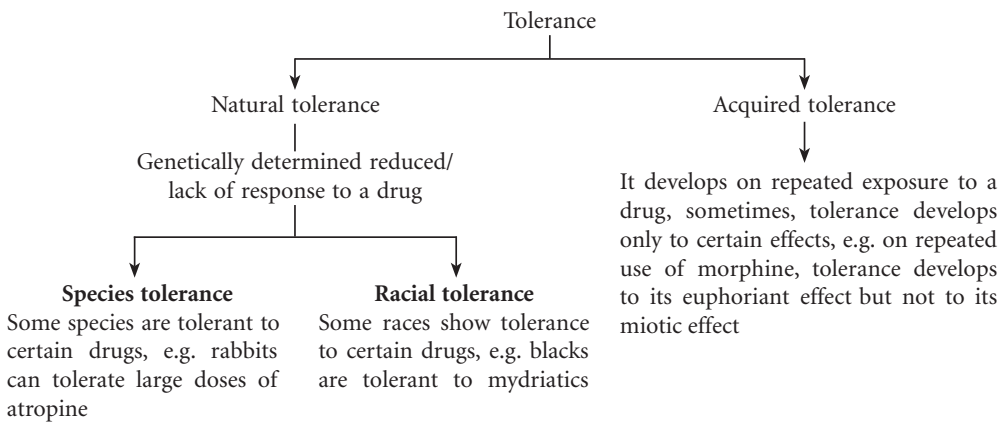
- 2) **Factors affecting placebo effect are:**

- a) **Patient factor:** Patients with neurotic symptoms often respond to placebo.
- b) **Drug factor:** The placebo response can be affected by the physical presentation or route of administration of the drug, e.g. colourful tablets, such as red, blue, green and injectable preparations give better placebo effect.
- c) **Doctor factor:** Personality of the doctor, motivation, way of instruction, doctor–patient relationship, etc. are important factors that also affect response to placebo.

7. **Pathological states:**

- a. **GI disorders:** Achlorhydria reduces the absorption of weakly acidic drugs in stomach by causing their ionization. In malabsorption syndrome, absorption of some drugs is reduced.

- b. *Liver disease*: In chronic liver diseases, metabolism of drugs is greatly reduced. This will increase bioavailability of drugs having high first-pass metabolism, e.g. propranolol.
 - c. *Renal failure*: Clearance of drugs that are excreted through kidney is impaired, e.g. the incidence of nephrotoxicity and ototoxicity with aminoglycosides is more in the presence of renal failure.
 - d. Absorption of iron from the gut is increased in iron deficiency anaemia.
- 8. Tolerance:** It means 'need for larger doses of a drug to produce a given response'. Tolerance develops to nasal decongestant effect of ephedrine on repeated use. Patients on organic nitrates for angina develop tolerance on long-term therapy. Tolerance is commonly seen with drugs like morphine, alcohol, amphetamine, etc.
- a. *Types of tolerance*



- b. **Mechanism of development of tolerance:** It could be pharmacokinetic or pharmacodynamic tolerance.
 - 1) *Pharmacokinetic tolerance (dispositional tolerance)*: It is due to reduced concentration of the drug at the site of action – may be as a result of decreased absorption, increased metabolism and excretion. For example, rifampin induces the metabolizing enzyme of oral contraceptives, enhances their metabolism, leading to contraceptive failure.
 - 2) *Pharmacodynamic tolerance (functional tolerance)*: The drug effect is reduced, which may be due to downregulation of receptors or decrease in receptor-coupled signal transduction. Repeated use of opioids, barbiturates, etc. results in the development of tolerance due to decrease in the number of receptors (downregulation).
 - c. *Cross-tolerance*: The phenomenon of tolerance exhibited by closely related (structural and mechanistic) drugs is called cross-tolerance, e.g. among nitrates, among opioids, between ether and alcohol.
 - d. *Tachyphylaxis (tachy = rapid; phylaxis = protection; acute tolerance)*: Repeated use of certain drugs at short intervals may result in rapid decrease in pharmacological response. This is known as tachyphylaxis or acute tolerance, e.g. tyramine, ephedrine and amphetamine. These drugs act by releasing noradrenaline from adrenergic nerve endings. Repeated administration of the drug causes gradual depletion of the neurotransmitter and hence reduction in the response (Fig. 1.13).
- 9. Drug dependence:** See p. 39.

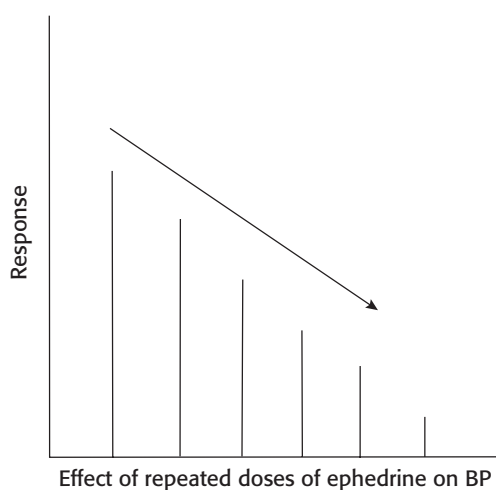
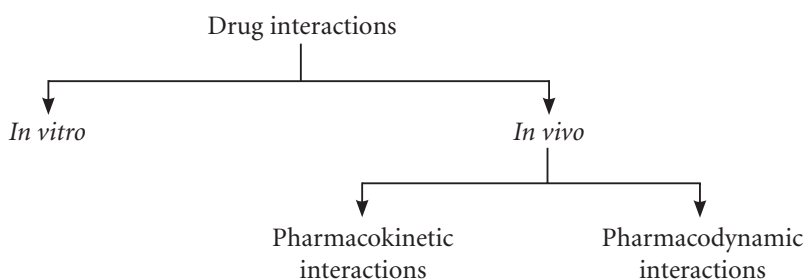


Fig. 1.13 Tachyphylaxis. BP, blood pressure.

Drug Interactions

PH1.8

When two or more drugs are given simultaneously, the effects of one drug may be altered by another drug. Drug interactions can occur *in vitro* (outside the body) or *in vivo* (inside the body).



Drug interactions can result in either beneficial or harmful effects.

Pharmaceutical interactions: These can occur as a result of incompatibility (physical or chemical) of a drug with an intravenous solution or when two or more drugs are mixed in the same syringe/i.v. infusion. This may result in precipitation or inactivation of one or more drugs.

Phenytoin should not be administered in dextrose solution as it gets precipitated.

Dextrose solution is not suitable for i.v. infusion of ampicillin as it is unstable at acidic pH of dextrose.

Gentamicin and carbenicillin should not be given in the same infusion as it may result in loss of potency.

Pharmacokinetic interactions: These occur when one drug alters the absorption, distribution, metabolism or excretion of another drug.

- **Absorption:** Antacids (containing aluminium, magnesium and calcium), iron, etc. interfere with the absorption of tetracyclines by forming unabsorbable complexes with it. Some drugs affect absorption of other drugs by altering GI motility. Metoclopramide increases the rate of gastric emptying and promotes absorption of aspirin.

- **Distribution:** Plasma protein binding can cause displacement interactions. More than one drug can bind to the same site on plasma protein. The drug with higher affinity will displace the one with lower affinity. This results in increase in concentration of unbound drug, e.g. salicylates displace warfarin from binding sites resulting in increased free warfarin levels and enhanced anticoagulant effect.
- **Metabolism:** This occurs when metabolism of one drug is increased (enzyme induction) or decreased (enzyme inhibition) by another drug, e.g. carbamazepine induces the metabolizing enzyme of warfarin, thus enhancing its metabolism and leading to decreased anticoagulant effect. Erythromycin inhibits the metabolizing enzyme of carbamazepine and may increase its toxicity.
- **Excretion:** Most of them occur in kidney.
 - Salicylates interfere with the excretion of methotrexate and potentiate its toxicity.
 - Probenecid decreases renal tubular secretion of penicillins/cephalosporins and prolongs their duration of action (beneficial interaction).

Pharmacodynamic interactions: The interaction is due to action of drugs on receptors or physiological system. This may result in either additive, synergistic or antagonistic effects (see pp. 29, 30). The interaction may result in harmful effects, e.g. enhanced nephrotoxicity seen with the concurrent use of aminoglycosides and amphotericin B; it may also result in beneficial effect, e.g. levodopa and carbidopa in parkinsonism.

Rational Use of Medicines

According to WHO, rational use of medicines requires that *'patients receive medications appropriate to their clinical needs in doses that meet their own individual requirements for an adequate period of time and at the lowest cost to them and their community'*.

It involves the administration of right drug, right dose, right duration, right cost to the right patient.

EXAMPLES OF IRRATIONAL PRESCRIBING

- Drug not prescribed as per standard treatment guidelines.
- Unnecessary use of drugs, e.g. antibiotics for viral infections.
- Underuse of drugs, e.g. not prescribing oral rehydration solution in acute diarrhoea.
- Incorrect use of a drug, e.g. selection of wrong drug, use of incorrect route and dose of a drug.
- Use of medicines with doubtful efficacy, e.g. appetite stimulants.
- Prescribing banned drugs, e.g. cisapride.
- Use of irrational combinations, e.g. ampicillin and cloxacillin for staphylococcal infections.
- Prescribing expensive medicines unnecessarily when cheaper, equally effective drugs are available.
- Polypharmacy.

Hazards of Irrational Use of Drugs

- Therapeutic failure.
- Increased incidence of adverse drug reactions (ADRs).
- Emergence of drug-resistant microorganisms.
- Increase in cost of treatment.
- Financial burden to society.
- Loss of patient's faith in the doctor.

Rational Prescribing (WHO)

- A diagnosis has to be made.
- The problem has to be defined.
- The therapeutic goals to be achieved, e.g. relief of symptoms, cure, etc. has to be set.
- The right drug - appropriate route, dose and duration of treatment has to be selected. Write a complete prescription.
- Proper instructions and information about the drug should be given.
- Monitor therapy.

Adverse Drug Effects**PH1.7****ADVERSE EFFECT**

Adverse effect is defined as any undesirable or unwanted effect of a drug. The WHO-suggested definition of ADR and adverse event (AE) are as follows:

ADR: *Any response which is noxious, unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.*

AE: *Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have causal relationship with the treatment.*

TYPES OF ADVERSE DRUG REACTIONS**Predictable Reactions (Type A or Augmented Reactions)**

These are predictable reactions to a drug which are related to its pharmacological actions. They include side effects, secondary effects and toxic effects.

Unpredictable Reactions (Type B or Bizarre Reactions)

These are nondose-related unpredictable reactions to a drug. They are not related to the pharmacological actions of the drug. Allergic reactions and idiosyncrasy are unpredictable reactions.

Predictable Reactions

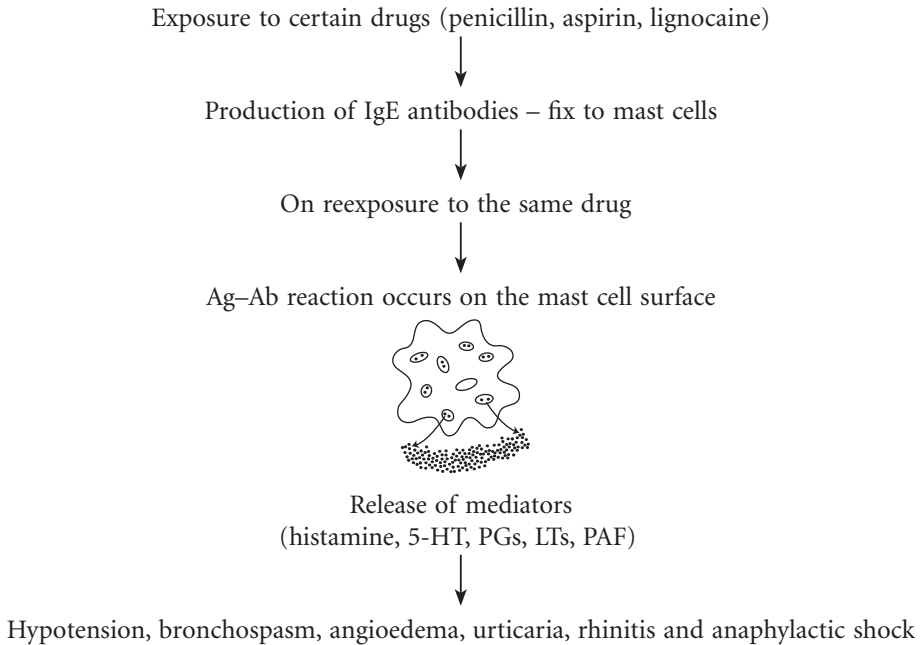
- *Side effects:* These are unwanted pharmacological effects of a drug, that are seen with therapeutic doses, e.g. atropine used in the treatment of heart block also produces dryness of mouth, blurring of vision, urinary retention, etc., which are the side effects.
- *Secondary effects:* The primary action of a drug may result in other effects, e.g. immunosuppression by corticosteroids can lead to development of opportunistic infections, e.g. oral candidiasis.
- *Toxic effects:* These are the effects of a drug, which are either due to overdosage or chronic use, e.g. bleeding due to chronic use/overdosage of anticoagulants and nephrotoxicity with aminoglycosides especially in patients with renal failure.

Unpredictable Reactions

- *Drug allergy:* It is an abnormal response (local or systemic), mediated by immune system, to a drug/foreign antigen. Different types of hypersensitivity reactions are discussed below.
 - Those associated with humoral antibodies: types I, II and III.
 - Those associated with cell-mediated immunity: type IV (delayed hypersensitivity).

Type I hypersensitivity (immediate type, anaphylactic) reactions

It is a rapidly occurring reaction, hence called immediate hypersensitivity reaction. The manifestations are itching, urticaria, hay fever, asthma or even anaphylactic shock. Itching, rhinitis and urticaria are treated with antihistamines,

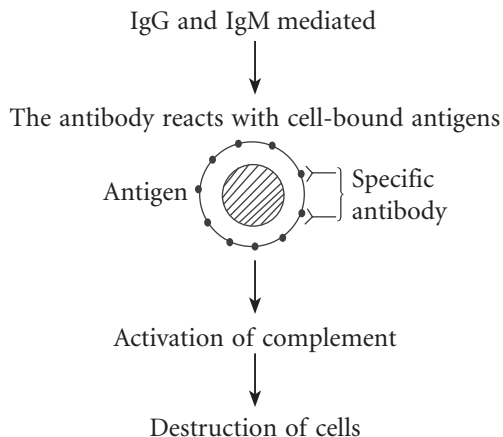


Anaphylactic shock is a medical emergency and should be treated promptly with:

1. Inj. adrenaline (1:1000) 0.3–0.5 mL intramuscularly.
2. Inj. hydrocortisone 100–200 mg intravenously.
3. Inj. pheniramine 45 mg intramuscularly/intravenously.
4. Maintenance of patent airway, intravenous fluids.

Type II hypersensitivity (cytotoxic) reactions

The antibodies (IgG and IgM) react with cell-bound antigen and cause activation of complement, which destroys the cells.



Examples are: blood transfusion reactions, haemolytic anaemias produced by quinine, quinidine, cephalosporins, etc.

Type III hypersensitivity (Arthus, serum sickness) reactions

In this type of reaction, antibodies involved are mainly IgG.

AG: AB complexes are formed → Fix complement → Deposition of complexes on vascular endothelium → Destructive inflammatory response.

For example, serum sickness (fever, urticaria, joint pain, lymphadenopathy) with penicillins and sulphonamides; acute interstitial nephritis with nonsteroidal anti-inflammatory drugs (NSAIDs) and Stevens–Johnson syndrome with sulphonamides.

Type IV hypersensitivity (cell-mediated or delayed hypersensitivity) reactions

It is mediated by sensitized T lymphocytes. Reexposure to the antigen leads to a local inflammatory response. The manifestations usually occur 1–2 days after exposure to the sensitizing antigen, e.g. contact dermatitis due to local anaesthetic creams, topical antibiotics and antifungal agents.

Types II, III and IV reactions are treated with glucocorticoids.

■ *Idiosyncrasy*

It is usually a genetically determined abnormal reaction to drugs, e.g. aplastic anaemia caused by chloramphenicol, prolonged succinylcholine apnoea, haemolytic anaemia seen with primaquine and sulphonamides.

■ *Drug dependence*

PH1.22, PH1.23

WHO defines drug dependence as ‘a state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug characterized by behavioural and other response that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects and sometimes to avoid the discomfort of its absence’, e.g. opioids, alcohol, barbiturates, amphetamine, etc. The dependence could be psychological or physical.

- a. **Psychological dependence:** There is an intense desire to continue taking the drug as the patients feel that their well-being depends on the drug.
- b. **Physical dependence:** Repeated drug use produces physiological changes in the body, which makes continuous presence of the drug in the body necessary to maintain normal function. Abrupt stoppage of the drug results in an imbalance wherein the body has to readjust to the absence of the drug resulting in the development of signs and symptoms known as *withdrawal syndrome*. The withdrawal signs and symptoms are generally opposite to the effects produced by the drug.

Principles of treatment of drug dependence are:

1. **Hospitalization.**
2. **Substitution therapy:** For example, methadone substitution for morphine addiction.
3. **Aversion therapy:** Disulfiram for alcohol addiction.
4. **Psychotherapy**
5. **General measures:** Maintain nutrition, family support and rehabilitation.

■ *Iatrogenic diseases*

It is physician-induced disease (‘iatros’ is a Greek word, means ‘physician’) due to drug therapy, e.g. parkinsonism due to metoclopramide; acute gastritis and peptic ulcer due to NSAIDs.

Table 1.8 ■ **Teratogenic effects of some drugs (Note the 'T's)**

Drug	Teratogenic effect
Thalidomide	Phocomelia
Tetracyclines	Yellowish discolouration of teeth
Antithyroid drugs	Fetal goitre

■ **Teratogenicity**

Certain drugs when given during pregnancy may cross the placenta and produce various dangerous effects in the fetus (Table 1.8). This is called teratogenesis. Administration of drugs during *early pregnancy* (conception to 16 days) could result in abortion; during 2–8 weeks of gestation, it can affect organogenesis and produce structural abnormalities; during *second and third trimester*, drugs can affect growth and development of the fetus. Hence, drug administration during pregnancy should be restricted.

The USFDA (Food and Drug Administration) had placed drugs in various categories (A, B, C, D, X) depending on the risk of the drug to cause birth defects. Category X drugs (e.g. warfarin, methotrexate) was contraindicated for use during pregnancy as risk to fetus was proven and outweighed benefits of its use. This system is being replaced by a revised labelling rule which will provide latest information about a drug pertaining to its use during pregnancy.

■ **Carcinogenicity and mutagenicity**

The ability of a drug to cause cancer is carcinogenicity and the agent is known as carcinogen. The abnormalities of genetic material in a cell produced by a drug is known as mutagenicity, e.g. anticancer drugs and oestrogens.

■ **Photosensitivity reactions**

It is a drug-induced cutaneous reaction (photoallergy/phototoxicity) following exposure to ultraviolet radiation. Sulphonamides cause photoallergy on exposure to light; they produce dermatitis due to immune response (cell mediated). Doxycycline and fluoroquinolones can cause phototoxicity – a local reaction (erythema, blisters) occurs on exposure to UV light. Use of sunscreen and avoidance of exposure to sunlight is advised. Calamine lotion and topical steroids are used for treatment.

■ **Hepatotoxicity**

Some of the hepatotoxic drugs are isoniazid, rifampicin, pyrazinamide, halothane, paracetamol, etc.

■ **Nephrotoxicity** (Vancomycin, aminoglycosides, cisplatin, cyclosporine, amphotericin B, tetracyclines [Fanconi syndrome], indinavir, gold salts, nystatin, etc. are nephrotoxic drugs)*

■ **Ototoxicity**

It can occur with aminoglycosides, loop diuretics, cisplatin, etc.

■ **Ocular toxicity**

Ethambutol, chloroquine, glucocorticoids, etc. can cause ocular toxicity.

*Mnemonic for nephrotoxic drugs: VACATION.

Pharmacovigilance. It is the ‘*science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems*’ (WHO). The aim of pharmacovigilance is to improve patient care and safety related to use of drugs, promote rational use of medicines, develop regulations for use of drugs and educate health care professionals about ADRs. **PH1.6**

Causality assessment: Some of the commonly used tools for causality assessment are Naranjo’s scale and WHO scale.

The National Pharmacovigilance Centre is located at Ghaziabad. The International Centre is Uppsala Monitoring Centre in Sweden. Any health care professional, e.g. doctors, dentists, nurses and pharmacists can report a suspected adverse drug event. Patients can also report ADRs.

Treatment of Poisoning

PH1.52

Toxicology is the study of poisons – their actions, detection, prevention and treatment of poisoning. All poisoning cases require hospitalization and careful observation till recovery. Poisoning may be suicidal, homicidal or accidental. All cases of poisoning are medico-legal cases; hence, the police should be informed.

GENERAL MANAGEMENT

1. Hospitalization.
 2. Airway should be cleared. In comatose patients, there is danger of respiratory obstruction by tongue, secretions and aspiration of vomitus. Hence, patient should be turned to his left lateral side. A cuffed endotracheal tube should be inserted and secretions should be aspirated regularly.
 3. Breathing should be assessed. If there is hypoxaemia, oxygen should be given. Patient may need mechanical ventilation if there is respiratory insufficiency.
 4. Circulation should be assessed (pulse rate and blood pressure) and an i.v. (intravenous) line should be maintained.
 5. To prevent further absorption of poison:
 - a. *Inhaled poisons (gases):* Patient should be moved to fresh air.
 - b. *Contact poisons:* Contaminated clothes should be removed and the body part should be washed with soap and water.
 - c. *Ingested poisons:* Gastric lavage can limit the absorption if done within 2–3 hours of poisoning. If patient is unconscious, endotracheal intubation should be done before gastric lavage. Gastric lavage is usually done with normal saline. Other solutions used are lukewarm water, potassium permanganate solution, sodium bicarbonate, etc. Lavage should be repeated till the returning fluid is clear. After the lavage, activated charcoal is administered which adsorbs many drugs and poisons (physical antagonism). Activated charcoal has a large surface area and is highly porous to bind with poisonous material. Gastric lavage should not be carried out in case of poisoning due to corrosives (except carbolic acid), petroleum products (kerosene), convulsants, etc. Mustard, common salt, ipecac syrup, etc. can be used to induce vomiting and prevent further absorption of ingested poisons. However, this method is rarely practiced now.
- Laxatives like magnesium sulphate or citrate can be used orally to promote elimination of the ingested poison. Oral polyethylene glycol electrolyte solution can be used for whole bowel irrigation of the GI tract in case of poisoning due to iron, lithium, cocaine, heroin, foreign bodies, etc.

Table 1.9 ■ Antidotes for various poisons

Poison	Antidote
Alkalies	Dilute acetic acid (vinegar)
Organophosphorus compounds	Atropine
Morphine (opioids)	Naloxone
Atropine	Physostigmine
Benzodiazepines	Flumazenil
Carbamates	Atropine
Cyanide	Sodium nitrite and sodium thiosulphate
Methanol	Fomepizole, ethyl alcohol
Paracetamol	<i>N</i> -acetylcysteine
Heparin	Protamine sulphate
Warfarin	Vitamin K ₁ (phytonadione)
Iron compounds	Desferrioxamine

- 6. To promote elimination of absorbed portion of the drugs:
 - a. **Diuretics** (i.v. mannitol or furosemide) are used to promote the elimination of absorbed portion of the drug. Renal elimination of some of the drugs can be increased by altering the pH of urine, e.g. alkalization of urine in salicylate poisoning and acidification of urine in amphetamine poisoning.
 - b. **Dialysis** is used in cases of severe poisoning, e.g. lithium, aspirin, methanol, etc.
- 7. Symptomatic treatment: Intravenous diazepam 5–10 mg if there are convulsions and external cooling for hyperpyrexia.
- 8. Maintenance of fluid and electrolyte balance: Hyponatraemia should be treated with i.v. normal saline and hypernatraemia with i.v. furosemide. Hypokalaemia is treated with potassium chloride, oral or slow i.v. infusion. Oral potassium chloride should be diluted in a tumbler of water to prevent intestinal ulceration. Potassium chloride should be given slow intravenously as it has cardiac depressant effect. Rapid injection can cause cardiac arrest and death. Thiazides or furosemide can be used to treat mild hyperkalaemia. Severe hyperkalaemia is treated with 10% calcium gluconate intravenously. Intravenous sodium bicarbonate is used to treat metabolic acidosis.

Note: Mnemonic for general management of poisoning: A to H.

SPECIFIC MANAGEMENT

Antidotes for some poisons are listed in [Table 1.9](#).

Poison Information Centres

WHO has established poison information centres in AIIMS, New Delhi and Ahmedabad. Computer software on poisons (INTOX) is used in these centres. Regional centres are in Chennai and Cochin (POISONDEX). These centres provide information about toxicity assessment and treatment over the phone throughout the day.

Pharmacoeconomics

PH1.60

It is a scientific discipline that deals with the evaluation of cost and consequences of drug therapy or other interventions to health care system and society. The commonly used pharmacoeconomic analytical methods are cost minimization analysis, cost-effectiveness analysis and cost-benefit analysis.

New Drug Development

PH1.64

Preclinical studies in animals: Before undertaking clinical trials, sufficient data about the drug must be obtained by testing it in animals. Animal studies generate pharmacodynamic, pharmacokinetic and toxicological data of the drug.

TOXICITY STUDIES

Acute toxicity studies

Acute toxicity is carried out in two animal species (one rodent, one nonrodent). Single, graded doses are administered to small groups of animals using two routes – one that is to be used in humans. It is done to determine the general behaviour and median lethal dose (LD_{50}) following exposure to the test drug. LD_{50} is the dose required to kill 50% of the animals. It is determined in a 24-hour period after administration of the drug.

Subacute toxicity studies

These are done in two species of animals to determine the maximum tolerated dose, identify target organ of toxicity and nature of toxicities. The test drug is administered daily for a period depending on the duration of treatment in humans. Animals are examined for general effects (food intake, change in the body weight, etc.), biochemical and haematological parameters are monitored; histological examination is done.

Chronic toxicity studies

Drugs are administered in two species (one rodent and one nonrodent) for 6–12 months. Monitoring is done as in subacute toxicity studies.

Special toxicity studies

These include tests for carcinogenicity, mutagenicity and teratogenic effects of the drug. It also includes effects on reproduction.

CLINICAL TRIALS

PH1.64

After completion of preclinical testing of the drug, the company files an investigational new drug (IND) application with the regulatory authority for permission to test the drug in humans. A drug should be scientifically and ethically evaluated by testing in human beings for safety and efficacy prior to its use in man for therapeutic purposes. Such study in humans is referred to as clinical trial. The principles of bioethics should be upheld during clinical trials. They include autonomy, beneficence, nonmaleficence and justice. Clinical trials are conducted in four phases, I–IV. Usually, the information obtained from one phase is analysed before proceeding to the next phase.

Phase I

This phase involves testing of the drug in humans for the first time. It is carried out in about 10–100 participants. This is usually carried out in healthy volunteers. For drugs with potential toxicity, e.g. anticancer drugs, phase I trials are carried out in cancer patients. The main objective of this phase is to determine safety of the drug and the maximum tolerated dose. Pharmacokinetic and pharmacodynamic data can be obtained. It is usually carried out by a clinical pharmacologist. No blinding is done (open label study).

Phase II (Therapeutic Exploratory Study)

It is carried out for the first time in patients with target disease for which the drug is intended to be used. It is conducted in about 50–500 patients and usually in three to four centres. The main objective of this phase is to assess the effectiveness of the drug and to determine effective dose range. Further evaluation of safety and pharmacokinetics is also done. The study is randomized and controlled, may be blinded.

Phase III (Therapeutic Confirmation Trial)

The aim is to confirm the efficacy of the drug in large number of patients of either sex. It is conducted in multiple centres. It is generally randomized, double blind comparative trial. Further data on kinetics and drug interactions can be obtained. Permission for marketing the drug is granted after successful completion of phase III trials.

Phase IV (Postmarketing Surveillance)

Once the drug is approved for marketing, postmarketing surveillance is carried out to obtain additional data about benefit and risk of a drug following its long-term use in a larger number of patients. It provides information on adverse reactions, drug interactions, new indications and evaluation of different formulations. Postmarketing surveillance helps to estimate incidence of adverse reactions, detect previously unknown adverse reactions and identify risk factors for the adverse reactions. There are ADR monitoring centres in different parts of the country. The ADRs observed in the patient should be reported to these centres. The drug company has to submit postmarketing data for the drug at regular intervals to the regulatory agency to continue its use.

Besides clinical trials, other types of clinical studies are case control study, cohort study and meta-analysis.

GOOD CLINICAL PRACTICE

PH1.64

International Council for Harmonization – Good Clinical Practice (ICH–GCP) guidelines is an international ethical and scientific standard for designing, conducting, monitoring, terminating, auditing, reporting and recording trials. It ensures that the data generated from the trials is credible, accurate and the rights, integrity and confidentiality of the participants are protected.

INFORMED CONSENT

Prior to enrolling the patient in the trial, the investigator should obtain informed consent from the subject. It is a process by which a subject voluntarily confirms his/her willingness to participate in a trial after having been informed of all aspects of the trial relevant to the subject's decision to participate in the trial. The consent should be obtained by the investigator in the subject's language without exerting undue influence.

The informed consent is documented by means of a written, signed and dated (by both investigator and subject) informed consent form. If a subject is illiterate, his legally accepted representative or an impartial witness should be present during informed consent process. The thumb impression of the subject is taken and his legally accepted representative should sign and date the informed consent form. In case of young children and mentally ill patients, consent is obtained from their guardian or legal representative.

ETHICS COMMITTEE

It is a committee or board designated by the institution to review research proposals and conduct periodic review of research involving humans so as to ensure the protection of the rights and welfare of human subjects. The number of persons in an ethics committee is about 7–15. A minimum of five persons are required to form the quorum.

Composition

1. Chairperson (from outside the institution to maintain independence of the committee)
2. Basic medical scientists (preferably one pharmacologist)
3. Clinicians
4. Legal expert or retired judge
5. Social scientist/philosopher/ethicist/theologist
6. Lay person from the community
7. Member secretary

RANDOMIZATION

It is a process where the subjects are randomly assigned to treatment groups in a clinical trial using a chance mechanism. This is usually done by a computer. The investigator has no role in deciding the allocation of a particular treatment to a particular patient in the trial. Randomization is done to avoid bias in the constitution of trial group.

BLINDING

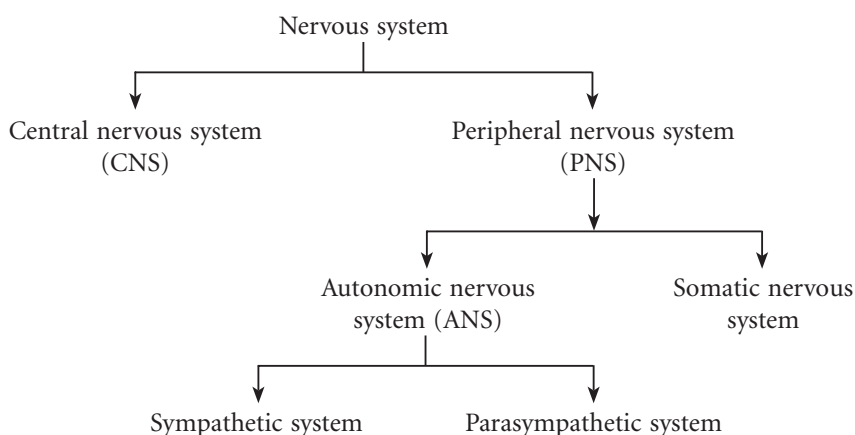
The purpose of blinding in a trial is to eliminate bias. It is done to conceal the identity of the drug from the investigator and the subject. It could be single blind or double blind.

In a double blind trial, both the investigator and the subject do not know the identity of the drug administered to the subject. In a single blind trial, the subject is unaware of the identity of the drug administered to him. A randomized double blind trial is a standard design for most of the clinical trials.

Autonomic Pharmacology

Introduction to Autonomic Nervous System

The nervous system is divided into central nervous system (CNS: brain and spinal cord) and peripheral nervous system (PNS). PNS can be further divided into somatic nervous system and autonomic nervous system (ANS). The differences between these two systems are given in [Table 2.1](#).



The ANS has two divisions – sympathetic and parasympathetic. The sympathetic division arises from thoracolumbar region (T_1 – L_3 , thoracolumbar outflow) and the parasympathetic division arises from two separate regions in the CNS. The cranial outflow arises from cranial nerves (III, VII, IX and X) and sacral outflow from S_2 , S_3 and S_4 spinal roots.

In sympathetic system, the preganglionic fibres are short and postganglionic fibres are long. On the contrary, the parasympathetic preganglionic fibres are long and postganglionic fibres are short ([Fig. 2.1](#)). Most of the visceral organs have dual nerve supply, i.e. they are supplied by both divisions of the ANS, but effects of one system predominate. The ciliary muscle, pancreatic and gastric glands receive only parasympathetic supply; sweat glands, hair follicles, spleen and most of the blood vessels have only sympathetic supply. Their stimulation usually produces opposite effect on the innervating organ ([Fig. 2.2](#)).

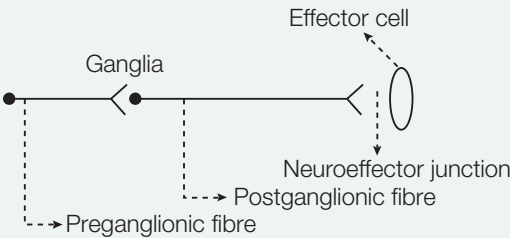
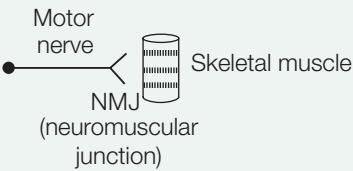
Cholinergic System

PH1.14

CHOLINERGIC TRANSMISSION

Acetylcholine (ACh) is the neurotransmitter in the cholinergic system. The sites of cholinergic transmission are shown in [Fig. 2.1](#). The neurons that synthesize, store and release ACh are called cholinergic neurons.

Table 2.1 ■ Differences between ANS and somatic nervous system

Autonomic nervous system	Somatic nervous system
<i>Auto</i> : self; <i>nomos</i> : governing; this system is involuntary and maintains homeostasis	Somatic nervous system is under voluntary control
Each autonomic fibre is made up of two neurons arranged in series	Each somatic fibre is made up of single motor neuron, which connects CNS to skeletal muscles
	
It innervates the heart, smooth muscles and exocrine glands	It innervates skeletal muscle
It controls visceral functions such as circulation, digestion and excretion	It controls skeletal muscle tone

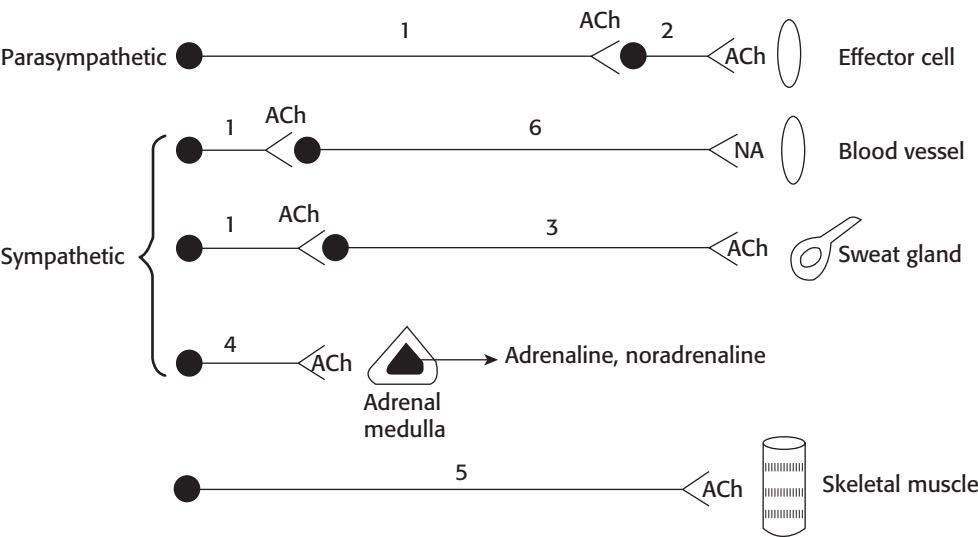


Fig. 2.1 Sites of acetylcholine (ACh) and noradrenaline (NA) release in the PNS: 1, preganglionic fibres of both sympathetic and parasympathetic system; 2, postganglionic fibres of parasympathetic system; 3, sympathetic postganglionic fibres supplying the sweat glands; 4, nerve fibres supplying the adrenal medulla; 5, motor nerve; 6, postganglionic fibres of sympathetic system that release NA. In addition, certain neurons in the brain and spinal cord release ACh and NA.

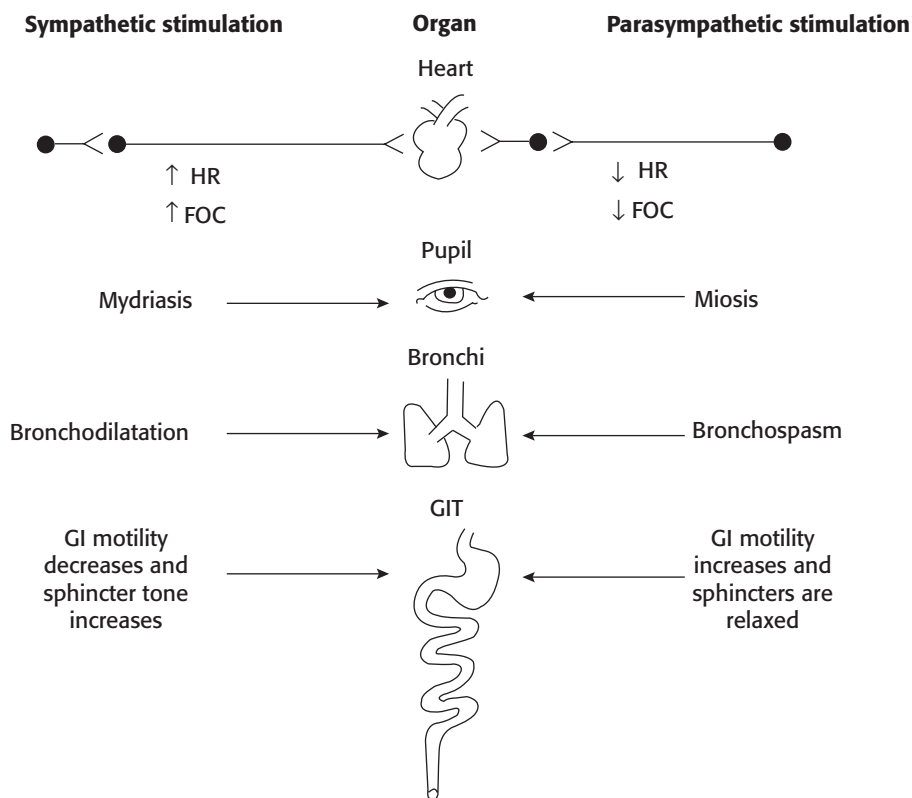


Fig. 2.2 Effects of sympathetic and parasympathetic stimulation on various organs. HR, heart rate; FOC, force of contraction; GIT, gastrointestinal tract.

Synthesis of Acetylcholine (Fig. 2.3)

Choline enters the cholinergic neuron by carrier-mediated transport, where it reacts with acetyl-CoA with the help of choline acetyltransferase (ChAT) to form ACh. The ACh is then stored in storage vesicles. It is released into synaptic cleft when an action potential reaches the nerve terminals. The released ACh interacts with cholinergic receptors on effector cell and activates them. In the synaptic cleft, ACh is rapidly hydrolysed by acetylcholinesterase (AChE) enzyme.

Cholinesterases

ACh is rapidly hydrolysed to choline and acetic acid by enzyme cholinesterases. There are two types of cholinesterase:

1. **True cholinesterase or AChE:** It is found in cholinergic neurons, ganglia, RBCs and neuromuscular junction (NMJ). It rapidly hydrolyses ACh and methacholine.
2. **Pseudocholinesterase or butyrylcholinesterase:** It is found in plasma, liver and glial cells. Pseudocholinesterase can act on a wide variety of esters including ACh (hydrolysis is slow) but does not hydrolyse methacholine.

Cholinergic Receptors

They are divided broadly into two types – muscarinic and nicotinic. Muscarinic receptors are further divided into five different subtypes: M_1 – M_5 . Only M_1 , M_2 and M_3 are functionally recognized. M_4 and M_5 subtypes are found in CNS. All muscarinic receptors

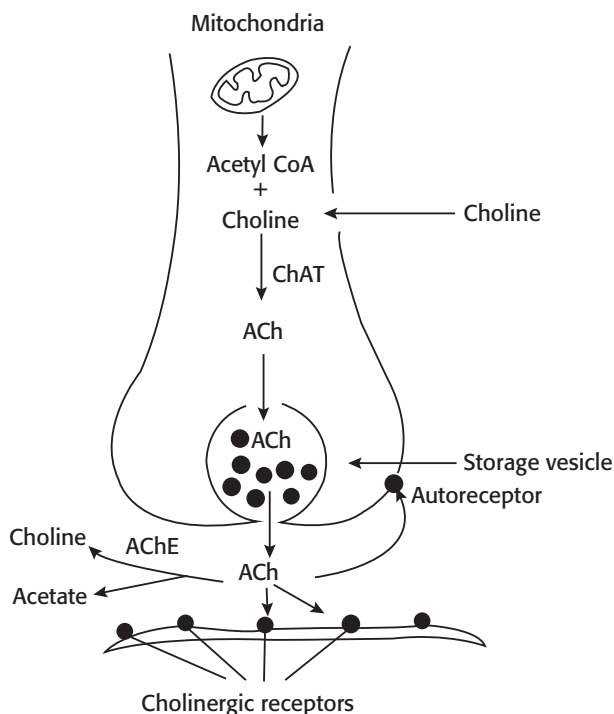
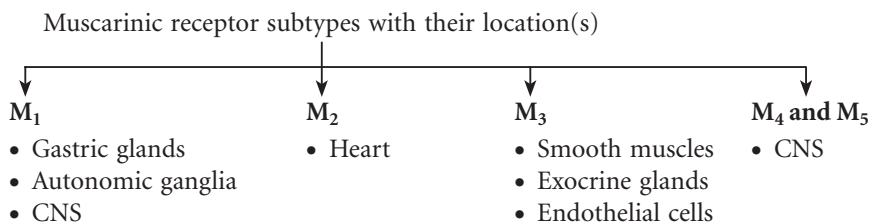


Fig. 2.3 Synthesis, storage and fate of released ACh at the cholinergic nerve endings. ChAT, choline acetyltransferase; AChE, acetylcholinesterase.

are G-protein–coupled receptors and regulate the production of intracellular second messengers.



Nicotinic receptors are divided into two subtypes – N_N and N_M . Activation of these receptors directly opens ion channels and causes depolarization of the membrane. The characteristics of muscarinic and nicotinic receptors are shown in [Table 2.2](#).

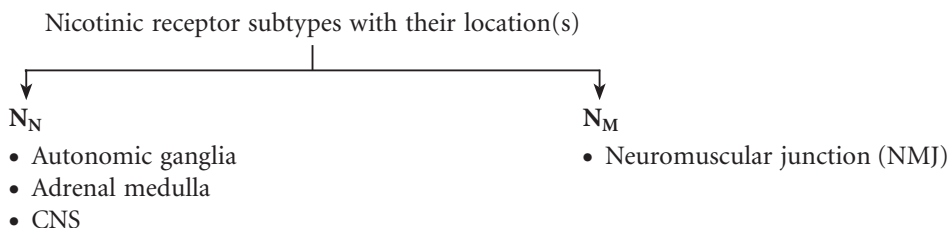


Table 2.2 ■ Characteristics of muscarinic and nicotinic receptor subtypes

Receptor type(s)	Intracellular effects	Response
M ₁ and M ₃	↑ Inositol triphosphate (IP ₃) and ↑ diacylglycerol (DAG)	- Increases learning and memory - Promotes glandular secretion and smooth muscle contraction
M ₂	↓ Cyclic adenosine monophosphate (cAMP), opening of K ⁺ channels	Hyperpolarization - Depresses SA node - Depresses AV node - Decreases atrial and ventricular contraction
N _N	Opening of ion channels (Na ⁺ , K ⁺)	Depolarization Release of adrenaline and nor-adrenaline from adrenal medulla
N _M	Opening of ion channels (Na ⁺ , K ⁺)	- Depolarization - Skeletal muscle contraction

Cholinergic Agents (Cholinomimetics, Parasympathomimetics)

PH1.14

ACh is a quaternary ammonium compound and is rapidly hydrolysed by cholinesterases. Hence, it has no therapeutic application. It has to be given intravenously to study its pharmacological actions. Even when given intravenously, a large amount of the drug is destroyed by pseudocholinesterase in blood.

Classification

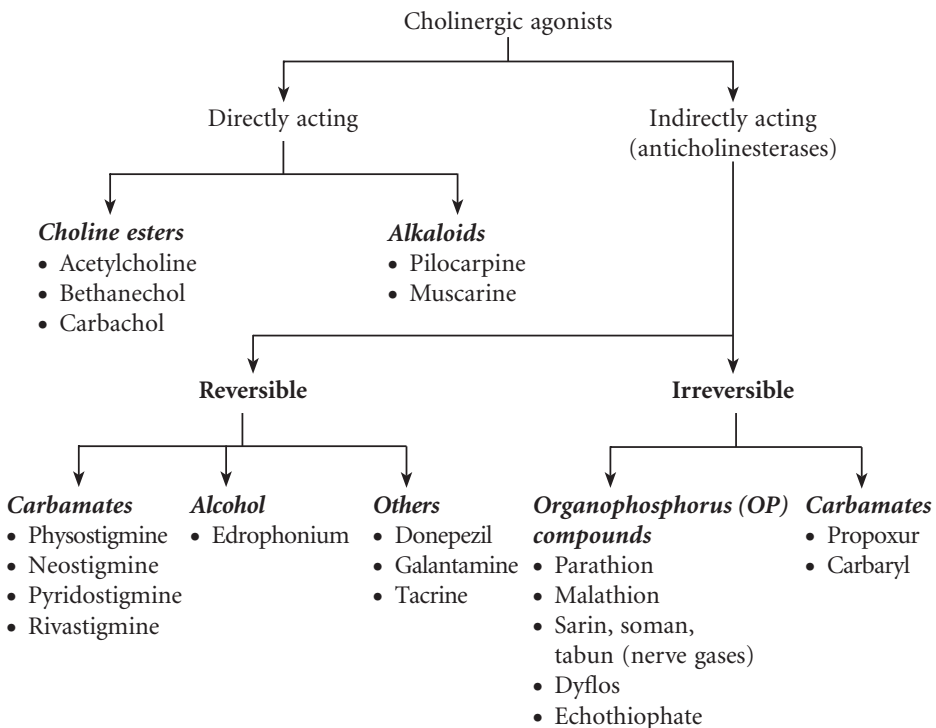


Table 2.3 ■ Pharmacological properties and uses of choline esters

	Acetylcholine	Carbachol	Bethanechol
Metabolized by	True and pseudo-cholinesterase enzymes	Resistant to both enzymes	Resistant to both enzymes
Muscarinic actions	+	+	+
Nicotinic actions	+	+	—
Effect of atropine	Muscarinic actions are completely blocked by atropine	Muscarinic actions are not completely blocked by atropine	Muscarinic actions are completely blocked by atropine
Uses	Not useful in therapy because of very short duration of action	Glaucoma	More selective for bladder and GIT – useful in postoperative urinary retention and paralytic ileus

+, present; –, absent.

Choline Esters

Choline esters include ACh, carbachol and bethanechol.

Acetylcholine. ACh produces muscarinic and nicotinic effects by interacting with respective receptors on the effector cells (Table 2.3).

Muscarinic Actions

1. Cardiovascular system

- Heart:** The effects of ACh are similar to those following vagal stimulation. ACh, by stimulating M_2 receptors of the heart, opens K^+ channels resulting in hyperpolarization. Therefore, SA and AV nodal activity is reduced (Fig. 2.4).
- Blood vessels:** ACh stimulates M_3 receptors of vascular endothelial cells, which release endothelium-dependent relaxing factor (EDRF; NO) leading to vasodilatation and a fall in blood pressure (BP) (Fig. 2.5).

2. Smooth muscles

- Gastrointestinal tract** (Fig. 2.6)
- Urinary bladder** (Fig. 2.7)
- Bronchi** (Fig. 2.8)

3. Exocrine glands: Increase in salivary, lacrimal, sweat, bronchial, gastric and other gastrointestinal (GI) secretions.

4. Eye (Fig. 2.9): ACh does not produce any effect on topical administration because of its poor penetration through tissues.

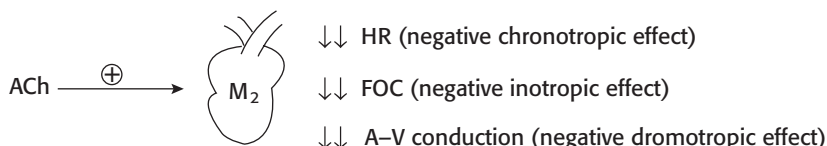


Fig. 2.4 Effects of acetylcholine (ACh) on heart. HR, heart rate; FOC, force of contraction.

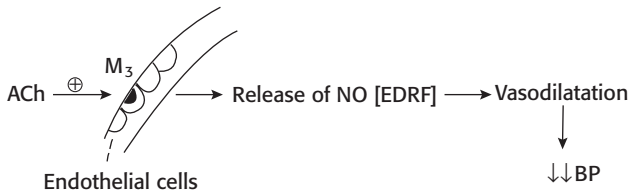


Fig. 2.5 The effect of acetylcholine (ACh) on blood vessels.

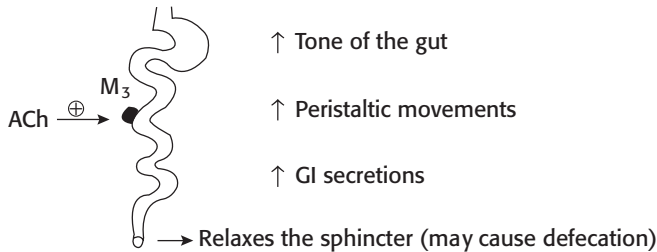


Fig. 2.6 Effects of acetylcholine (ACh) on gastrointestinal (GI) tract.

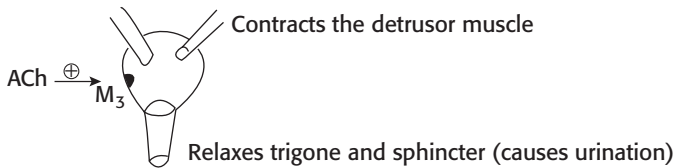


Fig. 2.7 Effects of acetylcholine (ACh) on urinary bladder.

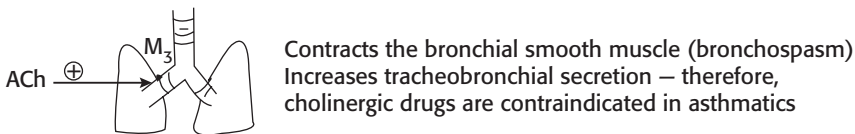


Fig. 2.8 The effect of acetylcholine (ACh) on bronchi.

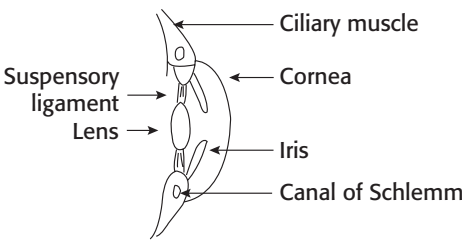
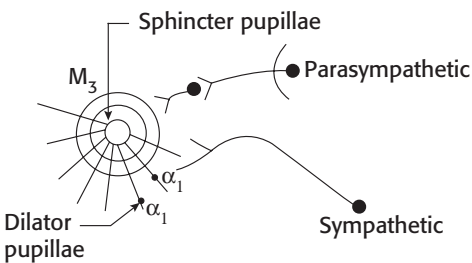
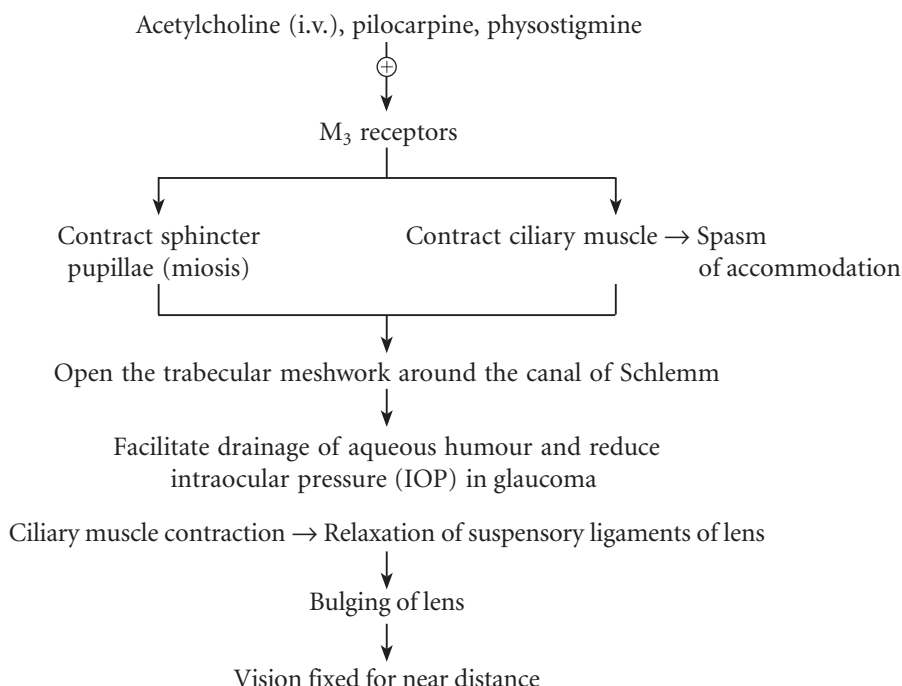


Fig. 2.9 Autonomic innervation of the eye.

Action of muscarinic agonists on eye can be depicted as follows:



Nicotinic Actions. To elicit nicotinic actions, larger doses of ACh are required.

1. Autonomic ganglia: Higher doses of ACh produce dangerous muscarinic effects especially on the heart. Hence, prior administration of atropine is necessary to elicit nicotinic actions.

Higher doses of ACh stimulate both sympathetic and parasympathetic ganglia (Fig. 2.10) causing tachycardia and rise in BP.

2. Skeletal muscles: At high concentration, ACh initially produces twitching, fasciculations followed by prolonged depolarization of NMJ and paralysis.

3. Actions on CNS: Intravenously administered ACh does not cause any central effects because of its poor penetration through the blood–brain barrier (BBB).

Bethanechol (Table 2.3). It has selective muscarinic actions on GIT and urinary bladder. It is preferred in postoperative urinary retention and paralytic ileus.

Cholinomimetic Alkaloids

They mimic the actions of ACh; examples are pilocarpine, muscarine and arecoline.

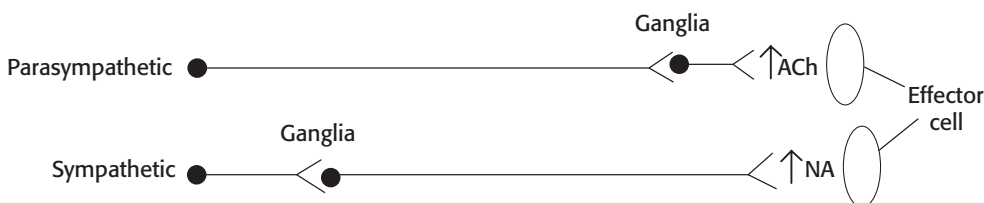


Fig. 2.10 Stimulation of parasympathetic and sympathetic ganglia.

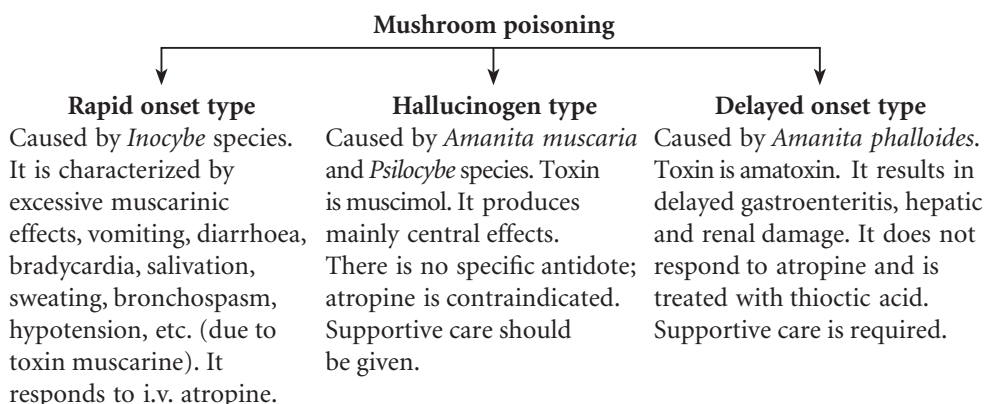
Pilocarpine. Pilocarpine is a cholinomimetic alkaloid obtained from *Pilocarpus* plant. It is a tertiary amine. It produces muscarinic and nicotinic effects by directly interacting with the receptors. It has predominant muscarinic actions especially on secretory activity.

Uses

1. Pilocarpine 0.5%–4% solution is used topically in the treatment of **open-angle glaucoma and acute congestive glaucoma**. It increases the tone of the ciliary muscle and causes miosis by contracting sphincter pupillae, opens the trabecular meshwork around the canal of Schlemm, facilitates drainage of aqueous humour and reduces intraocular pressure (IOP). It acts rapidly but has short duration of action. Pilocarpine ocusert that releases the drug slowly over 7 days is available (see p. 8).
2. It is used alternatively with mydriatics to **break adhesions between the iris and lens**.
3. It is used to **reverse the pupillary dilatation** after refraction testing.
4. Pilocarpine is used as a sialagogue (drug used to augment salivary secretion).

Adverse Effects. They are salivation, sweating, bradycardia, diarrhoea and bronchospasm; pulmonary oedema can occur following systemic therapy.

Muscarine. It is an active ingredient of poisonous mushroom, *Amanita muscaria* and *Inocybe* species. Some types of mushroom poisoning are explained as follows:



Treatment of mushroom poisoning is mainly supportive.

Arecoline. It is an alkaloid obtained from areca nut. It has muscarinic and nicotinic actions similar to choline esters.

Anticholinesterases (Fig. 2.11)

They inhibit the enzyme cholinesterase that is responsible for hydrolysis of ACh. Thus, ACh is not metabolized, gets accumulated at muscarinic and nicotinic sites and produces cholinergic effects. Hence, anticholinesterases are called indirectly acting cholinergic drugs.

Mechanism of action: ACh is rapidly hydrolysed by both true and pseudocholinesterases. ACh binds to anionic and esteratic sites of cholinesterase → acetylated enzyme → undergoes rapid hydrolysis → acetate and free enzyme.

- Carbamates bind to both the sites (i.e. anionic and esteratic) of cholinesterase (so ACh cannot bind the enzyme) → carbamoylated enzyme → undergoes slow hydrolysis to release the enzyme.

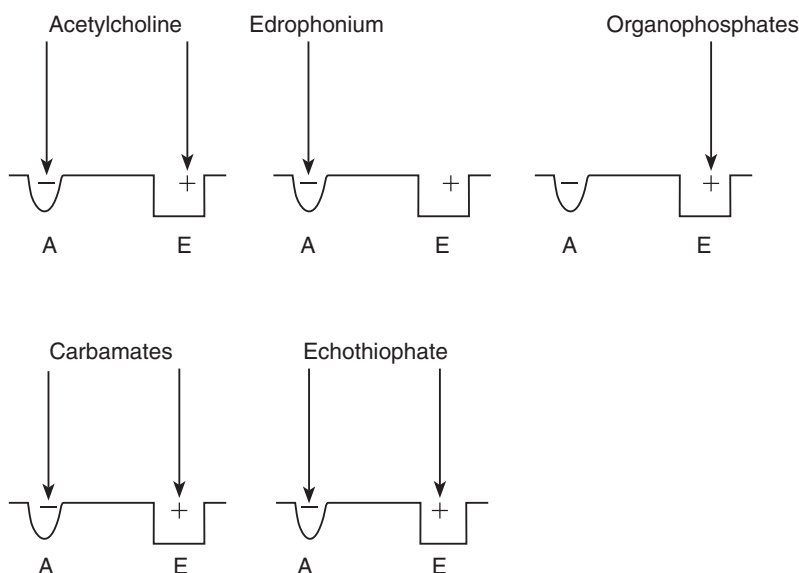


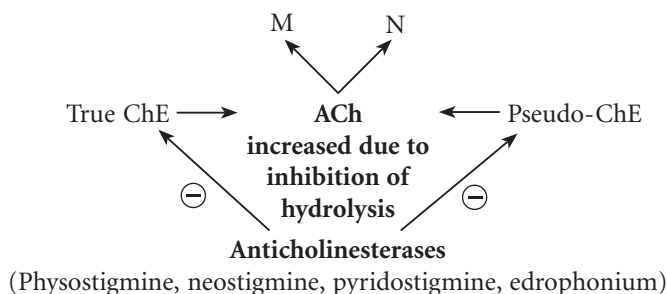
Fig. 2.11 Inactivation of acetylcholine and mechanism of action of anticholinesterases. A, anionic site; E, esteratic site.

- Edrophonium binds only to anionic site of ChE. It forms weak hydrogen bond with the enzyme. It diffuses away from the enzyme. Duration of action is 8–10 minutes.
- Organophosphates bind covalently to esteratic site of cholinesterases and inhibit them irreversibly as hydrolysis of phosphorylated enzyme is extremely slow. Echothiophate binds to both anionic and esteratic sites of the enzyme.

Reversible Anticholinesterases

- Physostigmine
- Neostigmine
- Pyridostigmine
- Edrophonium
- Galantamine
- Rivastigmine
- Donepezil

Reversible anticholinesterases inhibit both true and pseudocholinesterases reversibly.



Physostigmine (Eserine). It is an alkaloid obtained from *Physostigma venenosum*. It is a tertiary amine and has good penetration through tissues. Its actions are similar to those of other cholinergic agents.

Table 2.4 ■ Comparative features of physostigmine and neostigmine

Physostigmine	Neostigmine
Natural alkaloid obtained from <i>Physostigma venenosum</i>	Synthetic agent
Tertiary amine, has good penetration through tissues, hence topically effective	Quaternary ammonium compound, has poor penetration, hence topically not effective
Crosses BBB – produces both central and peripheral effects	Does not cross BBB, hence no central effects
Uses • Atropine poisoning • Glaucoma	Uses • Postoperative urinary retention and paralytic ileus • Myasthenia gravis • Curare poisoning

Uses

1. **Glaucoma:** Physostigmine reduces IOP by producing miosis, thus facilitates the drainage of aqueous humour. On chronic use, it accelerates cataract formation; hence, it is rarely used in glaucoma.
2. **Atropine poisoning:** Intravenous physostigmine is used for severe atropine and other antimuscarinic drug poisoning because it has both central and peripheral actions. It competitively reverses the effects of atropine poisoning, but it should be used cautiously by slow i.v. injection as it may cause bradycardia.

Neostigmine (Table 2.4; see Fig. 2.13). Neostigmine is a synthetic anticholinesterase agent. Its actions are pronounced on NMJ, gastrointestinal tract (GIT) and urinary bladder than on cardiovascular system (CVS) or eye. On skeletal muscle, it has both direct and indirect actions.

Indirect Actions. By inhibiting cholinesterases, neostigmine increases ACh concentration at NMJ.

Direct Actions. Because of structural similarity with ACh (i.e. quaternary ammonium compound), neostigmine also directly stimulates N_M receptors at NMJ. Thus, it improves muscle power in patients with myasthenia gravis.

Neostigmine does not cross BBB and has no central side effects. Therefore, neostigmine is preferred to physostigmine in myasthenia gravis. It is available for oral, s.c., i.v. and i.m. administration.

Pyridostigmine. All features are same as neostigmine. Pyridostigmine has a longer duration of action and can be given twice daily in sustained release form; hence, it is preferred to neostigmine in myasthenia gravis. Even though pyridostigmine is less potent than neostigmine, it is better tolerated by myasthenic patients.

Edrophonium. It is a quaternary ammonium compound. On i.v. administration, it has a rapid onset but short duration of action (8–10 minutes).

Uses

1. Edrophonium is used in the diagnosis of myasthenia gravis.
2. It is used to differentiate myasthenic crisis from cholinergic crisis.

3. In curare poisoning, edrophonium is preferred because of its rapid onset of action.

Adverse Effects of Anticholinesterases. They are due to overstimulation of both muscarinic and nicotinic receptors – increased sweating, salivation, nausea, vomiting, abdominal cramps, bradycardia, diarrhoea, tremors and hypotension.

Therapeutic Uses of Reversible Anticholinesterases

1. Eye
 - (a) Glaucoma
 - (b) To reverse pupillary dilatation after refraction testing
 - (c) Miotics are used alternatively with mydriatics to break adhesions between iris and lens
2. Myasthenia gravis
3. Postoperative urinary retention and paralytic ileus
4. Curare poisoning and reversal of nondepolarizing neuromuscular blockade
5. Belladonna poisoning
6. Alzheimer's disease

1. Glaucoma. The aqueous humour formed by ciliary process is drained mainly through trabecular meshwork (Fig. 2.12).

Glaucoma is optic nerve damage with loss of visual function that is frequently associated with raised IOP. Normal IOP varies between 10 and 20 mm Hg. Management of this disorder is almost always directed at lowering the existing IOP either by improving drainage or decreasing the formation of aqueous humour (Fig. 2.12).

Acute congestive glaucoma: It is usually precipitated by mydriatics in people with narrow iridocorneal angle and shallow anterior chamber. Acute congestive glaucoma is

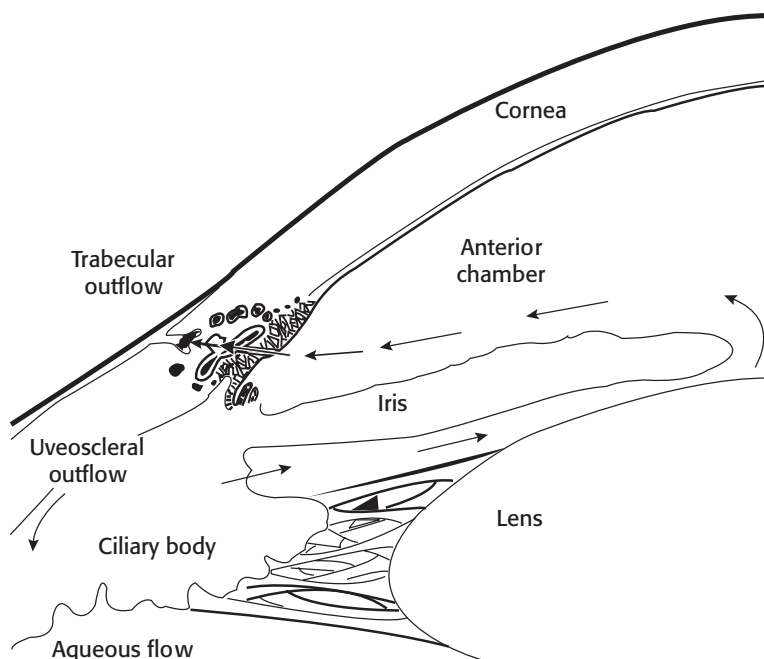


Fig. 2.12 Aqueous humour secretion and its pathway.

Table 2.5 ■ Drugs used for treating glaucoma

Acute congestive (narrow-angle) glaucoma	Chronic simple (wide-angle) glaucoma
Osmotic agents • Mannitol (20%) i.v. • Glycerol (50%) oral	β -Blockers* (topical) • Timolol (0.25%) • Betaxolol (0.25%) • Carteolol (1%)
Carbonic anhydrase inhibitor • Acetazolamide, i.v., oral	Prostaglandins • Latanoprost (0.005%), topical
β -Blockers • Timolol (0.5%), topical	Carbonic anhydrase inhibitors • Dorzolamide (2%), topical • Brinzolamide, topical • Acetazolamide, oral
Miotics • Pilocarpine (2%), topical	α -Adrenergic agonists • Dipivefrin (0.1%), topical • Apraclonidine (1%), topical
Prostaglandins • Latanoprost (0.005%), topical	Miotics • Pilocarpine (0.5%), topical
*Propranolol is not used in glaucoma as it anesthetizes cornea due to its membrane stabilizing effect	

a medical emergency. Once the attack is controlled, treatment is surgical or laser iridotomy.

Chronic simple glaucoma: It is a genetically predisposed condition affecting the patency of trabecular meshwork. The IOP rises gradually. Pharmacotherapy is the definitive treatment in a majority of cases.

Drugs for glaucoma (Table 2.5)

- Osmotic agents:** Mannitol (20%) i.v. infusion (1.5 g/kg body weight) and 50% glycerol oral (1.5 g/kg) are used. They draw fluid from the eye into the circulation by osmotic effect and reduce IOP in acute congestive glaucoma.
- Carbonic anhydrase inhibitors:** Acetazolamide (oral, i.v.), dorzolamide (topical) and brinzolamide (topical) are carbonic anhydrase inhibitors. They inhibit carbonic anhydrase enzyme, decrease bicarbonate formation in ciliary epithelium and decrease the formation of aqueous humour. Topical carbonic anhydrase inhibitors, which have a much lower risk of systemic side effects, are preferred to systemic carbonic anhydrase inhibitors in chronic simple glaucoma. In acute congestive glaucoma, acetazolamide is administered intravenously and orally.
- β -Adrenergic blockers:** Topical nonselective β -blockers are timolol, betaxolol, levobunolol and carteolol. They decrease aqueous humour formation by blocking β_2 -receptors on ciliary epithelium. β -Blockers also decrease ocular blood flow. Timolol is widely used in glaucoma because (i) it lacks local anaesthetic or partial agonistic properties; (ii) it does not affect pupil size or accommodation; (iii) it has longer duration of action; (iv) it is well tolerated; (v) it is less expensive. Topical timolol is safer and highly effective. Betaxolol is a selective β_1 -blocker used in glaucoma, but it is less effective than nonselective agents. Betaxolol is protective to

retinal neurons. Levobunolol is long acting. β -Blockers should be cautiously used in patients with bronchial asthma and heart failure.

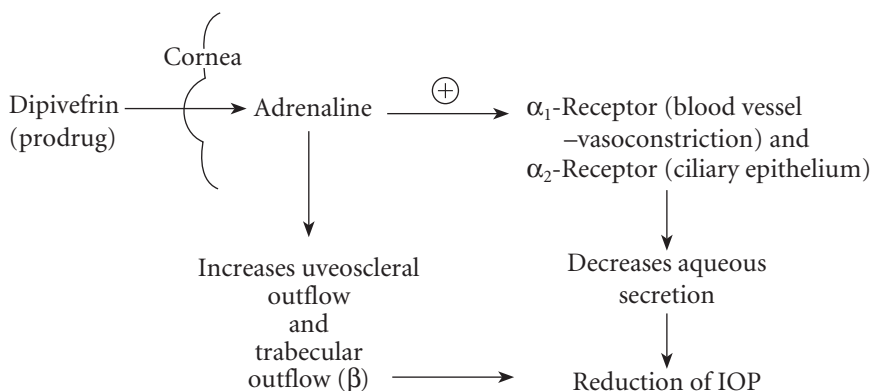
4. **Prostaglandins (PGs):** They reduce IOP probably by facilitating uveoscleral outflow. Topical PGs such as latanoprost, travoprost and bimatoprost (PGF_2 α -analogues) are the drug of choice in open-angle glaucoma because of their longer duration of action (once a day dosing), high efficacy and low incidence of systemic toxicity. They are also useful in acute congestive glaucoma. Latanoprost is also available in combination with timolol. They usually do not cause systemic side effects but may cause ocular irritation and iris pigmentation.
5. **Miotics:** Pilocarpine is a tertiary amine and is well absorbed through cornea. It is used topically in the treatment of open-angle and acute congestive glaucoma. It facilitates drainage of aqueous humour and reduces IOP.

6. α -Adrenergic agonists

- (a) Apraclonidine is used topically as an adjunct in glaucoma. It does not cross the BBB, hence has no hypotensive effect like clonidine. They act on α_2 -receptors on ciliary epithelium.

• Apraclonidine } $\Rightarrow \alpha_2$ -Agonists $\Rightarrow$ Reduce formation of aqueous humour $\Rightarrow$ Decrease IOP
 • Brimonidine }

- (b) Dipivefrin is a prodrug of adrenaline. It penetrates the cornea and with the help of esterases, gets converted into adrenaline.



2. Myasthenia Gravis. Myasthenia gravis is an autoimmune disorder where antibodies are produced against N_M receptors of NMJ resulting in a decrease in the number of N_M receptors. There is an increased incidence of myasthenia gravis in patients with thymoma. Thymectomy can induce remission in most of the cases. In myasthenia, there is marked muscular weakness varying in degree at different times. Myasthenia gravis is diagnosed by:

1. Typical signs and symptoms – weakness and easy fatigability.
2. Edrophonium test – edrophonium (2–10 mg) given slow intravenously shows dramatic improvement of symptoms in patients with myasthenia gravis but not in other muscular dystrophies; it is also useful to differentiate myasthenic crisis from cholinergic crisis.
3. Demonstration of circulating antibodies to N_M receptors.

Treatment. Anticholinesterases (neostigmine, pyridostigmine and ambenonium) are effective in providing symptomatic relief. They inhibit metabolism of ACh, thus prolonging its action at the receptors. Neostigmine also directly activates the N_M receptors. Pyridostigmine is commonly used.

Long-term use or overdose of anticholinesterases leads to cholinergic crisis (severe muscular weakness and neuromuscular paralysis due to prolonged depolarization). This may be differentiated from myasthenic crisis (severe weakness due to exacerbation of myasthenia) by injecting a small dose of edrophonium (2 mg, i.v.). If the patient shows improvement in muscle power → myasthenic crisis. If the muscular weakness deteriorates → cholinergic crisis. Ventilator should be kept ready before injecting edrophonium as it may aggravate cholinergic crisis, which is dangerous.

Corticosteroids and other immunosuppressants like azathioprine or cyclophosphamide are useful in the induction and maintenance of remission. Plasmapheresis and immune therapy may be useful in resistant cases.

Note: Drugs that aggravate myasthenia (drugs that are contraindicated in myasthenia) are aminoglycoside antibiotics, d-tubocurarine (d-TC) and other neuromuscular blockers, β -blockers, ether, phenytoin, etc.

3. Postoperative Urinary Retention and Paralytic Ileus (Fig. 2.13). Neostigmine is used because it increases the tone of the smooth muscle and relaxes the sphincters.

4. Curare Poisoning and Reversal of Nondepolarizing Neuromuscular Blockade (see p. 74). Edrophonium or neostigmine is used. They antagonize neuromuscular blockade by increasing the concentration of ACh at the NMJ. Prior administration of atropine is a must to block the muscarinic side effects.

5. Belladonna Poisoning (see p. 67). Physostigmine is preferred because it reverses both central and peripheral effects of atropine poisoning.

6. Alzheimer's Disease. It is a degenerative disease of the cerebral cortex. Donepezil, galantamine and rivastigmine are cerebroselective anticholinesterases. They increase cerebral levels of ACh and have shown to produce some benefit in these patients.

Irreversible Anticholinesterases

PH1.51, PH1.52

Organophosphorus Insecticides. All organophosphorus (OP) compounds except echothiophate have no therapeutic applications. Echothiophate is rarely used in resistant cases of glaucoma. OP compounds have only toxicological importance.

OP poisoning is one of the most common poisoning all over the world. Common OP compounds are parathion, malathion, dyflos, etc. They irreversibly inhibit cholinesterases and cause accumulation of ACh at muscarinic and nicotinic sites.

Signs and Symptoms

- 1. Muscarinic effects:** Profuse sweating, salivation, lacrimation, increased tracheo-bronchial secretions, bronchospasm, vomiting, abdominal cramps, miosis, bradycardia, hypotension, involuntary urination and defecation.

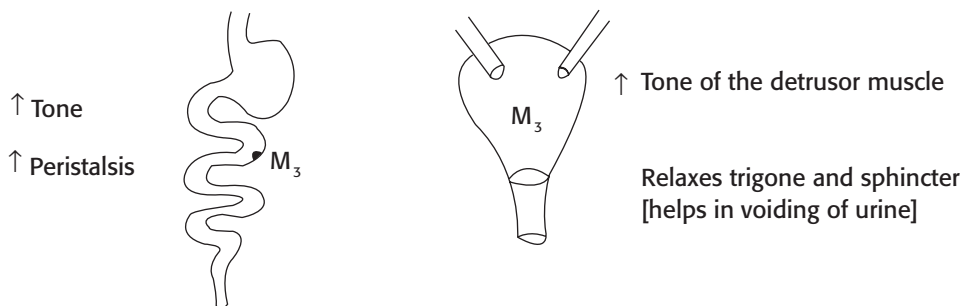


Fig. 2.13 Effects of neostigmine on smooth muscles of gut and urinary tract.

2. *Nicotinic effects:* Twitchings, fasciculations, muscle weakness and paralysis are due to prolonged depolarization.
3. *Central effects:* Headache, restlessness, confusion, convulsions, coma and death are usually due to respiratory failure.

Diagnosis. OP poisoning can be diagnosed by:

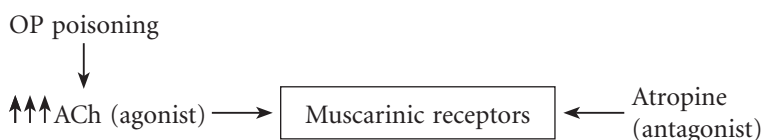
- History of exposure
- Characteristic signs and symptoms
- Estimating the cholinesterase activity in blood, which is decreased

Treatment. *General measures*

1. Remove the contaminated clothes; wash skin with soap and water.
2. Gastric lavage should be continued till the returning fluid is clear.
3. Airway should be maintained.
4. Artificial respiration is given, if necessary.
5. Diazepam should be used cautiously by slow i.v. injection to control convulsions.

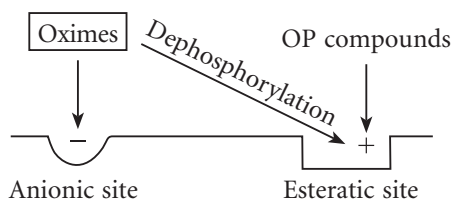
Specific Measures

1. **Atropine:** Atropine is the first drug to be given in OP poisoning. Inject atropine 2 mg i.v. stat and it should be repeated every 5–10 minutes doubling the dose, if required, till the patient is fully atropinized (fully dilated, nonreactive pupils, tachycardia, etc.). Atropine should be continued for 7–10 days.



Atropine competitively blocks the muscarinic effects of OP compounds (competitive antagonism).

2. **Oximes:** Atropine is not effective for reversal of neuromuscular paralysis. Neuromuscular transmission can be improved by giving cholinesterase reactivators such as pralidoxime and obidoxime. Pralidoxime is administered intravenously slowly in a dose of 1–2 g.



As shown above, OP compounds inactivate cholinesterases by phosphorylating esteratic site of the enzyme. Oximes bind with high affinity to anionic site, react with phosphorus atom of the OP compound, dephosphorylate the enzyme, and reactivate it. Early administration of oximes is necessary before the phosphorylated enzyme undergoes 'aging' (loses alkyl groups) and becomes resistant to reactivation.

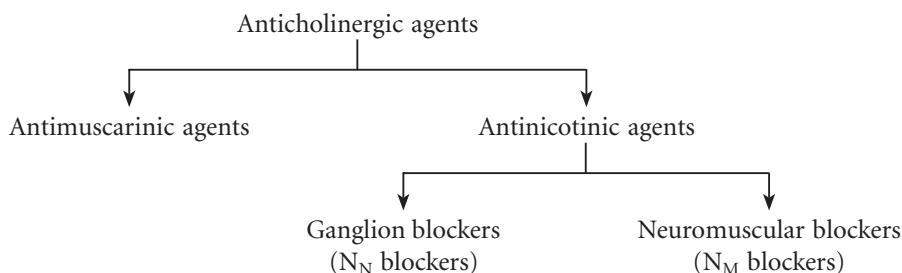
Oximes are not effective in carbamate poisoning; they also have mild anti-ChE activity

Delayed toxicity of organophosphates: Prolonged exposure to OP compounds can cause neurotoxicity.

ANTICHOLINERGIC AGENTS

PH1.14

Various anticholinergic agents are shown as follows:



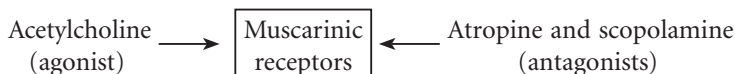
Generally, anticholinergics refer to antimuscarinic drugs.

Antimuscarinic Agents (Muscarinic Receptor Antagonists)

PH1.14

These drugs block muscarinic receptor mediated actions of ACh on heart, CNS, smooth muscles and exocrine glands. Atropine and scopolamine are belladonna alkaloids. Atropine is obtained from *Atropa belladonna* and scopolamine from *Hyoscyamus niger*.

Mechanism of Action. Both natural and synthetic drugs competitively block the muscarinic effects of ACh (competitive antagonism).



Classification of Antimuscarinic Agents

1. Natural alkaloids (*Belladonna alkaloids*): Atropine, scopolamine (hyoscine).
2. Semisynthetic derivatives:
 - Hyoscine butyl bromide
 - Homatropine (mydriatic)
 - Ipratropium bromide, tiotropium bromide (bronchial asthma)
3. Synthetic antimuscarinic agents:
 - (a) Used as mydriatic – cyclopentolate, tropicamide
 - (b) Used in peptic ulcer – pirenzepine, telenzepine, clidinium, propantheline
 - (c) Used as antispasmodic – dicyclomine, valethamate, flavoxate, oxybutynin, tolterodine, darifenacin
 - (d) Used as preanaesthetic agent – glycopyrrolate
 - (e) Used in parkinsonism – benzhexol (trihexyphenidyl), benztropine, biperiden, procyclidine

Atropine. Atropine is the prototype drug and the chief alkaloid of belladonna. It is a tertiary amine. It blocks actions of ACh on all the muscarinic receptors. Atropine is administered by topical (eye), oral and parenteral routes.

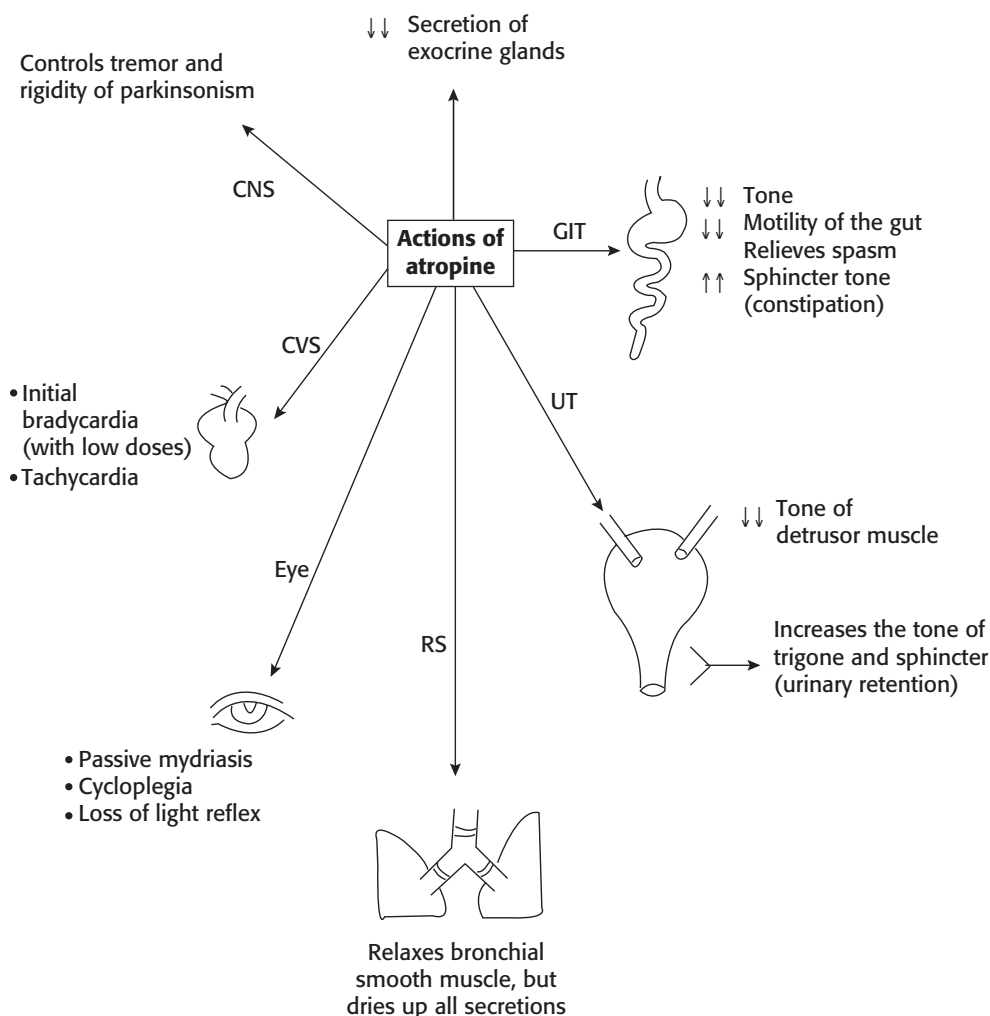
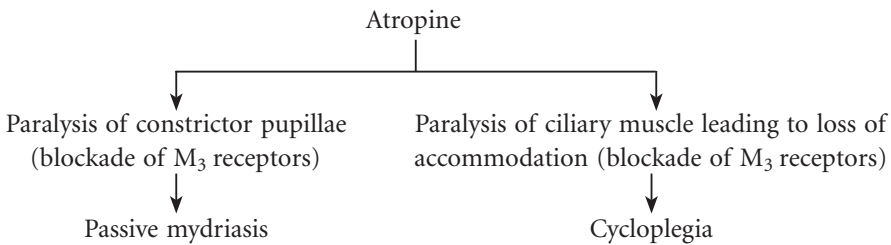


Fig. 2.14 Actions of atropine. UT, urinary tract; RS, respiratory system.

Pharmacological Actions of Atropine (Fig. 2.14)

- 1. CNS:** In therapeutic doses, atropine has mild CNS stimulant effect. It produces antiparkinsonian effect by reducing cholinergic overactivity in basal ganglia. It suppresses vestibular disturbances and produces antimotion sickness effect. Large doses can produce excitement, restlessness, agitation, hallucinations, medullary paralysis, coma and death.
- 2. CVS:** At low doses, atropine causes initial bradycardia due to blockade of presynaptic muscarinic autoreceptors (M_1) on vagal nerve endings. In therapeutic doses, tachycardia is seen due to blockade of M_2 receptors of the heart; it also improves A–V conduction. In high doses, flushing of the face and hypotension may occur due to cutaneous vasodilatation.
- 3. Glands:** All secretions under cholinergic influence are reduced due to blockade of M_3 receptors, i.e. sweat, salivary, nasal, throat, bronchial, gastric, lacrimal, etc. Milk and bile secretions are not affected. The skin and mucous membranes become dry.

4. **Eye:** Effects of atropine on eye are depicted as follows (also see [Table 2.6](#)):



Effects on eye last for 7–10 days following topical administration of atropine.

5. **Smooth muscles:**

- (a) **GIT:** Atropine decreases tone and motility of the gut, but increases sphincter tone and may cause constipation. It also relaxes smooth muscle of the gall bladder.
- (b) **Urinary bladder:** Atropine relaxes detrusor muscle of the bladder, but increases the tone of trigone and sphincter – may cause urinary retention, especially in elderly men with enlarged prostate.
- (c) **Bronchi:** Atropine relaxes the bronchial smooth muscle. It also reduces secretion and mucociliary clearance resulting in mucus plug that may block the airway.

Pharmacokinetics. Atropine, scopolamine and most of the synthetic tertiary amines are well absorbed from the conjunctiva and GI tract; are widely distributed all over the body; cross BBB; partly metabolized in liver and partly excreted unchanged in urine.

Atropine Substitutes: *Atropine acts on all subtypes of muscarinic receptors.* Atropine substitutes have selective or relatively selective action on a particular organ, hence produce less adverse effects than atropine.

Table 2.6 ■ Effects of atropine and phenylephrine/ephedrine on eye

Atropine	Phenylephrine/ephedrine
1. It is an anticholinergic agent – causes passive mydriasis	1. It is a sympathomimetic agent – causes active mydriasis due to contraction of radial muscle fibres of the iris
2. There is loss of accommodation (it is cycloplegic), photophobia and blurring of vision; cycloplegia is due to paralysis of ciliary muscle; the lens becomes flat and vision is fixed for distant objects.	2. It does not cause cycloplegia
3. There is loss of light reflex	3. There is no loss of light reflex
4. IOP may rise and acute congestive glaucoma may be precipitated in person with shallow anterior chamber; it causes mydriasis and relaxation of ciliary muscle which occlude the canal of Schlemm, resulting in obstruction to the flow of aqueous humour	4. IOP is reduced due to a decrease in the formation of aqueous humour

1. Atropine substitutes used in the eye(a) *Homatropine*

- Semisynthetic atropine derivative
- Less potent than atropine
- Duration of action (mydriasis and cycloplegia) is 1–3 days

(b) *Cyclopentolate and tropicamide*

- Synthetic atropine derivatives with rapid onset (tropicamide is the fastest acting) and shorter duration of action than atropine.
- Action of cyclopentolate lasts for 24 hours; tropicamide is the shortest acting and action lasts for 6 hours.

2. Antispasmodics(a) *Dicyclomine*

- Tertiary amine
- Has antispasmodic and antiemetic properties
- Useful in dysmenorrhoea and abdominal colic

(b) *Valethamate*

- Tertiary amine
- Has antispasmodic effect
- Useful in intestinal and urinary colic

(c) *Oxybutynin*

- Has selective action at M_1 and M_3 receptors in urinary bladder and salivary gland.
- Has vasoselective action – useful for relief of spasm after urologic surgeries, for increasing bladder capacity in paraplegics and in nocturnal enuresis.

(d) *Tolterodine*

- More selective for urinary bladder than salivary glands, hence dryness of mouth is less.
- Used to decrease frequency and urgency in detrusor overactivity.

(e) *Flavoxate*

- Similar to oxybutynin
- Used to relieve urgency and frequency due to cystitis, prostatitis or urethritis

(f) *Darifenacin, Solifenacin*

- Have selective action on urinary bladder (M_3) – useful for relief of spasm after urologic surgeries and urinary incontinence.
- Are longer acting than oxybutynin.
- *Oxybutynin, flavoxate, tolterodine, darifenacin and solifenacin are vasoselective anticholinergics.*

Drotaverine

- Not an anticholinergic agent
- Inhibits phosphodiesterase enzyme
- Used as antispasmodic for relief of uterine spasm, intestinal and renal colic

3. Ipratropium bromide and tiotropium bromide

- Quaternary compounds administered by inhalation route.
- Have a selective action on bronchial smooth muscle – bronchodilatation (mainly in the larger airways).
- Do not affect mucociliary clearance.
- Tiotropium (24 hours) is longer acting than ipratropium (6 hours).
- Dryness of mouth is the main side effect of these agents.

4. Pirenzepine

- Has selective action on gastric acid secretion (M_1) – useful in peptic ulcer.
- Anticholinergic side effects – dryness of mouth, constipation, tachycardia and urinary retention are rare.

5. Benzhexol and benztropine

- They are centrally acting anticholinergic agents used in parkinsonism.

6. Glycopyrrolate

- Quaternary compound – central side effects are rare.
- Used for preanaesthetic medication.

7. Propantheline

- Useful in peptic ulcer and as an antispasmodic.
- Rarely used at present.

8. Clidinium

- Quaternary compound
- Has antisecretory and antispasmodic properties
- Useful in peptic ulcer and irritable bowel syndrome

9. Hyoscine butylbromide

- Quaternary compound; available for oral and parenteral administration.
- Used as antispasmodic for relief of oesophageal and GI colics.

Therapeutic Uses of Atropine and Its Substitutes**1. Ophthalmic uses:**

- *As mydriatic and cycloplegic* – for refraction testing. Atropine, homatropine, cyclopentolate or tropicamide are used topically. The action of atropine lasts for 7–10 days. Tropicamide is the preferred mydriatic as it has a short duration of action. In children, atropine is preferred because of its greater efficacy.
- *As mydriatic* – for fundoscopic examination, short-acting agent is used.
- *In iridocyclitis* – atropinic mydriatics are used alternatively with miotics to break or prevent adhesions between iris and lens.

2. As preanaesthetic medication: Atropine or glycopyrrolate is used. They are used prior to the administration of general anaesthetics:

- To prevent vagal bradycardia during anaesthesia.
- To prevent laryngospasm by decreasing respiratory secretions.

Glycopyrrolate is a quaternary ammonium compound and has only peripheral anticholinergic effects.

3. Sialorrhoea: Synthetic derivatives (glycopyrrolate) are used to decrease excessive salivary secretion, e.g. in heavy metal poisoning and parkinsonism.**4. Chronic obstructive pulmonary disease (COPD) and bronchial asthma:** Ipratropium bromide and tiotropium bromide are used in COPD and bronchial asthma. They are administered by metered dose inhaler or nebulizer. They produce bronchodilatation without affecting mucociliary clearance, hence are preferred to atropine.**5. Anticholinergics** are useful as **antispasmodic** in dysmenorrhoea, intestinal and renal colic. They are less effective in biliary colic.**6. Urinary disorders:** Oxybutynin and flavoxate have more prominent effect on bladder smooth muscle, hence are used to relieve spasm after urologic surgery. Tolterodine has selective action on bladder smooth muscle (M_3), hence is used to relieve urinary incontinence.**7. Poisoning:**

- In OP poisoning, atropine is the life-saving drug (see p. 61).

- In some types of mushroom poisoning (*Inocybe* species), atropine is the drug of choice (see p. 54).
 - Atropine is used in curare poisoning with neostigmine to counteract the muscarinic effects of neostigmine.
8. **As vagolytic:** Atropine is used to treat sinus bradycardia and partial heart block due to increased vagal activity. It improves A–V conduction by vagolytic effect.
 9. **Parkinsonism:** Centrally acting anticholinergic drugs such as benzhexol (trihexyphenidyl), bztropine, biperiden, procyclidine, etc. are the preferred agents for prevention and treatment of drug-induced parkinsonism. They are also useful in idiopathic parkinsonism, but less effective than levodopa. They control tremor and rigidity of parkinsonism.

Adverse Effects and Contraindications. The adverse effects of atropine are due to the extension of its pharmacological actions.

1. **GIT:** Dryness of mouth and throat, difficulty in swallowing, constipation, etc.
2. **Eye:** Photophobia, headache, blurring of vision; in elderly persons with shallow anterior chamber, they may precipitate acute congestive glaucoma. Hence, anticholinergics are contraindicated in glaucoma.
3. **Urinary tract:** Difficulty in micturition and urinary retention especially in elderly men with enlarged prostate. So, they are contraindicated in these patients.
4. **CNS:** Large doses produce restlessness, excitement, delirium and hallucinations.
5. **CVS:** Tachycardia, palpitation and hypotension.
6. **Acute belladonna poisoning:** It is more common in children. The presenting features include fever, dry and flushed skin, photophobia, blurring of vision, difficulty in micturition, restlessness, excitement, confusion, disorientation and hallucinations.

Severe poisoning may cause respiratory depression, cardiovascular collapse, convulsions, coma and death.

Treatment of belladonna poisoning (Atropine poisoning): It is mainly symptomatic.

1. Hospitalization.
2. Gastric lavage with tannic acid in case poison was ingested.
3. Tepid sponging to control hyperpyrexia.
4. Diazepam to control convulsions.
5. The antidote for severe atropine poisoning is physostigmine (1–4 mg). It is injected intravenously slowly. It is a tertiary amine – counteracts both peripheral and central effects of atropine poisoning. Hence, physostigmine is preferred to neostigmine.

Scopolamine. Scopolamine (hyoscine), another belladonna alkaloid, produces all the actions of atropine. In therapeutic doses, it produces prominent CNS depression with sedation and amnesia. Scopolamine has shorter duration of action than atropine. It has more prominent actions on eye and secretory glands. By blocking cholinergic activity, scopolamine suppresses vestibular disturbances and prevents motion sickness (Fig. 2.15). It is the drug of choice for motion sickness – can be administered orally or as a transdermal patch. It is more effective for prevention of motion sickness, hence should be given (0.2 mg oral) at least half an hour before journey. The patch is placed behind the ear over the mastoid process. The patch should be applied at least 4–5 hours before the journey, and its effect lasts 72 hours. Scopolamine causes sedation and dryness of mouth. It can be administered parenterally as a preanaesthetic agent.

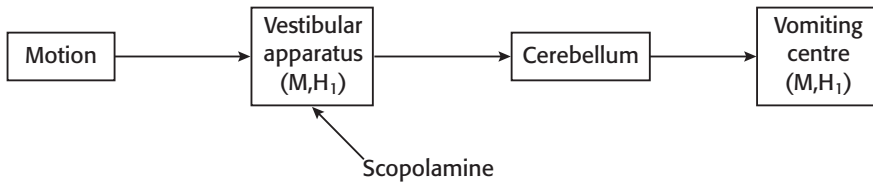


Fig. 2.15 Sites of action of scopolamine in motion sickness. M, muscarinic receptor; H₁, histamine receptor.

Drug Interactions of Anticholinergics. H₁-blockers, tricyclic antidepressants (TCAs), phenothiazines, etc. have atropine-like action, hence may potentiate anticholinergic side effects.

Atropine alters absorption of some drugs by delaying gastric emptying – the bioavailability of levodopa is reduced, whereas the absorption of tetracyclines and digoxin is enhanced due to increased GI transit time.

Ganglion Blockers

They act at N_N receptors of the autonomic ganglia (block both parasympathetic and sympathetic ganglia) and produce widespread complex effects (Fig. 2.16). The ganglion blockers have ‘atropine-like’ action on heart (palpitation and tachycardia), eyes (mydriasis and cycloplegia), GIT (dryness of mouth and constipation), bladder (urinary retention). They decrease sweat secretion and cause impotence in males. Blockade of sympathetic ganglia results in marked postural hypotension.

No selective ganglion blockers are available till now. Hence, they are rarely used in therapy.

Trimethaphan is a short-acting ganglion blocker that must be given by i.v. infusion. At present, the only use of trimethaphan is to produce controlled hypotension during neurosurgery.

Nicotine is obtained from tobacco leaves. It has initial stimulating, later a prolonged blocking effect on the autonomic ganglia. Tobacco smoking and chewing is a serious risk factor for oral, lung, heart and other diseases.

Treatment of nicotine addiction

Nicotine chewing gum and transdermal patch: They are useful as nicotine replacement therapy.

Bupropion: It inhibits NA and DA reuptake and is used for smoking cessation.

Varenicline: It is a partial agonist at nicotinic receptors. It decreases craving and withdrawal symptoms during smoking cessation.

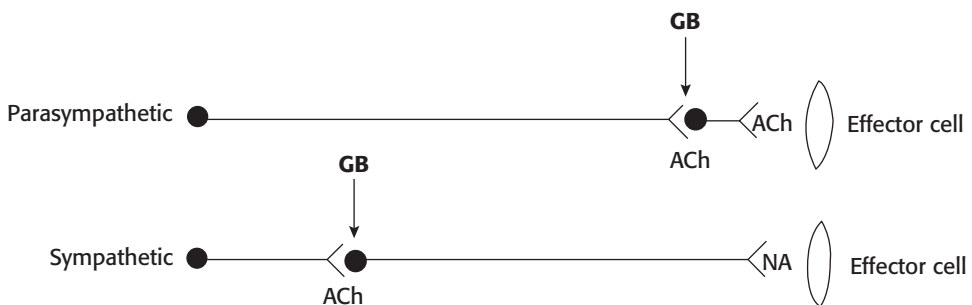


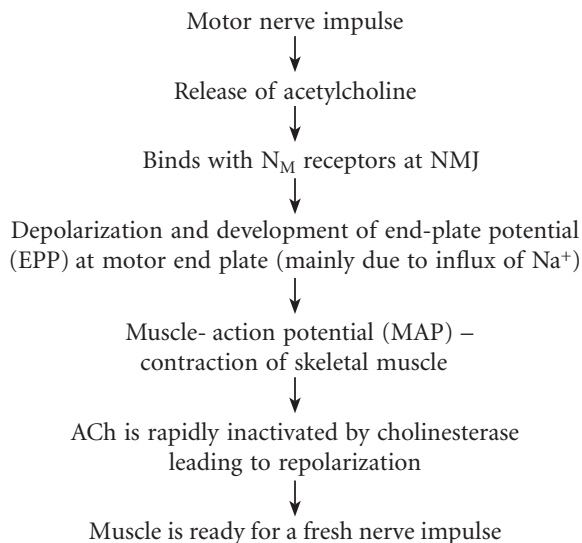
Fig. 2.16 Site of action of ganglion blocker (GB).

Skeletal Muscle Relaxants

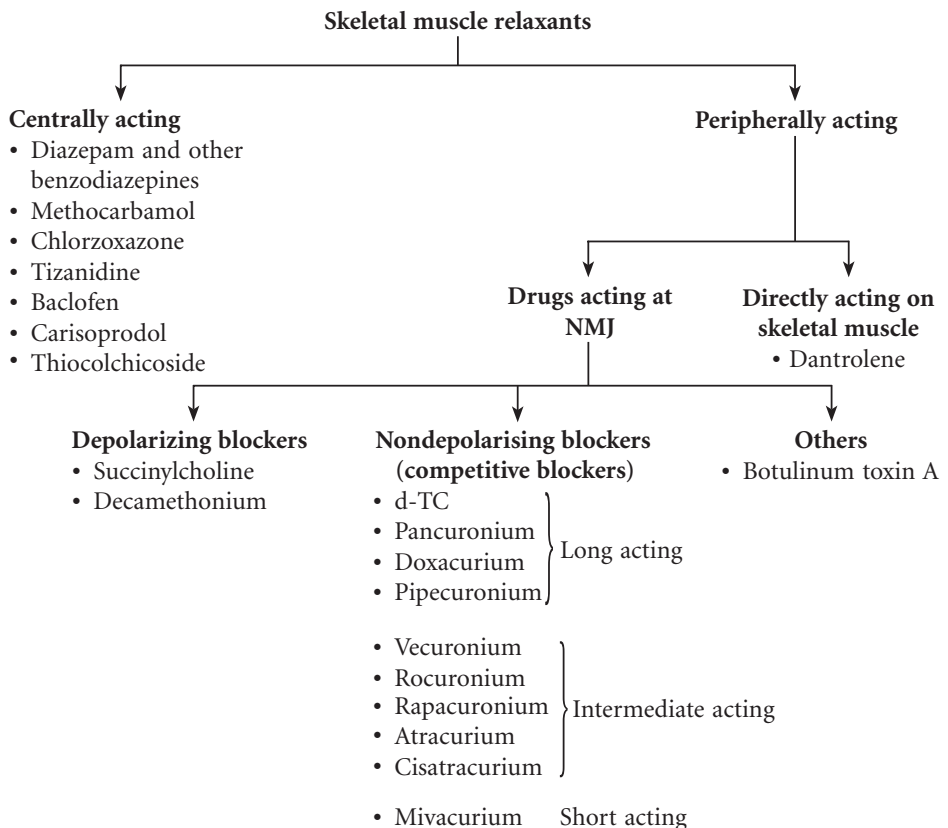
PH1.15

Skeletal muscle relaxants decrease skeletal muscle tone by peripheral or central action.

Physiology of Skeletal Muscle Contraction



Classification



Centrally Acting Skeletal Muscle Relaxants

Most of the centrally acting skeletal muscle relaxants are available in combination with one or other nonsteroidal anti-inflammatory drugs (NSAIDs). All of them cause certain degree of sedation. They act by depressing polysynaptic pathways in spinal and supra-spinal sites. They are used to reduce spasm associated with cerebral palsy, trauma, sprain, tetanus, multiple sclerosis, etc. (Table 2.7 for characteristics of these drugs).

Neuromuscular Blockers

Unlike centrally acting skeletal muscle relaxants, these drugs interfere with neuromuscular transmission, do not affect CNS and are administered intravenously. Neuromuscular blockers include nondepolarizing (competitive) and depolarizing blockers.

Depolarizing Blockers: Succinylcholine (Suxamethonium). Succinylcholine (SCh) is a quaternary ammonium compound. The structure resembles two molecules of ACh linked together. It acts as a partial agonist at N_M receptors, hence causes initial fasciculations and later flaccid paralysis due to prolonged depolarization (phase I block). With continued exposure to the drug, the membrane becomes desensitized that leads to phase II block, which resembles the nondepolarizing block and is partially reversed by anticholinesterases. Phase II block can occur in patients with atypical pseudocholinesterase.

SCh is rapidly hydrolysed by pseudocholinesterase, hence has a very short duration of action (3–8 minutes). Transient apnoea is usually seen at the peak of its action.

Table 2.7 ■ Characteristics of centrally acting skeletal muscle relaxants

Drug	Route	Uses	Side effects
^a Baclofen: GABA _B agonist	• Oral	• Spinal cord lesions • Multiple sclerosis • Amyotrophic lateral sclerosis	Drowsiness, dry mouth, diarrhoea, confusion, ataxia, vomiting
Diazepam and other benzodiazepines: GABA _A agonists	• Oral • Parenteral	• Tetanus and other conditions associated with muscle spasm	Sedation, drowsiness
^a Tizanidine: Central α ₂ -agonist	• Oral	• Multiple sclerosis • Spinal cord injury or disease	Drowsiness, dizziness, disorientation, ataxia, headache
Chlorzoxazone, methocarbamol: Act on spinal interneurons	• Oral	• Acute muscle spasm due to trauma	Drowsiness
Riluzole: Inhibits glutamate release	• Oral	• Amyotrophic lateral sclerosis	Diarrhoea
Carisoprodol: Mechanism of action not clearly known	• Oral	• Muscle sprain	Drowsiness
Thiocolchicoside	• Oral	• Sprain, muscle spasm due to trauma	Diarrhoea, drowsiness, rashes

^aBlock release of excitatory transmitter in the spinal cord → depresses polysynaptic reflexes.

In people with liver disease or atypical pseudocholinesterase due to genetic defect, the metabolism of SCh becomes slow which results in severe neuromuscular blockade leading to respiratory paralysis with prolonged apnoea. This is referred to as '*prolonged succinylcholine apnoea*'. There is no antidote available, therefore:

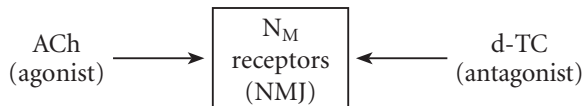
- Fresh frozen plasma should be infused.
- Patient should be ventilated artificially until full recovery.

Adverse Effects

1. Muscle pain is due to initial fasciculations (muscle soreness).
2. Increased IOP due to contraction of external ocular muscles and it lasts for few minutes.
3. Aspiration of gastric contents may occur due to increased intragastric pressure.
4. Hyperkalaemia – fasciculations release K^+ into the blood.
5. Sinus bradycardia is due to vagal stimulation.
6. SCh apnoea (prolonged apnoea).
7. Malignant hyperthermia especially when used with halothane in genetically susceptible individuals. This is treated with intravenous dantrolene, rapid cooling, inhalation of 100% oxygen and control of acidosis.

Competitive Blockers (Nondepolarizing Blockers; Table 2.8). Claude Bernard showed experimentally the site of action of curare. Curare is a mixture of alkaloids and was used as an arrow poison. Among them, d-TC is the most important alkaloid which has N_M blocking activity. d-TC is the prototype drug of competitive blockers.

Mechanism of Action. ACh is the agonist, whereas d-TC is the antagonist at N_M receptors. Curariform drugs competitively antagonize the actions of ACh at the N_M receptors of the NMJ. Anticholinesterases (neostigmine or edrophonium) are used to reverse the effects of competitive blockers by increasing the concentration of ACh.



Actions. Competitive blockers produce flaccid paralysis. The order of muscles affected is extrinsic eye muscles–neck (muscles of phonation and swallowing)–face–hands–feet–limbs–trunk and finally, the respiratory muscles (intercostal muscles and diaphragm). But recovery occurs in reverse order – the respiratory muscles are the first to recover. Consciousness and appreciation of pain are not affected.

- d-TC, mivacurium and atracurium cause histamine release which can manifest as hypotension, bronchospasm, etc.
- Pancuronium, vecuronium, doxacurium and rocuronium have minimal/no tendency to cause histamine release.
- Vecuronium, doxacurium and rocuronium have minimal tendency to cause cardiovascular effects like hypotension, cardiovascular collapse, etc. These effects are also less marked with pancuronium and pipecuronium. Cardiovascular side effects are prominent with d-TC and mivacurium.
- Among competitive neuromuscular blockers, rocuronium has a rapid onset of action; hence, it can be used for endotracheal intubation.
- Comparative features of d-TC and SCh are shown in Table 2.9.

Pharmacokinetics. Neuromuscular blockers are quaternary ammonium compounds. They are highly ionized, hence poorly absorbed from GI tract. They are administered

Table 2.8 ■ Features of nondepolarizing (competitive) blockers

Nondepolarizing blockers

1. **d-TC:** An alkaloid obtained from *Chondrodendron tomentosum*
 - Prototype competitive N_M blocker
 - Causes flaccid paralysis
 - Causes histamine release, ganglionic blockade
 - Has long duration of action
2. **Pancuronium**
 - Synthetic agent
 - Produces competitive blockade
 - Has long duration of action
 - Minimal/no histamine release
 - Has vagolytic action, hence causes tachycardia
3. **Pipecuronium**
 - Has long duration of action
 - May cause bradycardia and hypotension
4. **Doxacurium**
 - Minimal histamine release
 - Has long duration of action
5. **Vecuronium**
 - One of the commonly used neuromuscular blocker
 - Has intermediate duration of action
 - Minimal/no tendency to release histamine or cause cardiovascular effects
 - Does not cross placental barrier
6. **Rocuronium**
 - Has intermediate duration of action
 - Minimal/no tendency to release histamine
 - Has a rapid onset of action
7. **Atracurium**
 - Has intermediate duration of action
 - Undergoes spontaneous degradation in plasma (Hofmann degradation) in addition to destruction by cholinesterases
 - Causes histamine release
 - Safe in patients with hepatic and renal dysfunction
8. **Cisatracurium**
 - Has intermediate duration of action
 - More potent than atracurium
 - Does not cause histamine release
 - Undergoes spontaneous degradation in plasma (Hofmann degradation)
 - Safe in elderly and patients with hepatic and renal dysfunction
9. **Mivacurium**
 - Has short duration of action (15–20 minutes)
 - Rapidly inactivated by plasma cholinesterases
 - Does not require reversal
 - Causes histamine release
 - Duration of action is prolonged in patients with pseudocholinesterase deficiency

Table 2.9 ■ Comparative features of d-TC and succinylcholine

d-TC	Succinylcholine
1. Natural alkaloid	1. Synthetic
2. Nondepolarizing blocker	2. Depolarizing blocker
3. Long acting (80 minutes)	3. Rapidly metabolized by pseudocholinesterase, hence short acting (3–8 minutes)
4. Causes flaccid paralysis	4. Initially causes fasciculations and later flaccid paralysis
5. Causes histamine release (+++)	5. Causes histamine release (++)
6. Neostigmine reverses the block	6. Phase II block, which resembles nondepolarizing block is partially reversed by neostigmine
7. Uses: As adjuvant to general anaesthesia	7. Succinylcholine is preferred for short procedures, e.g. diagnostic endoscopies, endotracheal intubation and orthopaedic manipulations
8. Adverse effects (see p. 73)	8. Adverse effects (see p. 71)

intravenously. They are mainly confined to ECF space; do not cross placental and blood–brain barrier. They are metabolized in liver and some are excreted unchanged in urine.

Adverse Effects. The adverse effects of nondepolarizing drugs are hypotension, respiratory paralysis, bronchospasm and aspiration of gastric contents.

Drug Interactions of Skeletal Muscle Relaxants

1. Nondepolarizing blockers × antibiotics

Aminoglycosides inhibit the release of ACh from motor nerve and potentiate the effect of nondepolarizing blockers, hence require dose reduction in patients treated with aminoglycosides. Tetracyclines and clindamycin also potentiate the effect of nondepolarizing blockers.

2. Thiazides/loop diuretics × nondepolarizing blockers

Hypokalaemia caused by thiazides/loop diuretics may potentiate the effect of nondepolarizing blockers.

3. SCh × thiopentone

These drugs are chemically incompatible (in vitro; pharmaceutical interaction) hence result in precipitation when mixed in the same syringe.

4. General anaesthetics × nondepolarizing blockers

Ether has curarimimetic effect on skeletal muscle, hence enhances the effect of nondepolarizing blockers. Fluorinated anaesthetics (isoflurane, desflurane and sevoflurane) also produce similar effect but to a lesser extent.

Factors Affecting Action of Neuromuscular Blockers

1. pH changes: Metabolic acidosis and respiratory acidosis increase the duration of block.

2. Hypothermia: It potentiates neuromuscular block by delaying the metabolism and elimination of these drugs.

3. Myasthenia gravis: Myasthenic patients are highly sensitive to competitive neuromuscular blockers.

4. **Aminoglycoside antibiotics:** They potentiate the effect of both competitive and nondepolarizing blockers by inhibiting presynaptic release of ACh.
5. **Inhalational anaesthetics:** Anaesthetics like halothane, isoflurane and ketamine increase the effects of neuromuscular blocking agents.

Uses

1. The main use of neuromuscular blockers is as adjuvant to general anaesthetics for producing satisfactory skeletal muscle relaxation during surgical procedures in abdomen and thorax, orthopaedics, etc. SCh is preferred for short procedures, e.g. diagnostic endoscopies, endotracheal intubation and orthopaedic manipulations. Vecuronium is commonly used in routine surgeries. Pancuronium and pipecuronium are used in surgeries of long duration.
2. SCh /mivacurium is used during electroconvulsive therapy (ECT) to prevent trauma due to convulsions.
3. For tetanus and status epilepticus when not controlled by other drugs, competitive neuromuscular blockers can be used.
4. Competitive neuromuscular blockers, e.g. vecuronium, can be used for ventilatory support in critically ill patients.

Reversal of Neuromuscular Blockade. Edrophonium or neostigmine by increasing the concentration of ACh reverses the effect of d-TC and other competitive blockers at NMJ. Use of prior atropine administration is necessary to block the muscarinic effects of anticholinesterases (Fig. 2.17). Mivacurium (short acting), atracurium (intermediate acting), etc. do not require reversal.

Sugammadex. It is administered intravenously for rapid reversal of neuromuscular blocking action of rocuronium and vecuronium. It encapsulates the drugs, thus preventing their action.

Directly Acting Skeletal Muscle Relaxant: Dantrolene. Dantrolene is a directly acting skeletal muscle relaxant. It inhibits depolarization-induced Ca^{2+} release (by blocking ryanodine receptors) from sarcoplasmic reticulum and produces skeletal muscle relaxation. Intravenous dantrolene is the life-saving drug in malignant hyperthermia. It is used orally to reduce spasm in multiple sclerosis, cerebral palsy, spinal injuries, etc. The side effects are drowsiness, diarrhoea, dizziness, headache, fatigue and rarely hepatotoxicity.

Botulinum Toxin A. It is obtained from *Clostridium botulinum*, a gram-positive anaerobic bacterium. The toxin prevents release of ACh into the synaptic cleft by inhibiting proteins necessary for the release of ACh. Thus, it normalizes the tone in hyperreactive or spastic muscles when given locally. It is given intradermally for antiwrinkle effect in cosmetic procedures and into the muscle in multiple doses for spasticity or dystonia. Botulinum toxin A is injected under ultrasound guidance into salivary glands in sialorrhoea

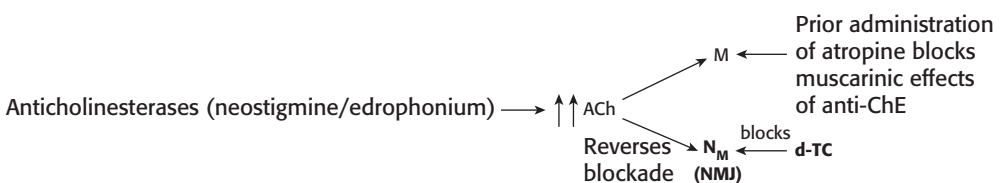


Fig. 2.17 Reversal of neuromuscular blockade. ACh, acetylcholine; NMJ, neuromuscular junction; N_M , nicotinic receptors; M, muscarinic receptor.

and drooling. Adverse effects are pain at the site of injection, muscle paralysis, myalgia and occasionally rashes.

Adrenergic Agonists (Sympathomimetic Agents)

PH1.13

Adrenergic agonists mimic the actions of sympathetic stimulation.

Adrenergic Transmission

The transmitter in the sympathetic system is noradrenaline (NA; norepinephrine). Nerves that synthesize, store and release NA are called adrenergic (sympathetic) nerves.

Synthesis of catecholamines begins with the amino acid tyrosine, which is transported into the adrenergic neuron by active transport. In the neuronal cytosol, tyrosine is converted to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase and DOPA to dopamine (DA) by dopa decarboxylase. DA enters storage vesicles of the nerve terminal by active transport, where it is converted to NA by the enzyme dopamine β -hydroxylase (this enzyme is present only in the storage vesicles); NA formed gets stored in the vesicles. In the adrenal medulla, NA is further converted to adrenaline by *N*-methyltransferase. Small quantities of NA are released continuously into the synaptic cleft and large quantities during nerve stimulation (Fig. 2.18).

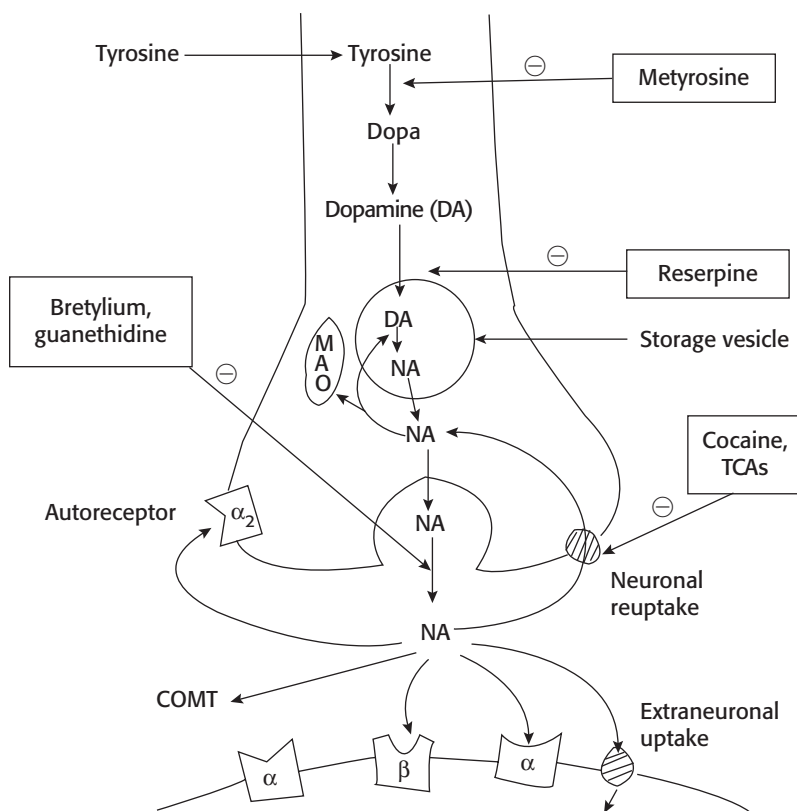


Fig. 2.18 Synthesis and release of NA from the adrenergic neuron and various drugs affecting the pathway (Table 2.10). MAO, monoamine oxidase; COMT, catechol-O-methyltransferase; TCAs, tricyclic antidepressants. (Source: Adapted from Bertram G. Katzung, Susan B. Masters., and Anthony J. Trevor, Editors: Basic and Clinical Pharmacology, 12e, McGraw Hill, 2012.)

Table 2.10 ■ Drugs affecting adrenergic transmission and their uses

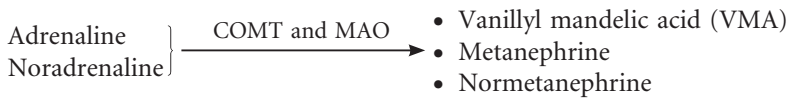
Drug	Action	Response/therapeutic uses
Metyrosine (α -Methyltyrosine)	Inhibits tyrosine hydroxylase enzyme	Blocks synthesis of NA – useful in the treatment of selected cases of pheochromocytoma
α -Methyldopa	Replacement of NA by false transmitter (α -Methyl-NA: central α_2 -agonist)	Decreases central sympathetic outflow; α -Methyl NA is an α_2 -agonist, used in hypertension especially in pregnancy
Reserpine	Blocks vesicular uptake and storage of NA	Depletion of NA; degradation by mitochondrial MAO; was used in hypertension
Bretylium, guanadrel	Prevent the release of NA	Ventricular fibrillation
Cocaine, tricyclic antidepressants (TCAs)	Inhibit neuronal reuptake of NA (uptake-1)	Accumulation of NA at receptors
Adrenergic agonists	Mimic the effects of neurotransmitter at receptor	Sympathomimetic effects
Tyramine, ephedrine, amphetamine	Promote the release of NA from adrenergic nerve terminals	Tyramine, amphetamine (indirectly acting) and ephedrine (mixed acting) sympathomimetics
Adrenergic antagonists	Block the effects of neurotransmitter at receptors	For uses: See pp. 90–91; 94–95.
Tranylcypromine (nonselective MAO inhibitor)	Potentiates tyramine action	As antidepressant
Selegiline (selective MAO-B inhibitor)	Inhibits degradation of DA in the brain	Increases DA level in the brain, adjunct in parkinsonism
Entacapone (peripheral COMT inhibitor)	Inhibits degradation of DA	Adjunct in parkinsonism
Tolcapone (peripheral and central COMT inhibitor)	Inhibits degradation of DA	Adjunct in parkinsonism

Three processes are involved in termination of action of released NA in the synaptic cleft (fate of released NA in the synaptic cleft):

1. Most of the released NA is taken back into adrenergic nerve terminals (neuronal reuptake), which is either stored in vesicles or inactivated by mitochondrial monoamine oxidase (MAO) in the cytosol. Neuronal reuptake is the most important mechanism through which termination of action of NA takes place in the synaptic cleft.
2. Small amount of NA from the synaptic cleft diffuses into circulation and gets inactivated in liver by catechol-O-methyltransferase (COMT) and MAO.
3. Small quantity of NA is transported into other tissues (extraneuronal uptake).

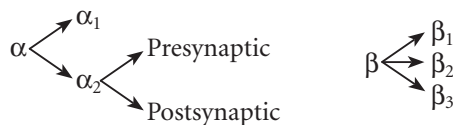
Metabolism of Catecholamines

Vanillylmandelic acid (VMA) is the main metabolite of catecholamines excreted in urine. Normal value of VMA is 4–8 mg per 24 hours urine. Its levels are raised in pheochromocytoma, a tumour of adrenal medulla and sympathetic ganglia. Estimation of the levels of catecholamines and their metabolites in blood and urine is of great value in the diagnosis of pheochromocytoma. CT (computed tomography) and MRI (magnetic resonance imaging) scan are the important diagnostic aids.



Types, Distribution and Functions of Adrenergic Receptors

Ahlquist divided adrenergic receptors into α and β types, which are located on the cell membrane. All adrenergic receptors are G-protein coupled receptors and regulate the production of intracellular second messengers; increase in IP_3/DAG (α_1), $\downarrow$ cAMP (α_2) and $\uparrow$ cAMP (β). They are further divided into various subtypes, which are as follows:



Distribution of various adrenergic receptors is indicated in [Fig. 2.19](#).

1. Effect of activation of α_1 -receptors

- Blood vessels: Constriction
- GI sphincter (anal): Increase in tone
- Urinary sphincter: Increase in tone
- Radial muscle (iris): Contraction (mydriasis)

2. Effect of activation of presynaptic α_2 -receptors

- Mediate negative feedback control on NA secretion (i.e. stimulation of α_2 -receptors decreases release of NA from sympathetic nerve endings)

3. Effect of activation of postsynaptic vascular α_2 -receptors

- Mediate stimulatory effects: Vasoconstriction and venoconstriction

4. Effect of activation of α_2 -receptors on various secretions

- Beta cells of islets of Langerhans in pancreas: Decrease in insulin secretion
- Ciliary epithelium: Reduction of aqueous humour secretion
- Sympathetic nerve endings: Decrease in NA release

5. Effect of activation of β_1 -receptors

- Heart: Cardiac stimulation
- Kidney: Promote renin release

6. Stimulatory effects due to activation of β_2 -receptors

- Liver: Stimulation of glycogenolysis
- Skeletal muscle: Contraction
- Ciliary epithelium: Increase in secretion of aqueous humour
- Uptake of K^+ into cells

7. Inhibitory effects due to activation of β_2 -receptors

- Bronchial, uterine (pregnant), vascular and bladder smooth muscles: Relaxation
- In GI smooth muscle, activation of both α - and β -receptors causes relaxation

8. Effect of activation of β_3 -receptors

- Adipose tissue: Lipolysis

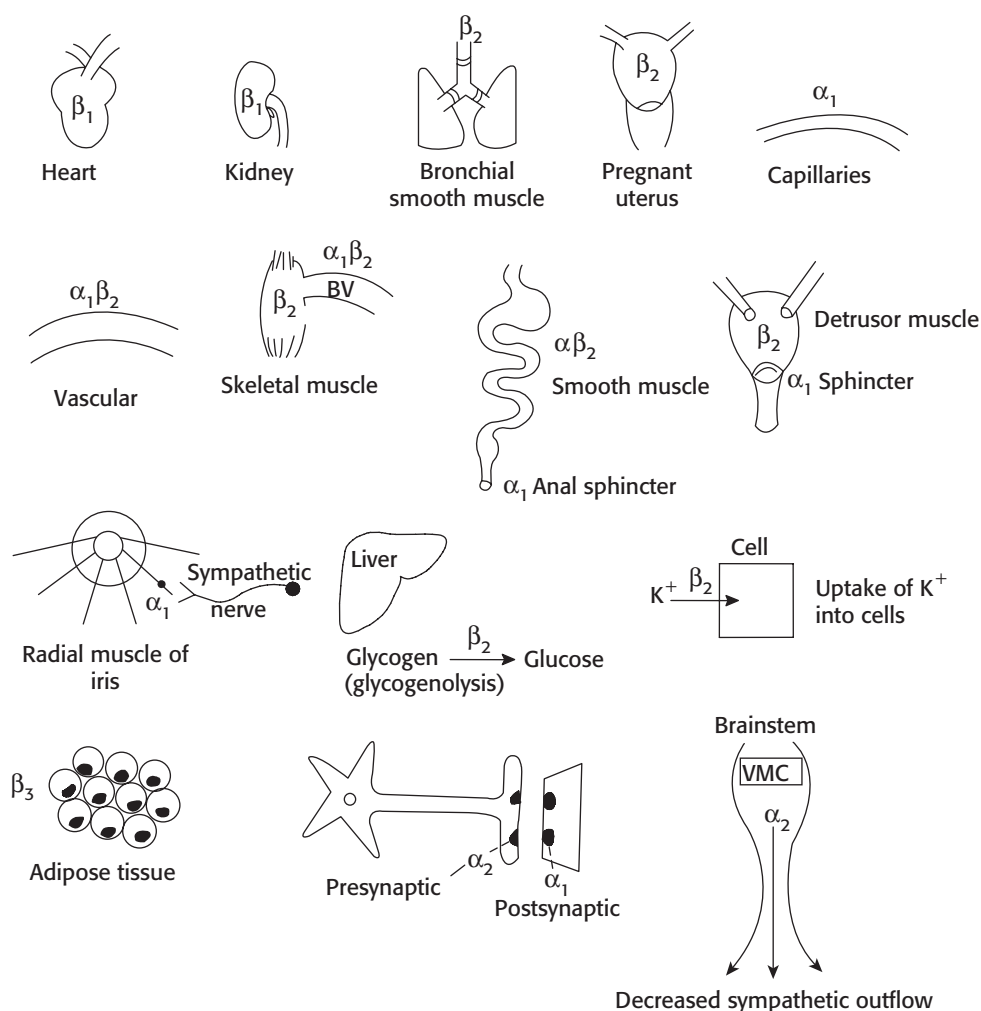


Fig. 2.19 Distribution of various adrenergic receptors. VMC, vasomotor centre; BV, blood vessel.

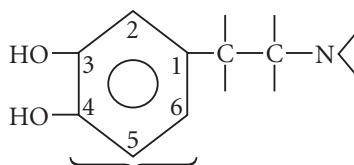
Adrenergic Drugs (Sympathomimetics)

The sympathomimetic drugs mimic effects of sympathetic stimulation (Fig. 2.20). They are also referred to as adrenergic agonists.

Classification of Adrenergic Drugs (sympathomimetics)

1. On the basis of their chemical structure

- (a) *Catecholamines*: Sympathomimetics with catechol nucleus (3,4-dihydroxy benzene) are called catecholamines, e.g. adrenaline, noradrenaline, DA, isoprenaline and dobutamine.



Catechol nucleus (3,4-dihydroxy benzene)

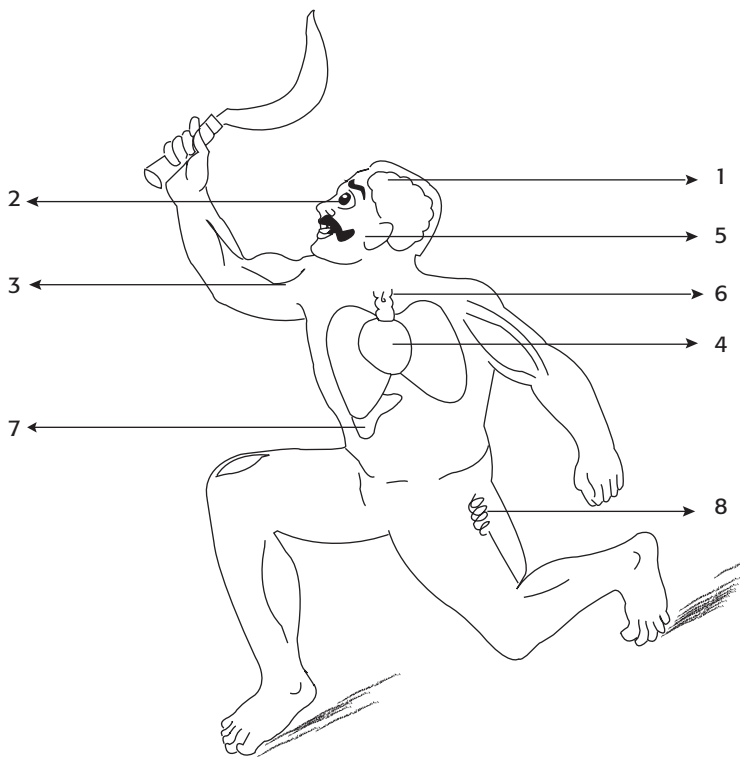


Fig. 2.20 An angry man symbolizing the sympathetic overactivity (Fight–Flight–Flight) – 1, anger, alert, aggressive; 2, pupillary dilatation (mydriasis); 3, increased muscle tone, tremors; 4, palpitation, increased cardiac output–increased blood flow to skeletal muscles; 5, flushing of the face; 6, tachypnoea, bronchodilatation; 7, liver–glycogenolysis–more energy; 8, adipose tissue–lipolysis–energy.

- (b) *Noncatecholamines*: Sympathomimetics that lack catechol nucleus are called noncatecholamines, e.g. tyramine, ephedrine, amphetamine, phenylephrine and salbutamol.

2. On the basis of their mechanism of action (Table 2.11):

- (a) *Direct acting*: They act directly by stimulating adrenergic receptors.
 (b) *Indirect acting*: They act by releasing noradrenaline from adrenergic nerve endings.
 (c) *Mixed acting*: These drugs act both directly and indirectly.

3. On the basis of their therapeutic use:

- (a) *To raise BP in shock*: DA, noradrenaline, ephedrine, phenylephrine, methoxamine, mephentermine.
 (b) *As bronchodilator*: Salbutamol, levalbuterol, pirbuterol, terbutaline, bambuterol, salmeterol, formoterol.
 (c) *As cardiac stimulant*: Adrenaline, isoprenaline, dobutamine.
 (d) *As CNS stimulant*: Amphetamine, dextroamphetamine, methamphetamine.
 (e) *As nasal decongestant*: Phenylephrine, xylometazoline, pseudoephedrine, oxymetazoline, naphazoline.
 (f) *As anorexiant*: Dextroamphetamine, mazindol, phentermine, sibutramine.
 (g) *As uterine relaxant*: Isoxsuprine, terbutaline, salbutamol, ritodrine.

Table 2.11 ■ Summary of sympathomimetic agents

Adrenergic agonists	Receptor action	Therapeutic uses
1. Directly acting		
Adrenaline	α_1 -, α_2 -, β_1 -, β_2 - and β_3 -agonist	Anaphylactic shock, Cardiac arrest, to prolong Duration of local anaesthesia, to control Epistaxis and other capillary oozing, Bronchial asthma (acute) (ABCDE)
Noradrenaline	α_1 -, α_2 - and β_1 -agonist	Hypotensive states
Isoprenaline	β_1 - and β_2 -agonist	Heart block, cardiac arrest
Dobutamine	Relatively selective β_1 -agonist	Cardiogenic shock due to acute myocardial infarction (MI), congestive cardiac failure (CCF) or cardiac surgery
- Salbutamol (Albuterol) - Levalbuterol - Pirbuterol - Terbutaline - Salmeterol - Formoterol	Selective β_2 -agonists	Bronchial asthma, to suppress premature labour (as uterine relaxant)
- Ritodrine - Isoxsuprine	Selective β_2 -agonists; main action on uterus	Uterine relaxants
- Phenylephrine - Methoxamine	Selective α_1 -agonists	Vasopressor agents, nasal decongestants, as mydriatic (phenylephrine), allergic or vasomotor rhinitis
- Naphazoline - Oxymetazoline - Xylometazoline	α_1 + α_2 -agonists	Nasal decongestants (α_1 stimulation); structural damage can occur due to intense vasoconstriction (α_2 stimulation)
Clonidine, α-Methyldopa	α_2 -agonists	Hypertension
- Apraclonidine - Brimonidine	α_2 -agonists	Glaucoma (topical)
2. Indirectly acting		
- Amphetamine - Methamphetamine - Methylphenidate	They act by releasing NA in the periphery; NA, DA and 5-hydroxytryptamine (5-HT) centrally	Narcolepsy, attention-deficit hyperactivity disorder (ADHD)
3. Mixed acting		
Ephedrine	α_1 , α_2 , β_1 and β_2 (direct action) + releases NA (indirect action)	Intravenous ephedrine is used for the treatment of hypotension due to spinal anaesthesia
Dopamine	α_1 , α_2 , β_1 and D_1 + releases NA	Cardiogenic shock, CCF with oliguria
Mephentermine	α_1 -agonist + releases NA	Hypotensive states

Direct-Acting Sympathomimetics

Adrenaline (Epinephrine): α_1 -, α_2 -, β_1 -, β_2 - and β_3 -Agonist. It is a catecholamine, which is secreted mainly by adrenal medulla. Adrenaline is a direct-acting, nonselective adrenergic agonist.

Pharmacological Actions. Adrenaline acts on α_1 -, α_2 -, β_1 -, β_2 - and β_3 -receptors.

1. Cardiovascular system

- (a) **Heart:** Adrenaline is a powerful cardiac stimulant. It acts mainly by interacting with β_1 -receptors and produces various effects. They are as follows:
 - Increase in heart rate – $\uparrow$ rate of spontaneous depolarization in SA node (positive chronotropic effect)
 - Increase in myocardial contractility (positive inotropic effect)
 - Increase in conduction velocity (positive dromotropic effect)
 - Increase in cardiac output
 - Increase in automaticity
 - Cardiac work and its oxygen requirement is markedly increased
 - Increase in the excitability and tendency to cause cardiac arrhythmias
- (b) **Blood vessels and BP:** Blood vessels of the skin and mucous membranes (α_1 -receptors) are constricted by adrenaline. It also constricts renal, mesenteric, pulmonary and splanchnic vessels, but dilates blood vessels of skeletal muscle and coronary vessels (β_2). Intravenous administration of adrenaline in moderate doses produces biphasic effect. There is an initial rise in BP due to α_1 (blood vessels) and β_1 (heart) actions, followed by a fall in BP due to β_2 -mediated dilatation of blood vessels in skeletal muscle. Administration of adrenaline after α -blocker produces only a fall in BP (β_2 -action). This is referred to as vasomotor reversal of Dale (Fig. 2.21).

If adrenaline is rapidly injected intravenously, there is an increase in both systolic and diastolic BP.

2. **Respiratory system:** Adrenaline rapidly relaxes (β_2) bronchial smooth muscle. It is a potent bronchodilator but has a short duration of action. It inhibits the release of inflammatory mediators from mast cells (β_2). It also reduces secretions and relieves mucosal congestion by vasoconstrictor effect (α_1).
3. **GIT:** It relaxes the smooth muscle of the gut (α and β_2). It reduces the intestinal tone and peristaltic movements but the effects are transient.
4. **Bladder:** It relaxes the detrusor muscle (β_2) and contracts the sphincter (α_1). As a result, it may cause difficulty in urination.

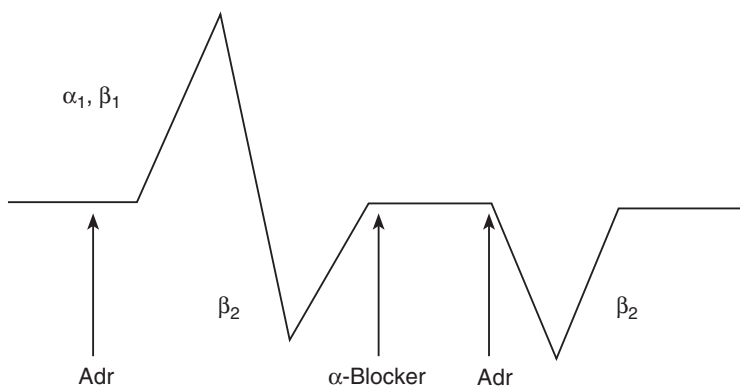


Fig. 2.21 Biphasic effect of adrenaline (Adr) on BP and Dale's vasomotor reversal.

5. **CNS:** In therapeutic doses, adrenaline does not cross BBB; hence, CNS effects are minimal. But in high doses, it may cause headache, restlessness and tremor.
6. **Eye:** Adrenaline has poor penetration through cornea when applied topically into the eye. Hence, it is administered as a prodrug (see p. 59).
7. **Metabolic effects:**
 - Adrenaline increases blood glucose level by:
 - (i) Stimulating hepatic glycogenolysis (β_2), which is the predominant effect.
 - (ii) Reducing insulin secretion through α_2 -action.
 - (iii) Decreasing uptake of glucose by peripheral tissues.
 - It increases blood lactic acid level by stimulating glycogenolysis in skeletal muscles.
8. **Other effects**
 - Adrenaline facilitates neuromuscular transmission and postpones fatigue.
 - It reduces plasma K^+ levels by promoting uptake of K^+ into cells, particularly into the skeletal muscle (β_2).

Pharmacokinetics. Adrenaline is not suitable for oral administration because of its rapid inactivation in the GI mucosa and liver. Adrenaline can be given subcutaneously. In anaphylactic shock, absorption of s.c. adrenaline is poor; hence, it is given intramuscularly. In cardiac arrest, it is given intravenously. It does not cross BBB; is rapidly metabolized by COMT and MAO, and the metabolites are excreted in urine.

Adverse Effects and Contraindications. The adverse effects of adrenaline are an extension of its pharmacological actions. They are tachycardia, palpitation, headache, restlessness, tremors and rise in BP. The serious side effects are cerebral haemorrhage and cardiac arrhythmias. In high concentration, adrenaline may cause acute pulmonary oedema due to shift of blood from systemic to pulmonary circulation. Adrenaline is contraindicated in most of the cardiovascular diseases such as hypertension, angina, cardiac arrhythmias and congestive cardiac failure (CCF). In patients on β -blockers, it may cause hypertensive crisis and cerebral haemorrhage due to unopposed action on vascular α_1 -receptors.

Therapeutic Uses of Adrenaline (ABCDE)

1. **Anaphylactic shock:** Adrenaline is the life-saving drug in anaphylactic shock. Adrenaline 0.3–0.5 mL of 1:1000 solution (1 mg/mL) is administered intramuscularly. It rapidly reverses the manifestations of severe allergic reactions. The beneficial effect of adrenaline in anaphylactic shock is shown below. Adrenaline produces the following effects:
 - β_1 -mediated cardiac stimulation ($\uparrow$ heart rate and $\uparrow$ force of contraction)
 +
 α_1 -mediated vasoconstriction $\longrightarrow$ $\uparrow$ peripheral resistance.
 These actions help to $\uparrow$ BP.
 - α_1 -mediated vasoconstriction $\longrightarrow$ $\downarrow$ mucosal oedema ($\downarrow$ laryngeal oedema).
 - β_2 stimulation $\longrightarrow$ bronchodilation
 $\downarrow$ release of mediators from mast cells.
 - It is physiological antagonist of histamine.
2. **Cardiac resuscitation:** In the treatment of cardiac arrest due to drowning or electrocution, adrenaline is injected intravenously in 1:10,000 (0.1 mg/mL) concentration along with other supportive measures such as external cardiac massage.

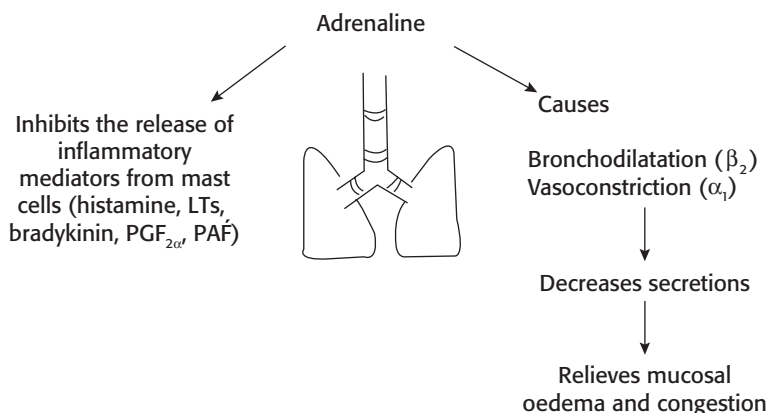


Fig. 2.22 Effects of adrenaline in bronchial asthma. LTs, leukotrienes; $\text{PGF}_{2\alpha}$, prostaglandin $\text{F}_{2\alpha}$; PAF, platelet-activating factor.

3. Prolongs the **Duration of local anaesthesia**: Adrenaline (1:100,000) with lignocaine. Adrenaline, by its vasoconstrictor effect (α_1) delays absorption of the local anaesthetic and prolongs the duration of local anaesthesia.
4. Controls **Epistaxis** and other capillary oozing: Adrenaline is used as a local haemostatic to control bleeding following tooth extraction and during surgical procedures in nose, throat, larynx, etc. because of its vasoconstrictor effect.
5. **Glaucoma**: Adrenaline has poor penetration when applied locally into the eye; hence, it is administered as a prodrug, dipivefrin (p. 59).
6. **Bronchial asthma**: Adrenaline is a powerful bronchodilator and has rapid onset but short duration of action. It is rarely used for acute asthma. Its use has declined because of its dangerous cardiac stimulant effect. The beneficial effects of adrenaline in bronchial asthma are shown in Fig. 2.22. Adrenaline 0.3–0.5 mL of 1:1000 solution is given subcutaneously. It can be given by nebulization (as inhalation).

Noradrenaline: α_1 -, α_2 - and β_1 -Agonist. Noradrenaline is a catecholamine. It is the neurotransmitter in adrenergic system. It acts on α_1 -, α_2 - and β_1 -adrenergic receptors and has negligible β_2 -action. The main action of NA is on CVS. It has a direct cardiac stimulant effect (β_1), constricts all the blood vessels (α_1) including those of skin, mucous membrane, renal, mesenteric, pulmonary, skeletal muscle, etc. The systolic, diastolic and pulse pressure are increased. There is reflex bradycardia. Noradrenaline, like adrenaline, is not effective orally. It is not suitable for s.c., i.m. or direct i.v. injection because of necrosis and sloughing of the tissues at the site of injection. It is administered by i.v. infusion. It can be used to raise BP in hypotensive states but it may decrease blood flow to vital organs by causing widespread vasoconstriction.

Isoprenaline (Isoproterenol): β_1 - β_2 and β_3 -Agonist. It is a synthetic, nonselective β -receptor agonist with a catechol nucleus. It has potent β -actions but no action at α -receptors. Isoprenaline is a powerful cardiac stimulant. It has positive inotropic, chronotropic and dromotropic effects. It dilates renal, mesenteric and skeletal muscle blood vessels. Systolic BP is minimally changed but the diastolic and mean arterial pressure are reduced. It relaxes bronchial and GI smooth muscles. Isoprenaline is not effective orally because of extensive first-pass metabolism. It can be given parenterally or as an aerosol. It is metabolized by COMT. Isoprenaline is used to increase the heart

rate in heart block. Side effects are tachycardia, palpitation, cardiac arrhythmias, etc. due to its powerful cardiac stimulant effect.

Dobutamine: Relatively Selective β_1 -Agonist. Dobutamine, a synthetic catecholamine, structurally resembles DA. It acts on β_1 -, β_2 - and α_1 -receptors. It does not act on dopaminergic (D_1 and D_2) receptors. It is a potent inotropic agent but causes only slight increase in heart rate. Total peripheral resistance is not significantly affected. This is because vasoconstriction (α_1 -mediated) is balanced by vasodilatation (β_2 -mediated). It is administered by i.v. infusion in patients with acute heart failure. The side effects are tachycardia (at high doses), rise in BP and tolerance, which can be avoided by intermittent therapy.

Salbutamol, Terbutaline, Salmeterol, Formoterol: Selective β_2 -Adrenergic Agonists. Selective β_2 -agonists are the main drugs used in bronchial asthma, e.g. salbutamol, levalbuterol, pirbuterol, terbutaline, salmeterol and formoterol. Nonselective β -agonist like adrenaline is rarely used because of its cardiac side effects.

Pharmacological Actions. Pharmacological actions of selective β_2 -agonists are depicted in Fig. 2.23. They cause bronchodilatation, relaxation of pregnant uterus, dilatation of blood vessels supplying the skeletal muscle, promote hepatic glycogenolysis and uptake of K^+ into cells.

Therapeutic Uses

- 1. Bronchial asthma:** Selective β_2 -agonists are usually administered by aerosol. They produce prompt bronchodilatation (salbutamol, terbutaline and formoterol) with minimal systemic side effects.
- 2. Premature labour:** On oral or parenteral administration, salbutamol and terbutaline relax pregnant uterus by interacting with β_2 -receptors, hence are used to delay premature labour.
- 3. Hyperkalaemia:** Selective β_2 -agonists are useful in hyperkalaemia as they promote uptake of K^+ into cells, especially into skeletal muscles.

Isoxsuprine. It relaxes smooth muscles of uterus and blood vessel by acting on β_2 -receptors. It can be used in dysmenorrhoea, threatened abortion and to delay premature labour. It is available for oral, i.m. and i.v. administration.

Ritodrine: Selective β_2 -Agonist with Main Action on Uterus. Ritodrine is a β_2 -agonist with selective action on uterus. It is used as a uterine relaxant to suppress premature labour.

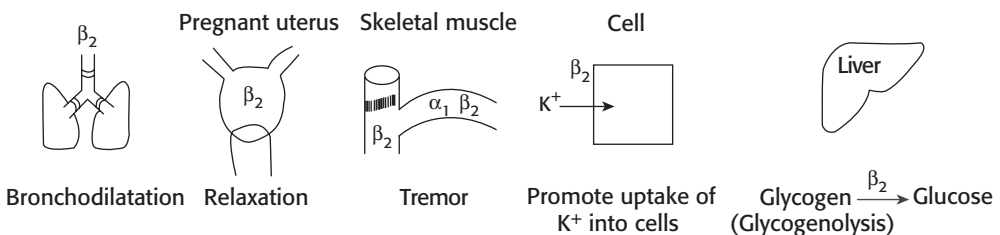
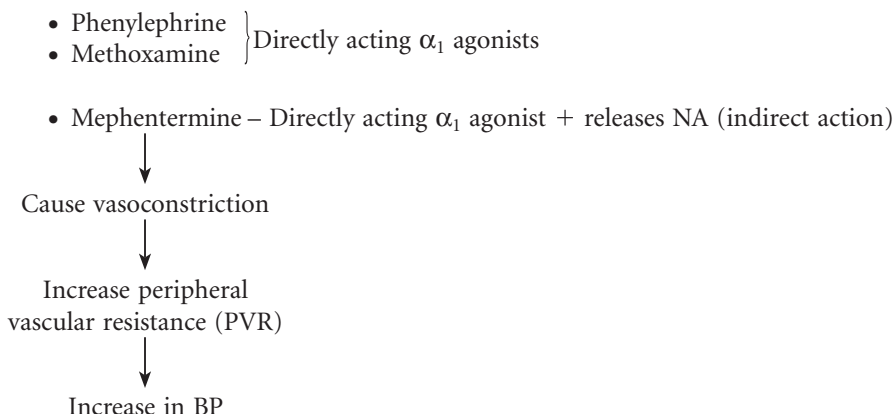


Fig. 2.23 Pharmacological actions of selective β_2 -adrenergic agonists.

Adverse Effects of Selective β_2 -Agonists

1. *Tremor* is due to stimulation of β_2 -receptors of skeletal muscle. Tolerance develops to this effect on continued administration.
2. *Tachycardia* and palpitation are due to stimulation of β_1 -receptors of heart (β_2 -selectivity is not absolute – may cause cardiac side effects).
3. *Hyperglycaemia* may occur in diabetes patients following parenteral administration of β_2 -agonists.
4. *Hypokalaemia* is due to shift of K^+ into cells.

Phenylephrine, Methoxamine, Mephentermine: Selective α_1 -Adrenergic Agonists

Like ephedrine, mephentermine also has cardiac stimulant effect. They are used parenterally to raise the BP in hypotensive states. Phenylephrine is also used topically as a mydriatic and as a nasal decongestant.

Nasal Decongestants. The commonly used α -agonists as nasal decongestants are naphazoline, oxymetazoline and xylometazoline (topical); pseudoephedrine (oral) and phenylephrine (oral and topical). They are used in allergic rhinitis, common cold, sinusitis, etc. These drugs stimulate α -receptors and cause vasoconstriction in the nasal mucous membrane, thus relieve nasal congestion. On prolonged use, they cause rebound congestion (after congestion). Atrophic rhinitis, anosmia and local irritation are the other adverse effects seen with topical decongestants. If systemically absorbed, these drugs may aggravate hypertension.

Pseudoephedrine and phenylephrine are the commonly used oral preparations. These drugs cause less rebound phenomenon, but systemic side effects like hypertension and CNS stimulation are common. They should not be combined with MAO inhibitors because of risk of hypertensive crisis, which could be fatal. Phenylpropanolamine was used as a nasal decongestant. It has been banned because of increased incidence of stroke.

Selective α_2 -Adrenergic Agonists. They include clonidine, α -methyldopa (see p. 106–107) and tizanidine (see p. 70, [Table 2.7](#)).

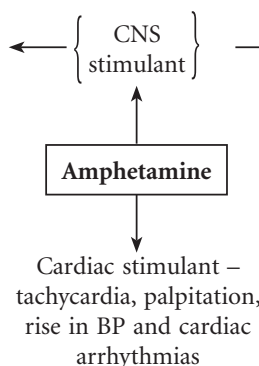
Apraclonidine and brimonidine, selective α_2 -agonists, are used topically in glaucoma (see p. 59).

Indirect-Acting Sympathomimetic Agents

Amphetamine. Amphetamine is an indirectly acting sympathomimetic agent and has a potent CNS stimulant effect. It occurs in two isomers. The *d*-isomer has more potent CNS effects and *l*-isomer on CVS.

Pharmacological Actions

In therapeutic doses – insomnia alertness, euphoria, increased motor and physical activity, tremor, restlessness, confusion, headache, etc.



- On chronic use – fatigue, depression, and impairs performance
- Suppresses appetite, (tolerance develops on chronic use)

Adverse Effects. Adverse effects are due to the extension of its pharmacological actions. They are restlessness, insomnia, confusion, fatigue, tremor, hallucinations and suicidal tendencies. The cardiac side effects are tachycardia, palpitation, hypertension, angina and cardiac arrhythmias.

Treatment of Acute Intoxication

1. Acidification of urine with ascorbic acid (vitamin C) promotes the excretion of amphetamine, which is a basic drug.
2. Sedatives are effective to control CNS symptoms and sodium nitroprusside for hypertension.

Uses

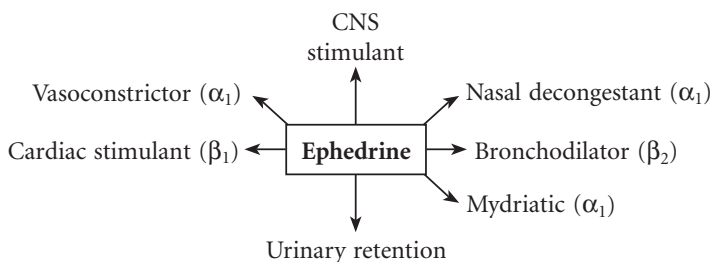
1. **Narcolepsy:** It is a sleep disorder characterized by recurrent episodes of uncontrollable desire for sleep. Amphetamine improves narcolepsy by its CNS stimulant effect.
2. **As an anorexiant:** Amphetamine-like drugs reduce body weight by suppressing hypothalamic feeding centre. Tolerance to this effect develops rapidly.
3. **Attention-deficit hyperactivity disorder:** Amphetamine acts paradoxically and controls the activity in children with hyperactivity disorder. The main adverse effects are loss of appetite and insomnia. **Methylphenidate, dextroamphetamine** and **atomoxetine** (selective noradrenaline reuptake inhibitor) are also useful in this disorder.

Modafinil. It is a CNS stimulant – useful in narcolepsy. Side effects and risk of dependence is lower than amphetamine.

Mixed Acting Sympathomimetic Agents

Ephedrine: α - and β -Agonist with NA Release. Ephedrine is a mixed acting adrenergic agonist. It is an alkaloid, acts on α_1 -, α_2 -, β_1 -, β_2 -receptors and releases NA from sympathetic nerve endings.

Pharmacological Actions



Uses. Intravenous ephedrine is the drug of choice to treat hypotension due to spinal anaesthesia as it increases peripheral vascular resistance (PVR), heart rate, cardiac output and thus BP. It was used in heart block, narcolepsy and bronchial asthma. Now, it has been replaced by more selective drugs. The side effects are insomnia, hypertension, tachycardia, palpitation, difficulty in urination; tachyphylaxis occurs on repeated administration.

Dopamine: α_1 -, α_2 -, β_1 -, and D_1 -Agonist with NA Release. DA is a catecholamine and the immediate metabolic precursor of NA. It acts on dopaminergic D_1 receptors as well as β_1 - and α_1 -adrenergic receptors. DA, like adrenaline and noradrenaline, is not effective orally. As DA is rapidly inactivated by COMT and MAO, it is administered by i.v. infusion.

Pharmacological Actions. At low doses (<2 mcg/kg/min), it selectively dilates renal, mesenteric and coronary blood vessels by acting on D_1 receptors resulting in an increase in GFR and urine output.

At moderate doses (2–5 mcg/kg/min), DA stimulates β_1 -receptors of heart, increases myocardial contractility and cardiac output, but tachycardia is less prominent. It also stimulates dopaminergic receptors resulting in increase in GFR.

At high doses (>10 mcg/kg/min), it stimulates vascular α_1 -adrenergic receptors and causes generalized vasoconstriction. This increases afterload and reduces blood flow to renal, mesenteric and other vital organs. So, the beneficial effect seen with low-to-moderate dose of DA is lost at higher doses.

Precautions and Adverse Effects. During DA infusion, the dose, BP, heart rate, ECG and urine output should be carefully monitored. The adverse effects seen are mainly due to sympathetic stimulation. They are nausea, vomiting, headache, hypertension, tachycardia, cardiac arrhythmias and angina.

Therapeutic Uses

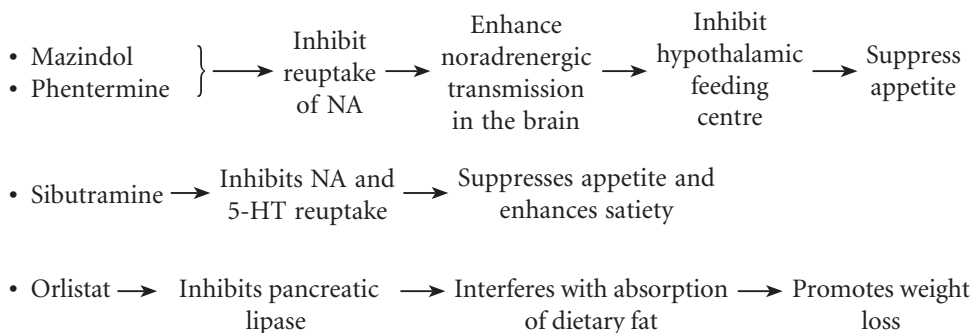
- 1. Cardiogenic and septic shock:** DA can be used because it increases BP as well as selectively dilates renal, mesenteric, coronary blood vessels and improves blood flow to vital organs.
- 2. Severe heart failure with renal impairment:** DA improves both cardiac and renal function.

Fenoldopam. D_1 agonist: It is administered as i.v. infusion in hypertensive emergencies.

Fenoldopam $\rightarrow D_1$ agonist $\rightarrow$ Peripheral vasodilatation $\rightarrow \downarrow$ BP

Its side effects are headache, flushing, reflex tachycardia and rise in intraocular tension.

Anorectics (Anorexiant). Amphetamine-like drugs promote weight loss by acting on hypothalamic feeding centre.



Sibutramine has been banned due to its adverse effects.

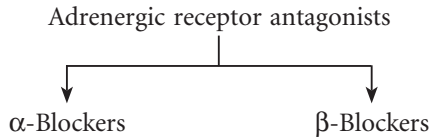
Other **antiobesity agents**

Leptin and rimonabant were used as anorectics. The main adverse effects of these agents are addiction liability, rise in BP, palpitation, sleep disturbances, depression and dry mouth.

Adrenergic Receptor Blockers

PH1.13

Adrenergic receptor antagonists block the effects of sympathetic stimulation and adrenergic agonists mediated through α - and β -receptors.

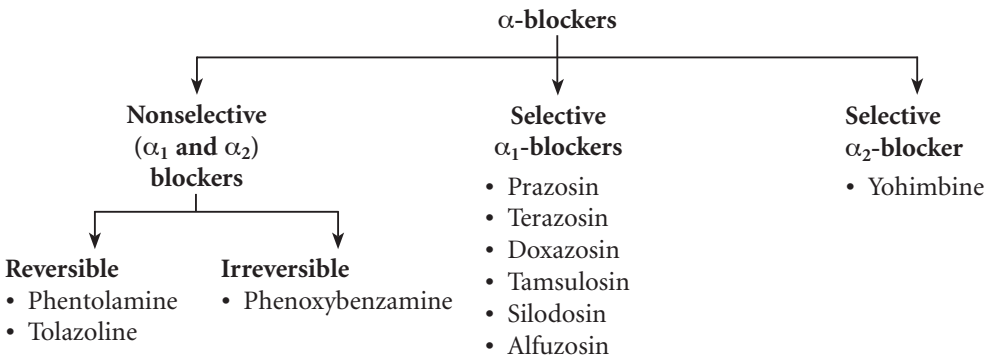


α -Adrenergic Blockers

Pharmacological Effects of α -Blockers (Fig. 2.24)

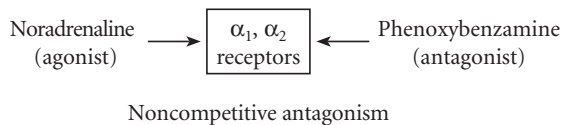
They block α -receptors, thus inhibiting the α -receptor-mediated responses of sympathetic stimulation and adrenergic agonists.

Classification



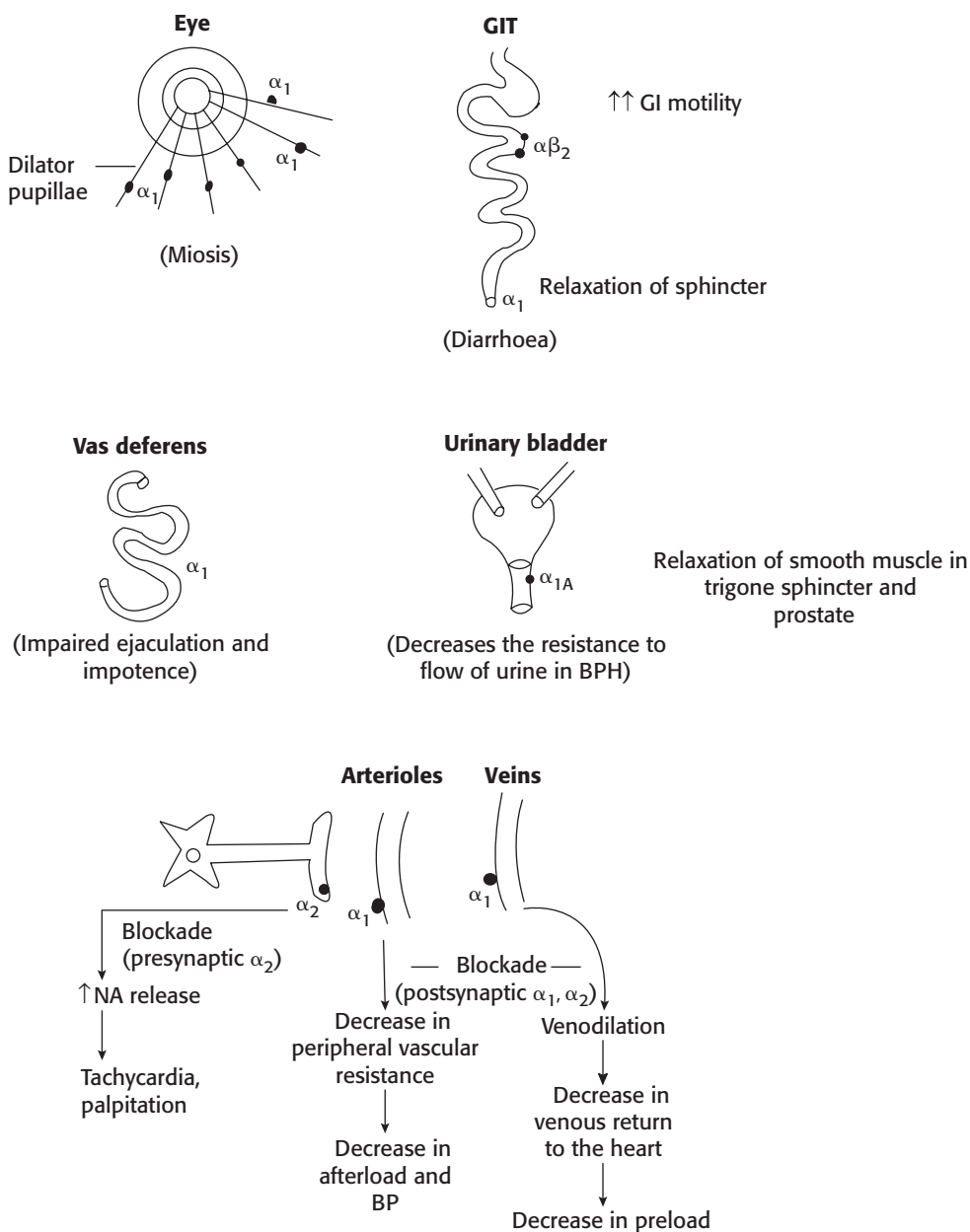
Irreversible Nonselective α -Blocker

Phenoxybenzamine. Phenoxybenzamine is a nonselective α -adrenergic blocker that blocks both α_1 - and α_2 -receptors. It binds covalently to α -receptors and causes irreversible blockade. It also inhibits the reuptake of NA into the adrenergic nerve endings. It also blocks histamine (H_1), cholinergic and serotonin receptors at higher doses.



Pharmacological Effects

1. PVR is reduced due to blockade of vascular α_1 -receptors; has predominant venodilating effect.



Other effects: Blockade of α receptors in nasal blood vessels results in nasal stuffiness.

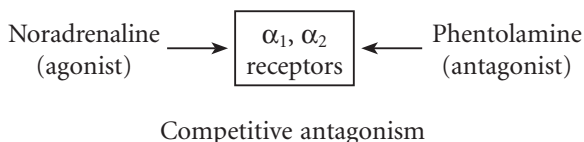
Fig. 2.24 Effect of α -blockade at various sites. GIT, gastrointestinal tract; BPH, benign prostatic hyperplasia; NA, noradrenaline.

2. Increased release of NA from the adrenergic nerve endings due to blockade of presynaptic α_2 -receptors. This may cause cardiac stimulation and produce tachycardia, palpitation, cardiac arrhythmias, etc. Other effects shown in Fig. 2.24.

Phenoxybenzamine is given orally or through slow i.v. infusion. It has a slow onset but long duration of action because of irreversible blockade of α -receptors. Its main use is in the treatment of pheochromocytoma. The side effects are postural hypotension (mainly due to venodilatation), tachycardia, palpitation, diarrhoea, nasal stuffiness, giddiness and impotence.

Reversible Nonselective α -Blockers

Phentolamine. Phentolamine is an imidazoline derivative. It competitively blocks the effects of NA at both α_1 - and α_2 -adrenergic receptors (competitive antagonism). Venodilatation is more than arteriolar dilation. It can also block 5-hydroxytryptamine (5-HT) receptors, K^+ channels; causes histamine release from mast cells.



Phentolamine is given intravenously and has a rapid onset but short duration of action.

Adverse Effects. They include tachycardia, palpitation, arrhythmias; angina and MI may be precipitated.

Tolazoline. Tolazoline is similar to phentolamine and is rarely used.

Other competitive, nonselective α -blockers are ergot alkaloids (ergotamine, ergotamine) and hydrogenated ergot alkaloids (dihydroergotamine).

Selective α_1 -Blockers

Prazosin is a potent and selective α_1 -adrenergic receptor blocker. It is given orally. It is well absorbed from GI tract but undergoes extensive first-pass metabolism. The effects of α -blockade are depicted in Fig. 2.24. Unlike nonselective α -blockers, selective α_1 -blockers produce minimal or no tachycardia (as presynaptic α_2 -receptors are not blocked). It causes both arteriolar and venodilatation; arteriolar dilatation is more prominent.

Adverse Effects. First-dose phenomenon (mechanism): Within 30–90 minutes of oral administration of first dose of prazosin, postural hypotension and syncopal attacks may be seen. Therefore, the initial dose should be small (1 mg). It is usually given at bed time so that the patient remains in bed for several hours and the risk of syncopal attack is reduced.

It may cause nasal stuffiness, tachycardia, impaired ejaculation and impotence.

Other Selective α_1 -Blockers

- *Terazosin* is similar to prazosin, but less potent than prazosin. It is almost completely absorbed after oral administration and has a longer duration of action.
- *Doxazosin* is the longest acting selective α_1 -blocker. The haemodynamic effects, bioavailability and extent of metabolism are similar to prazosin.
- *Alfuzosin* blocks all subtypes of α_1 -receptors (α_{1A} , α_{1B} and α_{1D}). It is orally effective and used in benign prostatic hyperplasia (BPH).
- *Tamsulosin* is an uroselective α_1 -blocker (α_{1A}). At low doses, it reduces the resistance to flow of urine with little effect on BP. It is administered orally and is the preferred α_1 -blocker for treatment of BPH in normotensive patients. It may cause retrograde ejaculation.
- *Silodosin* is a selective α_{1A} -blocker; useful orally in BPH. The adverse effects are postural hypotension and retrograde ejaculation.

Therapeutic Uses of α -Blockers

1. **Pheochromocytoma:** It is a tumour of adrenal medulla, which releases large amounts of adrenaline and NA. The signs and symptoms include a sudden and paroxysmal rise in BP with headache, palpitation and excessive sweating. The

diagnosis of pheochromocytoma is usually made by estimating catecholamines, VMA and other metabolites in blood and urine (normal VMA: 4–8 mg per 24 hours urine sample), CT and MRI scan.

The definitive treatment for pheochromocytoma is surgery. In the preoperative period, phenoxybenzamine is used to control hypertension and restore blood volume. It is a nonselective and irreversible α -blocker. Blockade of vascular α_1 -receptors causes vasodilatation and fall in BP. It can also be used in inoperable cases of pheochromocytoma.

β -Blockers (propranolol) are used to control the cardiac manifestations – tachycardia and arrhythmias due to excess catecholamines. β -Blockers should not be given alone in pheochromocytoma because the blockade of vascular β_2 -receptors causes unopposed α_1 -action which leads to severe rise in BP due to vasoconstriction. This may be fatal. Therefore, prior administration of α -receptor blocker is a must before giving β -blockers.

Metyrosine is used as an adjuvant in pheochromocytoma. It inhibits tyrosine hydroxylase enzyme and reduces the synthesis of catecholamines.

During surgery, handling of the tumour results in sudden release of large quantity of catecholamines, which may cause marked rise in BP that can be controlled by i.v. phentolamine. It is a nonselective α -blocker with rapid onset of action.

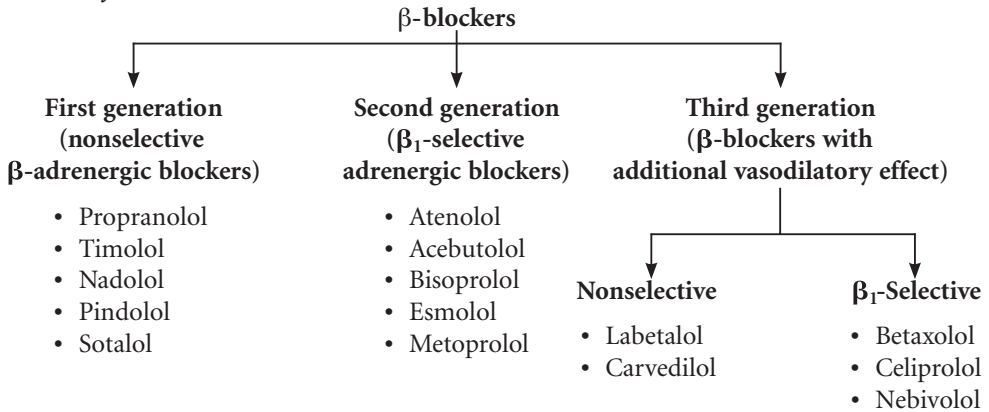
2. **Hypertensive emergencies:** Intravenous phentolamine can be used in the following conditions, because of its rapid onset of action:
 - To control hypertensive episodes intraoperatively during surgery of pheochromocytoma.
 - To control hypertensive crisis due to clonidine withdrawal.
 - To control hypertensive crisis due to 'cheese reaction'.
3. **Essential hypertension:** Among α -blockers, selective α_1 -antagonists are preferred to nonselective α -blockers in the treatment of mild-to-moderate hypertension. Selective α_1 -antagonists cause less tachycardia and have favourable effects on lipid profile.
4. **Benign prostatic hyperplasia:** Selective α_1 -blockers are used in BPH; they decrease tone of smooth muscle in the neck of bladder and prostate resulting in reduction in resistance to urinary flow. Prazosin, doxazosin, terazosin and alfuzosin are particularly useful in patients who also have hypertension. Tamsulosin is preferred for BPH in normotensive patients.
5. **Tissue necrosis:** Phentolamine is infiltrated locally to prevent tissue necrosis due to extravasation of α -agonists.
6. **Male sexual dysfunction:** Local injection of phentolamine with papaverine may be used in the treatment of male sexual dysfunction. PH1.40
7. Other uses include congestive cardiac failure and peripheral vascular diseases.

Selective α_2 -Adrenergic Blocker

Yohimbine. Yohimbine is an alkaloid. It competitively blocks α_2 -receptors. It also has 5-HT receptor blocking effect. It is an aphrodisiac, but is rarely used therapeutically.

β -Adrenergic Blockers

β -adrenergic antagonists block the β -receptor-mediated effects of sympathetic stimulation and adrenergic drugs.

Classification

Pindolol, acebutolol and labetalol have partial agonistic activity (intrinsic sympathomimetic activity [ISA]). They stimulate β -receptors partially in the absence of catecholamines.

Propranolol, pindolol, acebutolol, metoprolol and labetalol have membrane-stabilizing activity (local anaesthetic activity).

Mechanism of Action. Propranolol is the prototype drug. β -Blockers competitively block the β -receptor-mediated actions of catecholamines and other adrenergic agonists.

**Pharmacological Properties of β -Blockers****1. Cardiovascular system:**

(a) **Heart:** β -Blockers depress all cardiac properties.

- (i) Decrease heart rate (negative chronotropic effect).
- (ii) Decrease force of myocardial contractility (negative inotropic effect).
- (iii) Decrease cardiac output.
- (iv) Depress SA node and AV nodal activity.
- (v) Increase refractory period of AV node.
- (vi) Decrease conduction in atria and AV node (negative dromotropic effect).
- (vii) Decrease automaticity of ectopic foci.
- (viii) Decrease cardiac work, thus reduce O_2 requirement of the myocardium.

Only in high doses, some of them have membrane-stabilizing effect.

(b) **Blood vessels:** Blockade of β_2 -receptors of blood vessels initially may cause rise in PVR due to unopposed α_1 -action. However, continued administration of these drugs leads to a fall in PVR in patients with hypertension due to chronic reduction in cardiac output. Both systolic and diastolic BP is reduced.

(c) They also reduce the release of renin from juxtaglomerular apparatus due to blockade of β_1 -receptors and decrease central sympathetic outflow.

2. Respiratory system: Blockade of β_2 -receptors in bronchial smooth muscle can produce severe bronchospasm in patients with COPD and asthma. Therefore, β -blockers should be avoided in patients with asthma and COPD. Selective β_1 -blockers such as atenolol and metoprolol are less likely to cause bronchospasm.

3. Skeletal muscle: On chronic use, β -blockers may cause skeletal muscle weakness and tiredness due to blockade of β_2 -receptors of the skeletal muscle and blood vessels supplying it. They also reduce stress-induced tremors.

4. **Metabolic effects:** β -Blockers inhibit glycogenolysis and delay recovery from hypoglycaemia. They also mask the warning signs and symptoms of hypoglycaemia. Therefore, β -blockers should be used cautiously in diabetes patients on hypoglycaemic agents. Chronic use of nonselective β -blockers decreases high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol ratio which may increase the risk of coronary artery disease.
5. **Eye:** β -Blockers on topical administration decrease IOP by reducing the secretion of aqueous humour (see p. 58).

Pharmacokinetics. Propranolol is highly lipid soluble and is well absorbed from GI tract. However, the bioavailability of propranolol is low because of its extensive first-pass metabolism. It is highly bound to plasma proteins; has large volume of distribution; freely crosses BBB, and metabolites are excreted in urine.

Adverse Effects of β -Blockers. They are mainly an extension of pharmacological actions.

1. **CVS:**

- Bradycardia, heart block and may precipitate congestive heart failure in patients with low-cardiac reserve.
- Blockade of vascular β_2 -receptors causes unopposed α_1 -action, reduces further blood supply and may worsen peripheral vascular disease.
- β -Blockers can exacerbate Prinzmetal angina (variant angina) due to unopposed α_1 -action, hence are contraindicated (see p. 117) in this condition.

2. **Respiratory system:** Blockade of β_2 -receptors in the bronchial smooth muscle can cause severe bronchospasm in patients with asthma and COPD. Hence, β -blockers are contraindicated in the above conditions.
3. **CNS:** Sleep disturbances, hallucinations, fatigue and mental depression.
4. **Metabolic:** Recovery from hypoglycaemia (induced by antidiabetic drugs) is delayed by β -blockers. β -Blockers may mask the warning signs and symptoms of hypoglycaemia.
5. **Muscular weakness and tiredness:** These are due to reduced blood flow to skeletal muscle.
6. **Withdrawal symptoms:** Abrupt withdrawal of β -blockers after chronic use is dangerous because angina or frank myocardial infarction (MI) and even sudden death can occur. This is due to upregulation (supersensitivity) of β -receptors in response to prolonged blockade (see p. 27).

Drug Interactions

1. **Propranolol $\times$ verapamil:** They produce additive cardiac depressant effects and may cause CCF, bradyarrhythmias, heart block or even cardiac arrest.
2. **Insulin/sulphonylureas $\times$ β -blockers:** Nonselective β -blockers inhibit glycogenolysis and delay recovery from hypoglycaemia (Fig. 2.25). They mask warning signs and symptoms of hypoglycaemia.
3. **Cholestyramine and colestipol $\times$ β -blockers:** Cholestyramine and colestipol are bile acid-binding resins. They bind to β -blockers in the gut and interfere with the absorption of β -blockers.
4. **Propranolol $\times$ lignocaine:** Propranolol reduces the clearance of lignocaine by decreasing hepatic blood flow.
5. **Propranolol $\times$ NSAIDs:** NSAIDs by inhibiting PG synthesis promote Na^+ and water retention on chronic use. Thus, they decrease antihypertensive effect of β -blockers.
6. **Propranolol $\times$ chlorpromazine:** Propranolol interferes with the first-pass metabolism of chlorpromazine and increases its bioavailability.

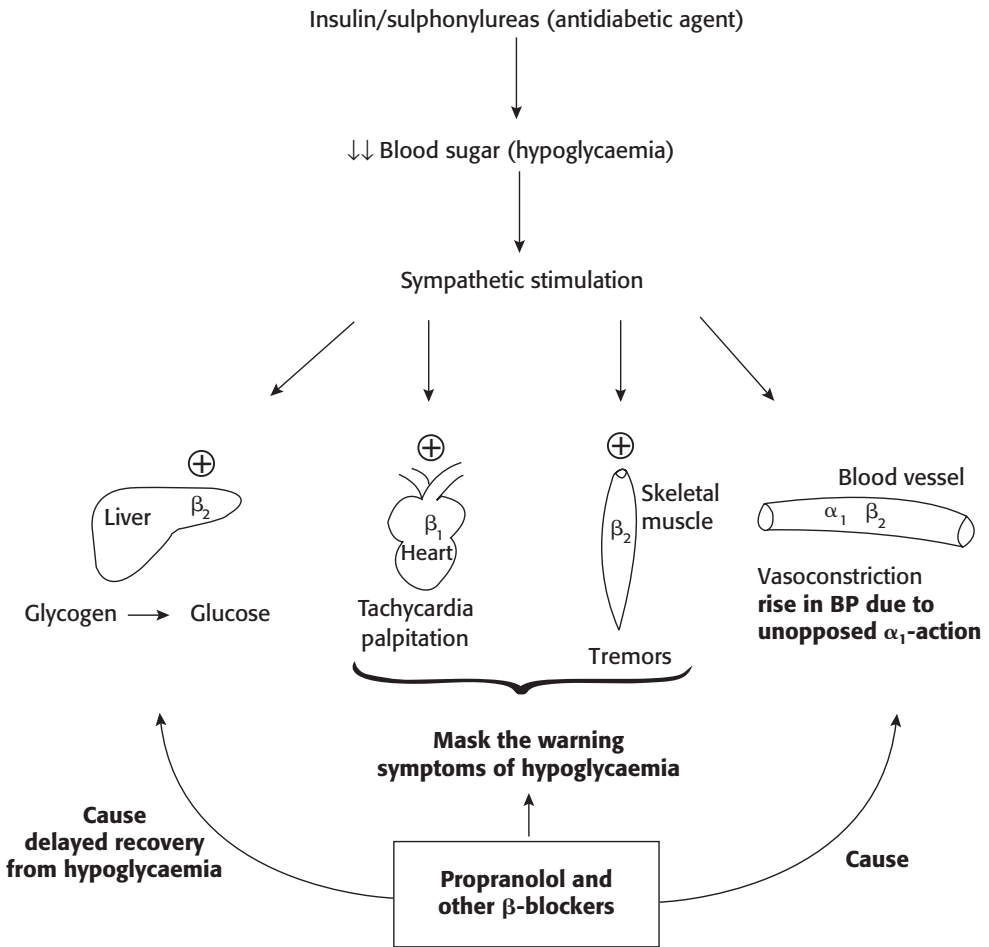


Fig. 2.25 Interaction between insulin/sulphonylureas and β -blockers.

Therapeutic Uses of β -Blockers

- Hypertension:** β -Blockers are useful for all grades of hypertension. These drugs are preferred especially in patients with angina, MI or cardiac arrhythmias (see p. 105).

The advantages of β -blockers are as follows:

- Sodium and water retention is rare.
- Cheaper.
- Have a long duration of action.
- Well tolerated.

- Angina prophylaxis and MI:** β -Blockers reduce myocardial O_2 demand by decreasing heart rate, myocardial contractility and arterial pressure. They improve exercise tolerance and reduce frequency of anginal episodes. Use of β -blockers early in acute phase of MI may limit infarct size. Long-term use of β -blockers may reduce mortality and reinfarction.
- Cardiac arrhythmias:** β -Blockers are mainly used in atrial arrhythmias such as atrial fibrillation, atrial flutter and paroxysmal supraventricular tachycardia (PSVT) but rarely for ventricular arrhythmias (see p. 135).

4. **Congestive cardiac failure** (see p. 125): Chronic use of β -blockers such as carvedilol, metoprolol and bisoprolol has shown to reduce mortality rate in chronic heart failure.
5. **Pheochromocytoma**: β -Blockers are used to control the cardiac manifestations of pheochromocytoma, but should not be given alone (see p. 90-91).
6. **Glaucoma** (p. 58): β -Blockers decrease the IOP by reducing the production of aqueous humour. Timolol, carteolol, levobunolol, betaxolol, etc. are used topically in glaucoma. Timolol is the most frequently used β -blocker in glaucoma. Betaxolol is a selective β_1 -blocker; hence, systemic adverse effects (cardiovascular and pulmonary) are rare.
7. **Prophylaxis of migraine**: Propranolol and metoprolol are effective in reducing the frequency of migraine headache. The mechanism is not known.
8. **Hyperthyroidism**: The signs and symptoms of hyperthyroidism such as tachycardia, palpitation, tremor and anxiety are reduced due to blockade of β -receptors. Propranolol inhibits the peripheral conversion of T_4 to T_3 . It is also used in thyroid storm.
9. **Essential tremors**: Oral propranolol may give some benefit in patients with essential tremors.
10. **Acute anxiety states**: β -Blockers are useful in controlling the symptoms of acute anxiety such as palpitation, tachycardia, tremor and sweating.
11. **Alcohol withdrawal**: Propranolol may produce some benefit in the treatment of alcohol withdrawal.
12. **Hypertrophic obstructive cardiomyopathy**: Propranolol decreases outflow resistance.
13. **Dissecting aortic aneurysm**: β -Blockers are useful in the management of dissecting aortic aneurysm – they decrease cardiac contractility and the rate of development of pressure during systole.

Important features of β -blockers are given in Table 2.12.

Selective β_1 -Adrenergic Blockers

Selective β_1 -blockers have a lower risk of bronchoconstriction, less effect on carbohydrate metabolism, lipid profile and exercise capacity.

Esmolol

- It is administered intravenously.
- It is rapidly metabolized by esterases in RBCs; $t_{1/2}$ is about 10 minutes.
- It has no membrane-stabilizing effect; no intrinsic sympathomimetic activity.
- It is a selective β_1 -blocker and has short duration of action.

Esmolol is used for rapid control of ventricular rate in supraventricular arrhythmias. It is also useful in hypertensive emergencies.

Atenolol

See Table 2.13.

β -Blockers with Additional Vasodilatory Action

Labetalol

It is a competitive blocker at β_1 -, β_2 - and α_1 -adrenergic receptors. In addition, it has partial agonistic activity (ISA) at β_2 -receptors. It is administered orally or intravenously. It undergoes extensive first-pass metabolism after oral administration; hence, its

Table 2.12 ■ **β-Blockers with important features**

β-Blocker	ISA	MSA	Lipid solubility	Route(s)	Daily dose (mg)
Propranolol	–	++	High	Oral, i.v.	20–400
Timolol	–	–	Moderate	Oral, topical (eye drops)	10–40
Nadolol	–	–	Low	Oral	20–160
Pindolol	++	+	Low	Oral	10–60
Atenolol	–	–	Low	Oral	25–200
Acebutolol	+	+	Low	Oral, i.v.	200–1000
Esmolol	–	–	Low	i.v.	0.5 mg/kg stat. 0.05–2 mg/kg/min infusion
Metoprolol	–	+	Moderate	Oral, i.v.	50–200
Bisoprolol	–	–	Low	Oral	2.5–10
Labetalol	+	+	Low	Oral, i.v.	200–1000
Carvedilol	–	++	Moderate	Oral	12.5–100
Celiprolol	+	–	Low	Oral	200–500
Betaxolol	–	+	Moderate	Oral	10–40
Nebivolol	–	–	Low	Oral	2.5–5

Note: Both atenolol and metoprolol have preparation of active enantiomer S (–); require half the dose of their racemate.

ISA, intrinsic sympathomimetic activity; MSA, membrane-stabilizing activity; –, no activity; +, some activity; ++, moderate activity.

Table 2.13 ■ **Differences between propranolol and atenolol**

Propranolol	Atenolol
It is a nonselective β-blocker	It is a selective β ₁ -blocker
In large doses, it has membrane-stabilizing effect (local anaesthetic)	It has no membrane-stabilizing effect
It is highly lipid soluble, freely crosses BBB and produces central side effects (sleep disturbances, depression)	It is poorly lipid soluble, hence central side effects are rare
It has shorter duration of action, but propranolol SR formulation has a duration of 24 hours	It has longer duration of action, given once daily
It is less potent	It is more potent
Effective in suppressing essential tremors	Ineffective in essential tremors

bioavailability is poor. Oral labetalol is useful in the treatment of essential hypertension and i.v. labetalol for hypertensive emergencies. It is safe for use during pregnancy. The important side effects are postural hypotension and hepatotoxicity.

Carvedilol

Like labetalol, it also blocks β_1 -, β_2 - and α_1 -adrenergic receptors. In addition, carvedilol has antioxidant, antiproliferative, membrane-stabilizing and vasodilatory properties; has no intrinsic sympathomimetic activity. It has cardioprotective effect; hence, long-term use reduces mortality in patients with CHF.

Celiprolol

It is a third-generation selective β_1 -blocker and has weak vasodilating (due to nitric oxide release) and bronchodilating effects (β_2 -agonism); has no membrane-stabilizing effect. It is effective in the treatment of hypertension and angina.

Nebivolol

- Third-generation selective β_1 -blocker.
- Has (NO-mediated) vasodilating activity.
- No membrane-stabilizing effect.
- No intrinsic sympathomimetic activity.
- No unfavourable effect on lipid profile.
- It is used for control of hypertension and congestive cardiac failure.

Beta-blockers with intrinsic sympathomimetic activity (e.g. pindolol, acebutolol)

They are less likely to cause withdrawal symptoms, bradycardia and alteration of lipid profile.

Drugs Affecting Cardiovascular Function

Antihypertensive Drugs

PH1.26, PH1.27

Hypertension is a common cardiovascular disease affecting worldwide population. A persistent and sustained high blood pressure has damaging effects on the heart, brain, kidneys and eyes. Hypertension could be:

1. **Primary or essential hypertension:** It is the most common type. There is no specific underlying cause.
2. **Secondary hypertension:** It can be due to renal, vascular, endocrine disorders, etc.

BLOOD PRESSURE

Various guidelines for hypertension are available (JNC 8 – 2014, American College of Cardiology [ACC] and American Heart Association [AHA] Guidelines, 2017). A systolic blood pressure of <120 mm Hg and diastolic pressure <80 mm Hg is considered as normal BP. The risk of cardiovascular disease (CVD) increases with increase in blood pressure. This risk is taken into consideration while determining the target BP to be achieved following initiation of treatment with antihypertensive drugs.

- **Systolic blood pressure (SBP):** It is the maximum pressure recorded during ventricular systole.
- **Diastolic blood pressure (DBP):** It is the minimum pressure recorded during ventricular diastole.
- **Pulse pressure (PP):** It is the difference between SBP and DBP ($PP = SBP - DBP$).
- **Mean arterial pressure:** $DBP + 1/3 PP$.

CLASSIFICATION OF ANTIHYPERTENSIVE DRUGS (Fig. 3.1)

1. **Angiotensin converting enzyme (ACE) inhibitors:** Captopril, enalapril, lisinopril, perindopril, ramipril, benazepril, fosinopril.
2. **Angiotensin receptor blockers (ARBs):** Losartan, candesartan, irbesartan, valsartan, telmisartan, olmesartan, eprosartan.
3. **Direct renin inhibitor:** Aliskiren.
4. **Calcium channel blockers (CCBs):** Diltiazem, verapamil, nifedipine, amlodipine, cilnidipine, nicardipine, benidipine, isradipine, felodipine, lacidipine, lercanidipine.
5. **Diuretics**
 - (a) **Thiazides and related agents:** Hydrochlorothiazide, chlorthalidone, indapamide.
 - (b) **Loop diuretics:** Furosemide, bumetanide, torsemide.
 - (c) **Potassium-sparing diuretics:** Amiloride, triamterene, spironolactone, eplerenone.

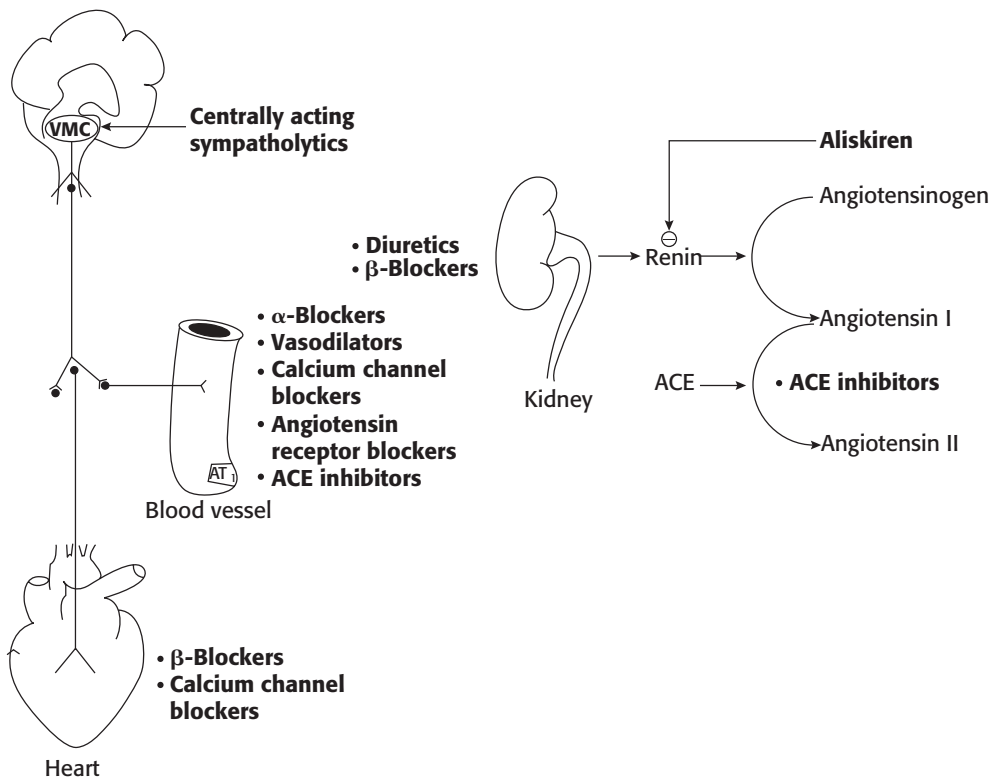


Fig. 3.1 Sites of action of major groups of antihypertensive drugs. VMC, vasomotor centre (medulla); ACE, angiotensin converting enzyme; AT₁, angiotensin receptor. (Source: Adapted from Bertram G. Katzung, Susan B. Masters., and Anthony J. Trevor, Editors: Basic and Clinical Pharmacology, 12e, McGraw Hill, 2012.)

6. Sympatholytic agents

- Centrally acting sympatholytics:** Clonidine, α -methyldopa.
- β -Adrenergic blockers:** Atenolol, metoprolol, esmolol, betaxolol, propranolol, timolol.
- β -Adrenergic blockers with additional α -blocking activity:** Labetalol, carvedilol, nebivolol.
- α -Adrenergic blockers:**
 - **Selective:** Prazosin, terazosin, doxazosin.
 - **Nonselective:** Phenoxybenzamine, phentolamine.

7. Vasodilators

- Arteriolar dilators:** Hydralazine, minoxidil, diazoxide, fenoldopam.
- Primarily venodilator:** Nitroglycerin.
- Arteriolar and venodilator:** Sodium nitroprusside.

Angiotensin Converting Enzyme Inhibitors (Fig. 3.2)

PH1.26

ACE inhibitors are frequently used as first-line antihypertensive drugs.

Mechanism of Action. ACE inhibitors

- Inhibit the generation of angiotensin II resulting in:
 - Dilatation of arterioles $\rightarrow \downarrow$ peripheral vascular resistance (PVR) $\rightarrow \downarrow$ BP.

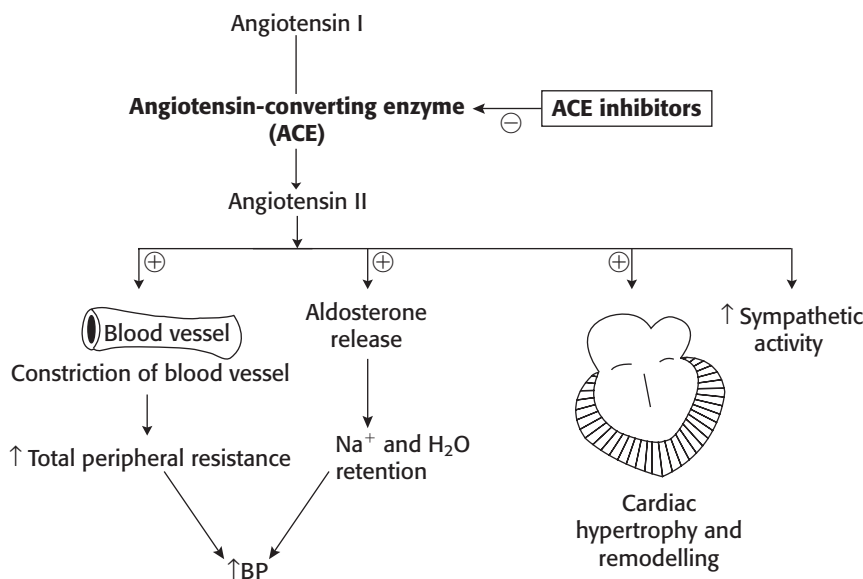


Fig. 3.2 Site of action of ACE inhibitors. Effects of angiotensin II are prevented by ACE inhibitors. (Source: Adapted from Bertram G. Katzung, Susan B. Masters., and Anthony J. Trevor, Editors: Basic and Clinical Pharmacology, 12e, McGraw Hill, 2012.)

- Decrease in aldosterone production → decrease in Na^+ and H_2O retention → ↓ BP.
- Decrease in sympathetic nervous system activity.

2. Inhibit degradation of bradykinin (potent vasodilator) by ACE.

3. Stimulate synthesis of vasodilating prostaglandins through bradykinin.

All these actions contribute to their **antihypertensive effect**. They also reverse ventricular and vascular hypertrophy

Pharmacokinetics. ACE inhibitors are usually given orally. In hypertensive emergency, enalaprilat can be given intravenously. Food reduces the absorption of captopril; hence, it should be given 1 hour before meals. ACE inhibitors poorly cross the blood–brain barrier (BBB), are metabolized in the liver and excreted in urine (Table 3.1).

Adverse Effects* and Contraindications

1. Cough (dry cough): Bradykinin is metabolized by ACE. Inhibition of ACE results in increased bradykinin levels in the lungs and causes cough. Appearance of intractable cough is an indication to stop the drug. It subsides following discontinuation of the drug.
2. Angioedema: Swelling in the nose, lips, mouth, throat, larynx and glottis. There can be airway obstruction – patient's airway should be protected. If required, adrenaline, glucocorticoids and antihistamines should be administered.
3. Proteinuria can occur rarely. The drug should be discontinued.
4. Teratogenic effect (growth retardation, foetal hypotension, renal failure and neonatal death) – hence contraindicated in pregnancy.

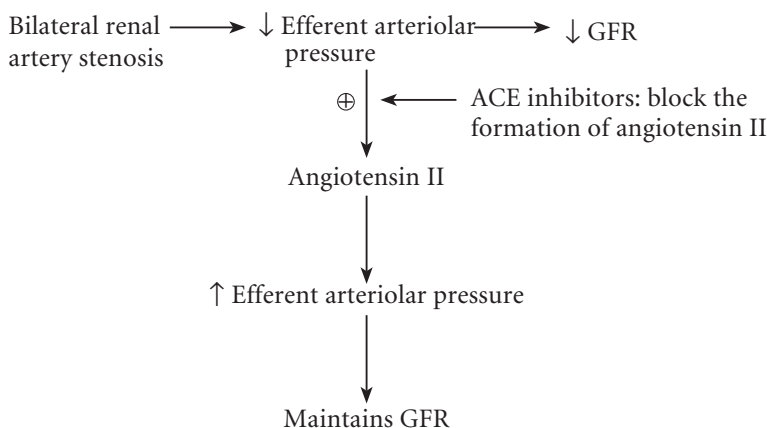
*Mnemonic for adverse effects of ACE inhibitors: 'CAPTOPRIL'.

Table 3.1 ■ Pharmacokinetic features of ACE inhibitors

Features	<i>Drug</i>								
	Captopril	Enalapril	Lisinopril	Perindopril	Ramipril	Fosinopril	Benazepril	Trandolapril	Quinapril
	Active	Prodrug	Active	Prodrug	Prodrug	Prodrug	Prodrug	Prodrug	Prodrug
Absorption	Well absorbed; food reduces absorption, hence given 1 hour before food	Rapidly absorbed but undergoes extensive first-pass metabolism; food does not reduce its absorption	Slowly and incompletely absorbed; food does not affect its absorption	Poorly absorbed; food does not affect its absorption	Rapidly absorbed	Poorly absorbed; rate of absorption is affected by food	Poorly absorbed	Moderately absorbed; food does not affect its absorption	Rapidly absorbed
Duration of action	8–12 h	24 h	>24 h	>24 h	>24 h	24 h	24 h	24 h	24 h
Route of excretion	Kidney	Kidney	Kidney	Kidney	Kidney	Kidney and bile	Kidney	Kidney and stools	Kidney and stools

5. **HypO**tension may occur following the first dose of ACE inhibitor – this can be marked in patients who are volume depleted or have congestive heart failure (CHF).
6. **NeutroP**enia is rare.
7. **Rashes**.
8. **Itching**: Discontinuation of the drug is not required.
9. **Loss of taste sensation (dysgeusia)**.
10. **Hyperkalaemia**: In patients receiving ACE inhibitors, hyperkalaemia may occur in the presence of renal insufficiency or when they are combined with potassium-sparing diuretics.

ACE inhibitors are contraindicated in patients with bilateral renal artery stenosis as acute renal failure can be precipitated. When renal perfusion pressure is low, angiotensin II maintains glomerular filtration rate (GFR) by constriction of efferent arteriole. This is blocked by ACE inhibitor.



ACE inhibitors are also contraindicated in patients with single kidney with renal artery stenosis as they can precipitate renal failure.

Drug Interactions

1. **ACE inhibitors × potassium-sparing diuretics**: Simultaneous administration of these drugs can cause dangerous hyperkalaemia.
2. **ACE inhibitors × lithium**: ACE inhibitors retard renal elimination of lithium and potentiate its toxicity.
3. **ACE inhibitors × NSAIDs**: NSAIDs by inhibiting PG synthesis promote Na^+ and water retention on chronic use. Thus, they decrease antihypertensive effect of ACE inhibitors.
4. **Thiazides × ACE inhibitors**: Diuretics increase the antihypertensive effect of ACE inhibitors by promoting the loss of Na^+ and water. Serum potassium levels are maintained by the combination.

Therapeutic Uses of ACE Inhibitors

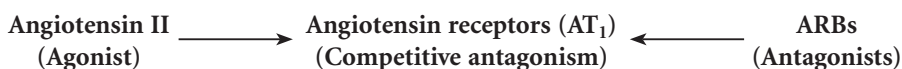
1. **Hypertension**: (Mode of action: see p. 100) ACE inhibitors are used in all grades of hypertension. They decrease cardiovascular and cerebrovascular morbidity and mortality (fatal and nonfatal myocardial infarction (MI), fatal and nonfatal stroke, CHF and sudden death). They do not cause electrolyte disturbances, hyperuricaemia, alterations in lipid levels and sexual dysfunction. They are preferred in hypertensive

patients with diabetes because they delay or prevent progression of renal complications. They are also preferred in hypertensives with coexisting CHF, left ventricular (LV) hypertrophy and peripheral vascular disease.

2. **Acute MI:** ACE inhibitors should be started within 24 hours in patients with MI. They have shown both short-term and long-term improvement in survival and decrease in reinfarction.
3. **CHF:** ACE inhibitors should be prescribed to all patients with impaired LV function (for explanation see p. 125).
4. **Diabetic nephropathy:** ACE inhibitors and angiotensin II receptor blockers (ARBs) are the preferred drugs in diabetic nephropathy in hypertensive as well as normotensive patients.
They decrease systemic blood pressure and dilate renal efferent arteriole $\rightarrow$ ↓ intraglomerular pressure; inhibit angiotensin II-mediated mesangial cell growth. They decrease microalbuminuria.
5. **Scleroderma renal crisis:** ACE inhibitors prevent the effects of angiotensin II in the renal artery; thus, they are effective in the treatment of scleroderma renal crisis. Survival rate is increased.

Angiotensin Receptor Blockers or Angiotensin Receptor Antagonists

They are losartan, irbesartan, candesartan, olmesartan, valsartan and telmisartan; administered orally. The two types of angiotensin II receptors are AT₁ and AT₂. Most of the effects of angiotensin II are mediated by AT₁ receptors. They are vasoconstriction, aldosterone secretion and the release of noradrenaline from sympathetic nerve endings. The role of AT₂ receptors is not known.



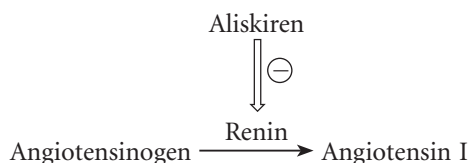
Angiotensin receptor blockers competitively inhibit the binding of angiotensin II to AT₁-receptor subtype and block its effects. Angiotensin receptor blockers produce effects similar to those of ACE inhibitors. Angiotensin receptor blockers do not affect bradykinin degradation.

Adverse Effects. Angiotensin receptor blockers are better tolerated as compared to ACE inhibitors. They cause headache, hypotension, weakness, rashes, nausea, vomiting and teratogenic effects. They may cause hyperkalaemia in patients with renal failure or in patients on K⁺-sparing diuretics. They are less likely to produce cough or angioedema than ACE inhibitors.

Uses. Angiotensin receptor blockers are used in hypertension, congestive cardiac failure (CCF), MI and diabetic nephropathy. The antihypertensive efficacy of ARBs is comparable with that of ACE inhibitors. Like ACE inhibitors, ARBs prevent/delay the development of renal complications in diabetes patients. Angiotensin receptor blockers are mainly indicated in patients who develop cough with ACE inhibitors.

In CCF and MI, ARBs are used in patients who are intolerant to ACE inhibitors.

Direct Renin Inhibitor: Aliskiren



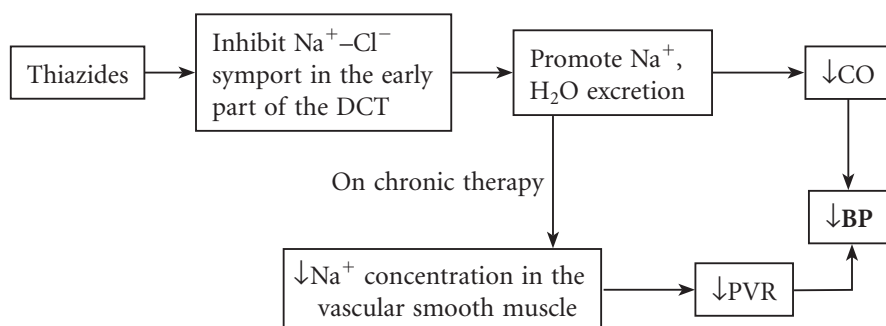
Aliskiren, by inhibiting renin, decreases levels of angiotensin I and angiotensin II. It is useful in hypertension in combination with diuretics, ACE inhibitors or ARBs (increased antihypertensive efficacy). It is administered orally. Adverse effects include diarrhoea, abdominal pain, headache and angioedema.

Diuretics

Thiazides and related drugs are widely used drugs for uncomplicated hypertension. Chlorothiazide, hydrochlorothiazide and chlorthalidone are the commonly used thiazides.

Thiazide Diuretics. These are used in uncomplicated mild to moderate hypertension and have a long duration of action. They should be administered in a low dose, i.e. 12.5 mg of chlorthalidone or hydrochlorothiazide. If the antihypertensive response is not adequate, the dose can be increased up to 25 mg/day. Beyond this dose, thiazides are not safe. Potassium-sparing diuretics are usually given with thiazides to counteract K^+ loss and increase antihypertensive efficacy. Use of ACE inhibitors with thiazides decreases K^+ loss by thiazides and enhances antihypertensive effect.

Mechanism of Action of Thiazides



Adverse Effects. They are hypokalaemia, hyperglycaemia, hyperuricaemia, hyperlipidaemia, hypercalcaemia, impotence and decreased libido.

Advantages of Thiazides

- Have long duration of action (administered once daily).
- Are cheap.
- Are well tolerated by elderly patients.
- Decrease the incidence of fracture in elderly patients by reducing urinary Ca^{2+} excretion.
- Have synergistic effect when used in combination with other antihypertensive drugs.

Chlorthalidone is a frequently used thiazide-like diuretic in hypertension as it has a long duration of action. Indapamide and metolazone are more potent, longer acting and produce fewer adverse effects than thiazides.

Loop Diuretics. These drugs have short duration of action, so a sustained Na^+ deficit is not maintained; therefore, they are not used routinely in hypertension except in the presence of renal or cardiac failure.

Calcium Channel Blockers

Verapamil, diltiazem and dihydropyridines (DHPs; nifedipine, amlodipine, cilnidipine, felodipine, nica-dipine, isradipine, etc.) are useful in all grades of hypertension.

The antihypertensive effect is mainly due to peripheral vasodilatation. DHPs are more likely to cause headache, flushing, ankle oedema, palpitation and reflex tachycardia. The use of sustained-release preparations reduces the incidence of side effects. β -Blockers can be used with nifedipine to counteract the reflex tachycardia. Reflex tachycardia is minimal or absent with verapamil and diltiazem because of their greater cardiac depressant effect. Verapamil and diltiazem should be avoided in patients with cardiac dysfunction because of their cardiac depressant effect. CCBs are particularly useful in elderly patients, in patients with angina, asthma, peripheral vascular disease, migraine, hyperlipidaemia, diabetes and renal dysfunction. They are used as monotherapy or in combination with other antihypertensives. They decrease albuminuria and also slow the progression of nephropathy in diabetes patients. Intravenous clevidipine is useful in treating severe hypertension.

Sympatholytics

β -Adrenergic Blockers. β -Blockers are effective in all grades of hypertension.

- Selective β -blockers (block only β_1), e.g. atenolol, metoprolol, esmolol and betaxolol
- Nonselective β -blockers (block both β_1 and β_2), e.g. propranolol and timolol

During initial therapy with β -blockers, cardiac output (CO) decreases but peripheral vascular resistance may increase. On chronic therapy, peripheral vascular resistance gradually decreases because of sustained reduction in CO – BP falls. Other mechanisms of antihypertensive effect are shown in Fig. 3.3. β -Blockers are mainly useful in:

- Young hypertensives with high renin levels.
- Patients with associated conditions, such as angina, post-MI, migraine and psychosomatic disorders.
- Patients receiving vasodilators to counteract reflex tachycardia.

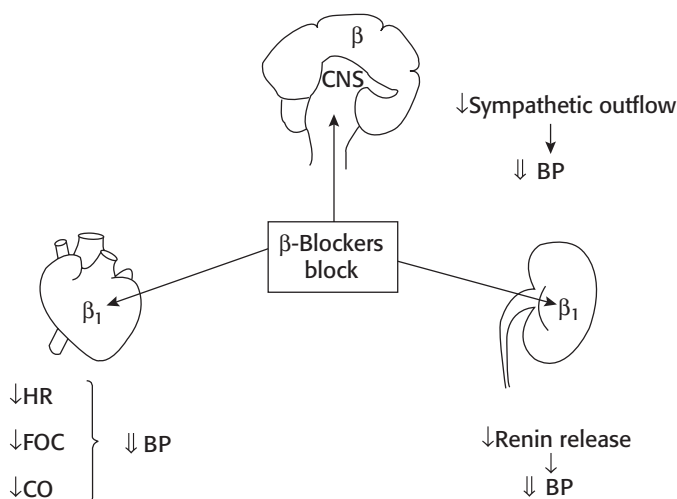


Fig. 3.3 Mechanism of antihypertensive effect of β -blockers.

β -Blockers may precipitate CCF and bronchospasm in susceptible individuals. They can cause sexual dysfunction in males and nightmares. They must be used with caution in diabetes patients receiving hypoglycaemic drugs. Sudden stoppage of β -blockers, after prolonged therapy, can produce withdrawal syndrome due to sympathetic overactivity (Table 1.6).

Centrally Acting Sympatholytics

Clonidine. Clonidine is a centrally acting antihypertensive drug.

Mechanism of Action (Fig. 3.4). Clonidine is effective orally; it is highly lipid soluble and rapidly crosses the BBB. It has a short duration of action, requires twice a day administration. Transdermal patch of clonidine controls BP for a week.

Adverse Effects. Dryness of mouth and eyes, sedation, depression, bradycardia, impotence, nausea, dizziness, parotid gland swelling and pain are the adverse effects of clonidine. Postural hypotension may occur.

Sudden stoppage of clonidine after prolonged use may cause withdrawal syndrome – headache, nervousness, tachycardia, sweating, tremors, palpitation and rebound hypertension. This is due to:

- Supersensitivity of α -receptors.
 - Precipitous release of large amount of stored catecholamines.
- This is treated with intravenous sodium nitroprusside or labetalol.

Uses. Clonidine is useful:

1. In hypertension.
2. To treat withdrawal symptoms in opioid and alcohol addicts and smoking cessation.
3. As preanaesthetic agent.
4. As antidiarrhoeal in diabetic neuropathy.
5. To reduce postmenopausal hot flushes.
6. For prophylaxis of migraine.

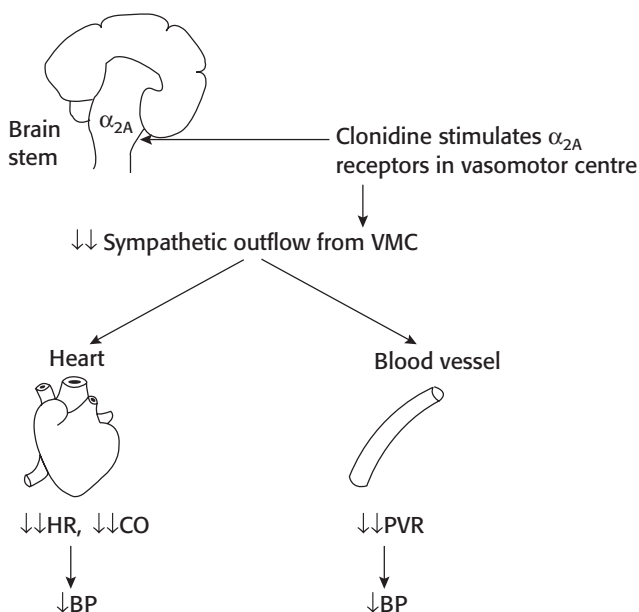
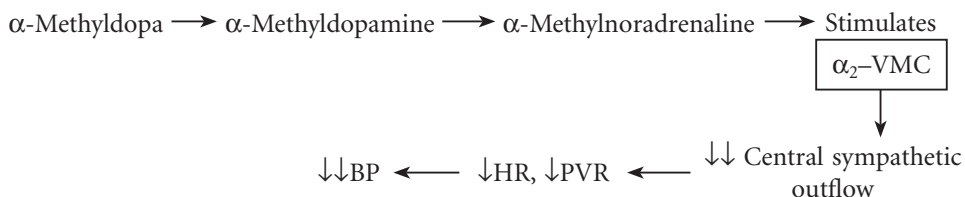


Fig. 3.4 Mechanism of action of clonidine.

α -Methyldopa. It is a centrally acting sympatholytic agent.

Mechanism of Action

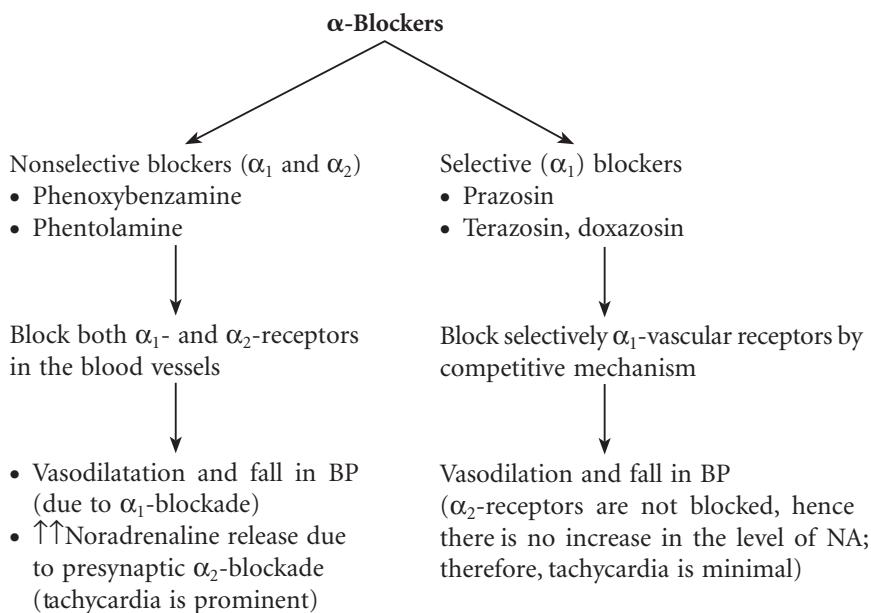


α -Methyldopa, a prodrug, which enters the adrenergic neuron, is converted into an active form and stored in the neurons. α -Methylnoradrenaline is a false transmitter that is released during nerve stimulation instead of noradrenaline. α -Methylnoradrenaline acts by stimulating α_2 -receptors in vasomotor centre.

Adverse Effects. These include nasal stuffiness, headache, sedation, mental depression, dryness of mouth, bradycardia, impotence, gynaecomastia, hepatitis and rarely haemolytic anaemia.

Clonidine and α -methyldopa are usually employed as the second- or third-line agents in hypertension because of high incidence of side effects. α -Methyldopa is one of the preferred antihypertensive drugs during pregnancy.

α -Adrenergic Blockers



Nonselective α -blockers are not preferred for essential hypertension. They are useful to treat hypertension in special conditions like pheochromocytoma, clonidine withdrawal and cheese reaction.

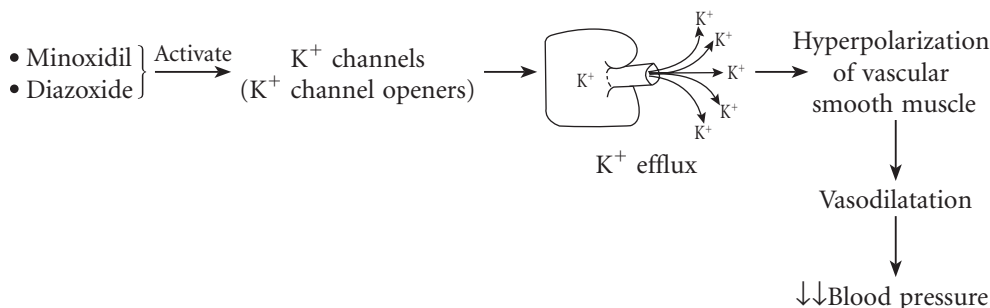
Pharmacokinetics, adverse effects and uses of α -blockers are discussed on p. 89–91.

Selective α_1 -blockers: Prazosin causes first-dose phenomenon – postural hypotension that occurs after the first dose. Therefore, the initial dose should be small (1 mg)

and usually given at bedtime so that the patient remains in bed for several hours, hence reduces the risk of fainting attacks.

Terazosin and doxazosin are longer acting than prazosin, given once daily in the treatment of hypertension.

Vasodilators

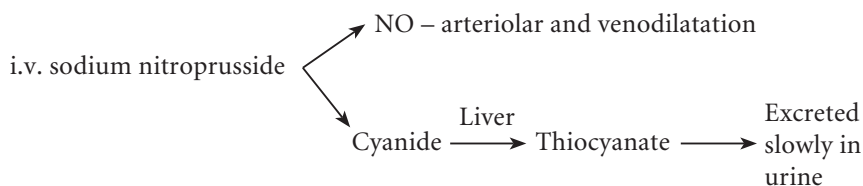


Minoxidil. It is a powerful arteriolar dilator. It is effective orally. It causes reflex tachycardia, Na^+ and water retention. Hence, minoxidil is used with a β -blocker and a diuretic. Topical minoxidil is used to promote hair growth in male type of baldness. (Minoxidil topical solution and spray are available.)

Diazoxide. It is used in the treatment of hypertensive emergencies. It is administered intravenously and has a long duration of action (6–24 hours). It also relaxes uterine smooth muscle. Adverse effects are reflex tachycardia, hyperglycaemia, sodium and water retention.

Hydralazine. It is a directly acting arteriolar dilator. It is administered orally. The side effects are reflex tachycardia, palpitation, sodium and water retention, which can be countered by combining hydralazine with a diuretic and a β -blocker. Other side effects are headache, hypotension, flushing, angina, MI, coronary steal phenomenon, etc. Immunological reactions, such as lupus syndrome, may occur.

Sodium Nitroprusside. It is a powerful arteriolar and venodilator (balanced arteriovenous dilator; Fig. 3.5). It is unstable, rapidly decomposes on exposure to light. So the solution should be prepared fresh; the infusion bottle and the entire drip set should be covered with black paper. It has a short duration of action, hence administered by i.v. infusion. It is rapid acting and dose is titrated according to response; tolerance does not develop to its action.



Sodium nitroprusside is useful for treatment of hypertensive crisis; can also be used to improve CO in severe CCF. Nitroprusside can cause severe hypotension; hence, close monitoring of BP is required. Prolonged administration may cause anorexia, nausea,

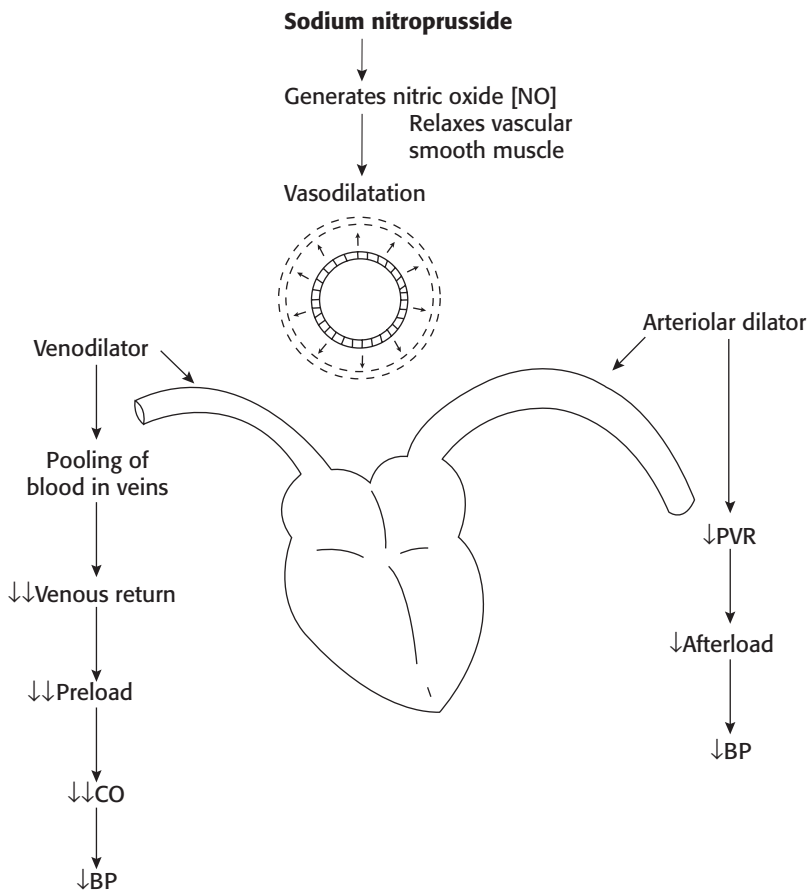


Fig. 3.5 Mechanism of action and effects of sodium nitroprusside.

vomiting, fatigue, disorientation, toxic psychosis due to accumulation of cyanide, which in turn may lead to severe lactic acidosis and convulsions.

Nitroglycerin. It is primarily a venodilator. Intravenous nitroglycerin is used in hypertension associated with acute LVF/MI. It acts rapidly but tolerance develops after prolonged infusion.

Fenoldopam

Fenoldopam (i.v. infusion) → D₁ agonist → Dilatation of peripheral arteries and natriuresis → ↓BP

Fenoldopam is used in hypertensive emergencies and postoperative hypertension. Adverse effects include headache, flushing and reflex tachycardia.

TREATMENT OF HYPERTENSION

1. Nonpharmacological approaches helpful to control hypertension are weight reduction, sodium restriction, alcohol restriction, exercise, mental relaxation, cessation of smoking and consumption of potassium-rich diet.

2. Drug treatment (Tables 3.2 and 3.3): Selection of antihypertensive drugs in individual patients depends on: (i) comorbidity, (ii) associated complications, (iii) age, (iv) sex, (v) cost of the drug and (vi) concomitant drugs.
 - Preferred drugs for initial treatment of hypertension: ACE inhibitors, ARBs, CCBs and thiazides.
 - Therapy usually started with a single agent.
 - Combination therapy is used in patients who do not respond to single drug; can be used as initial therapy in patients with high BP.

Combination therapy: ACE inhibitors/ARBs with either thiazides/CCBs/diuretic. If response is not satisfactory, antihypertensives from other classes are added. ACE inhibitors are not to be combined with ARBs. A combination of non-DHPs (verapamil/diltiazem) with β -blocker should be avoided.

Table 3.2 ■ Dosage and indications of antihypertensive drugs

Drug	Dosage	Indications
Hydrochlorothiazide	12.5–25 mg o.d. oral	Mild hypertension
Chlorthalidone	12.5–25 mg o.d. oral	Mild hypertension
Captopril	12.5–75 mg b.d. oral	Mild to severe hypertension – especially in diabetes patients
Enalapril	2.5–40 mg o.d. oral	Mild to severe hypertension – especially in diabetes patients
Lisinopril	5–40 mg o.d. oral	Mild to severe hypertension – especially in diabetes patients
Ramipril	1.25–20 mg o.d. oral	Mild to severe hypertension – especially in diabetes patients
Losartan	25–50 mg o.d. or b.d. oral	Mild to severe hypertension – especially in diabetes patients
Propranolol	10–120 mg, b.d. or q.i.d. oral	Mild to moderate hypertension
Atenolol	25–100 mg o.d. oral	Mild to moderate hypertension
Nebivolol	2.5–5 mg o.d. oral	Hypertension, congestive cardiac failure
Prazosin	1–10 mg b.d. oral	Mild to moderate hypertension
Clonidine	0.05–0.6 mg b.d.	Mild to moderate hypertension
Sodium nitroprusside	0.25–1.5 mcg/kg/minute i.v. infusion in 5% dextrose	Hypertensive emergencies (hypertensive crisis)
Nifedipine SR	30–90 mg o.d. oral	Mild to moderate hypertension
Amlodipine	2.5–10 mg o.d. oral	Mild to moderate hypertension
α -Methyldopa	250 mg–2 g/day oral	Hypertension during pregnancy

Table 3.3 ■ Commonly used drugs for hypertension associated with the following comorbid conditions

Comorbid conditions	Drugs
Angina/post-MI	β -Blockers, ACE inhibitors, ARBs
Congestive cardiac failure/left ventricular failure	ACE inhibitors, loop diuretics, ARBs
Diabetes mellitus and diabetic nephropathy	ACE inhibitors, ARBs, CCBs
Poststroke (secondary prevention)	ACE inhibitors, ARBs, thiazides
Bronchial asthma/COPD	Calcium channel blockers (CCBs)
Hypertensive emergencies	Sodium nitroprusside, labetalol, nitroglycerin
Benign prostatic hyperplasia (BPH)	Selective α_1 -blockers
Pregnancy	Nifedipine (sustained release), labetalol, α -methyldopa, hydralazine

Drugs to be Avoided in Specific Conditions

Bronchial asthma/chronic obstructive pulmonary disease (COPD)	Nonselective β -blockers
Peripheral vascular disease	Nonselective β -blockers
Diabetes mellitus	Nonselective β -blockers
Hyperlipidaemias	Thiazides and β -blockers
Gout	Thiazides
Sexually active males	α_1 -Blockers and diuretics

HYPERTENSIVE CRISIS

Hypertensive emergency is characterized by a very high blood pressure (systolic > 180 and/or diastolic > 120 mm Hg) with progressive end organ damage such as retinopathy, renal dysfunction and/or hypertensive encephalopathy. It is a medical emergency. If there is no end organ damage, it is hypertensive urgency. For hypertensive urgency, oral clonidine, labetalol or a DHP (e.g. amlodipine) is used.

In a patient with hypertensive emergency, the BP should be reduced by not more than 25% over 1 hour, then to 160/100 mm Hg over next 2–6 hours and to normal over next 48 hours.* The drugs are administered intravenously – e.g. labetalol, nicardipine, nitroglycerin, sodium nitroprusside, furosemide (hypertensive crisis with acute pulmonary oedema), clevidipine, esmolol (in patients with aortic dissection), hydralazine, fenoldopam, enalaprilat, phentolamine (hypertensive crisis in pheochromocytoma), etc. Some of the regimens are described as follows:

Nicardipine: Start i.v. infusion with 5 mg/hour, increase by 2.5 mg/hour every 5 minutes to maximum 15 mg/hour. It is rapid acting and has a short duration of action. Reflex tachycardia can occur.

Labetalol: Start with 0.4–1.0 mg/kg/hour i.v. infusion up to 3 mg/kg/hour. It is avoided in patients with COPD/bronchial asthma/heart failure.

Sodium nitroprusside: Start i.v. infusion with 0.3–0.5 mcg/kg/minute; increase by 0.5 mcg/kg/minute to maximum dose 10 mcg/kg/minute. Monitor for cyanide toxicity (see p. 109).

*Source: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).

Antianginal Drugs

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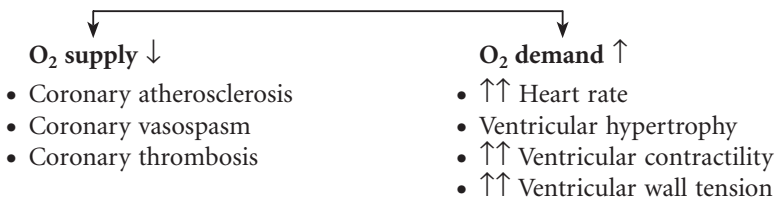
ANGINA AND MYOCARDIAL INFARCTION

Angina pectoris is a symptom of ischaemic heart disease.

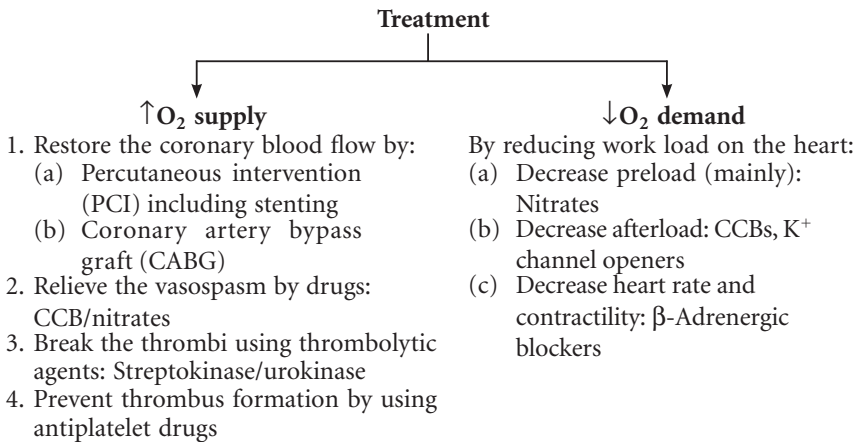
Types of angina pectoris:

1. **Stable angina (classical angina):** It is characterized by episodes of chest pain commonly associated with exertion.
2. **Unstable angina:** It is characterized by angina at rest or increased frequency and duration of anginal attacks. In most cases, it is commonly due to rupture of an atheromatous plaque and platelet deposition in the coronary artery, leading to progressive thrombosis.
3. **Prinzmetal angina (variant angina):** Angina that occurs at rest and is due to spasm of coronary arteries.

Pathophysiology. Angina occurs due to imbalance in oxygen supply and oxygen demand by the myocardium.



Treatment. Treatment is aimed at maintaining the balance between O₂ supply and demand.



Classification

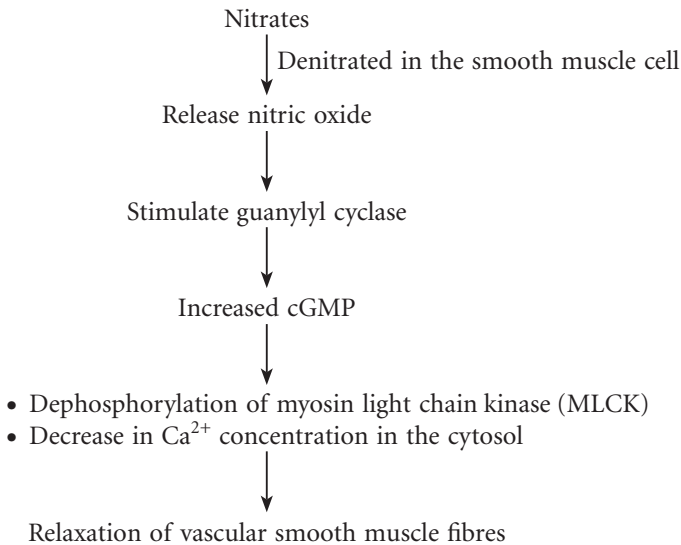
1. **Nitrates:** Nitroglycerin (glyceryl trinitrate), isosorbide dinitrate, isosorbide mononitrate, erythrityl tetranitrate, pentaerythritol tetranitrate.
2. **β-Adrenergic blockers:** Propranolol, metoprolol, atenolol, timolol, bisoprolol.
3. **CCBs:** Verapamil, diltiazem, nifedipine, felodipine, amlodipine, cilnidipine, nitrendipine, nimodipine, lacidipine, lercanidipine.
4. **Potassium channel opener:** Nicorandil.
5. **Others:*** Antiplatelet agents (low-dose aspirin, clopidogrel, prasugrel), Statins, Trimetazidine, Ranolazine, Ivabradine.

*Mnemonic: STAIR.

Organic Nitrates

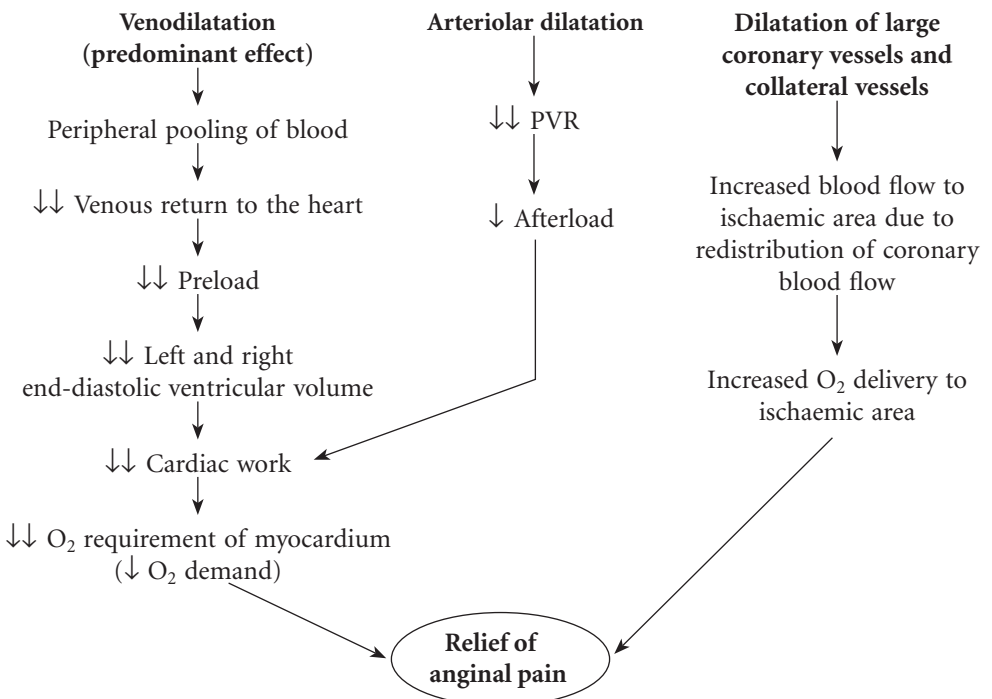
Organic nitrates are prodrugs – they release nitric oxide (NO). Nitrates are mainly venodilators, also cause arteriolar dilatation, thus reduce both preload and afterload.

Mechanism of Action



Pharmacological Actions of Nitrates. Nitroglycerin is the prototype drug. Nitrates have no direct action on the heart.

1. **On vascular smooth muscle:** Nitroglycerin quickly relieves anginal pain by decreasing the O_2 requirement and increasing O_2 delivery to the myocardium.



- 2. On other smooth muscles:** Smooth muscles of the bronchi, oesophagus, biliary tract, etc. are relaxed by nitrates.

Pharmacokinetics. Organic nitrates are readily absorbed through the buccal mucous membrane, skin and gastrointestinal (GI) tract. All nitrates except isosorbide mononitrate undergo extensive first-pass metabolism; hence, oral bioavailability of nitrates is very low. Sublingual route produces rapid onset (2–5 minutes) but short duration of action. Absorption through skin is slow; hence, transdermal route is used for a prolonged effect. The metabolites are excreted mainly in urine as glucuronide derivatives.

Adverse Effects. Adverse effects are due to extensive vasodilatation. They are headache, postural hypotension, tachycardia, palpitation, weakness, flushing and rarely syncope. To avoid these symptoms, the tablet may be spit out as soon as the pain is relieved. Overdosage may cause methaemoglobinaemia.

Tolerance. Tolerance to nitrates occurs on prolonged use of nitrates orally/as transdermal patch/i.v. infusion. Development of tolerance is rare following intermittent exposure (e.g. sublingual glyceryl trinitrate [GTN]). Tolerance is due to decreased NO generation, depletion of sulphhydryl radicals in the cell or generation of free radicals, etc. Nitrates also exhibit cross-tolerance. Tolerance can be prevented by giving a nitrate-free interval (8–12 hours) each day.

Isosorbide Dinitrate. It can be used sublingually for acute anginal attack and orally for chronic prophylaxis. Its oral bioavailability is low because of first-pass metabolism.

Isosorbide Mononitrate. It is preferred over dinitrate for chronic prophylaxis of angina, because it has:

- Longer duration of action.
- High oral bioavailability, as it does not undergo first-pass metabolism.

Therapeutic Uses of Nitrates

1. Angina

(a) For acute attack of angina:

- Nitroglycerin is the drug of choice. For an acute attack, nitroglycerin is commonly administered sublingually with an initial dose of 0.5 mg that usually relieves pain in 2–3 minutes. Patient is advised to spit out the tablet as soon as the pain is relieved to avoid side effects (hypotension and headache). If the pain is not relieved, the tablet can be repeated after 5 minutes but not more than three tablets in 15 minutes. Nitroglycerin undergoes extensive first-pass metabolism when swallowed. Nitroglycerin buccal spray can also be used for acute attack of angina.
- Isosorbide dinitrate (sublingual) can also relieve acute attack of angina.

- (b) For prophylaxis of angina:** Longer acting nitrate preparations are used – isosorbide mononitrate orally; isosorbide dinitrate orally; nitroglycerin oral sustained-release preparation/ointment/disc/patch. Transdermal nitroglycerin produces prolonged effect, up to 24 hours (Table 3.4). To avoid tolerance, the patch should be removed for a few hours (at least 8 hours). Oral nitrates are used for long-term prophylaxis of angina pectoris. They decrease the frequency of anginal attacks and improve exercise tolerance. Sublingual nitroglycerin may be used prophylactically, immediately before exercise or stress. The main disadvantage with long-term use of nitrates is development of tolerance which can be minimized by a nitrate-free interval of 8–10 hours/day.

- 2. Variant angina (Prinzmetal angina):** It is due to coronary vasospasm. Episodes of coronary vasospasm are treated with nitrates; for prophylaxis, nitrates and CCBs (amlodipine, nifedipine SR and diltiazem) are effective. Addition of a CCB

Table 3.4 ■ Nitrates used in the treatment of angina

Drug	Dosage	Duration of action
Glyceryl trinitrate (GTN; nitroglycerin)	• 0.5 mg (500 mcg) sublingual • 0.4 mg (400 mcg) lingual spray • 5–10 mg transdermal patch • 5–15 mg oral SR	• 10–30 minutes • 10–30 minutes • Up to 24 hours Transdermal patch should be removed for few hours each day to avoid the development of tolerance
Isosorbide dinitrate	• 2.5–10 mg sublingual • 5–40 mg oral	• 20–60 minutes • 6–8 hours
Isosorbide mononitrate	20–40 mg oral	6–10 hours
Erythryl tetranitrate	20–40 mg oral	4–6 hours
Pentaerythritol tetranitrate	80 mg oral	10–12 hours

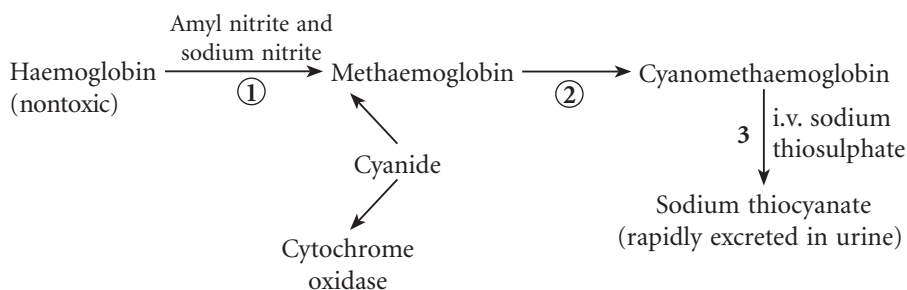
with nitrate produces better efficacy in variant angina; also reduces the incidence of MI.

3. Unstable angina: It requires treatment with multiple drugs.

- Antiplatelet agents:** Low-dose aspirin, clopidogrel or prasugrel are used. Glycoprotein IIb/IIIa receptor antagonists (tirofiban, eptifibatide or abciximab) are useful in high-risk patients with acute coronary syndromes.
- Anticoagulants:** Low-molecular-weight heparin, unfractionated heparin or fondaparinux.
- Nitrates:** Nitroglycerin (sublingual) is usually effective. Intravenous nitroglycerin is administered if pain persists or recurs. Nitrates reduce myocardial oxygen consumption and relieve coronary vasospasm (BP should be monitored during i.v. infusion of nitroglycerin).
- β -Blockers:** They (atenolol, metoprolol) are routinely administered in unstable angina unless contraindicated.
- CCBs:** Amlodipine, nifedipine SR, diltiazem or verapamil are used if symptoms persist in patients on nitrates and β -blockers or if β -blockers are contraindicated.
- Statins:** They have been shown to improve outcome in unstable angina.

- MI:** For management of acute MI, intravenous infusion of nitroglycerin is useful for persistent or recurrent ischaemic pain and treatment of LV failure. It should be avoided if there is hypotension and in patients who received sildenafil or tadalafil in the past 24 hours.
- CCF:** The role of nitrates in CCF is discussed on p. 124. Intravenous infusion of nitroglycerin is used mainly for acute heart failure. Monitoring of BP is necessary to avoid hypotension. Headache may limit the dose of nitrates.
- Hypertensive emergency:** Intravenous infusion of nitroglycerin is used because of rapid onset of action, but the disadvantage is development of tolerance.
- Biliary colic:** Sublingual nitroglycerin can be used to relieve biliary spasm and associated pain.
- Cyanide poisoning:** In cyanide poisoning, the oxygen carrying capacity of blood is not affected. Cyanide inhibits cytochrome oxidase and prevents

oxygen utilization by cells. All tissues suffer from anoxia (histotoxic type of anoxia).



Treatment of Cyanide Poisoning. The main objective of treatment is to inactivate cyanide in the cells. In the absence of nitrites, cyanide binds to cytochrome oxidase causing inhibition of oxidative phosphorylation.

Step 1. Amyl nitrite and sodium nitrite are used in the treatment of cyanide poisoning. Nitrites rapidly convert haemoglobin to methaemoglobin.

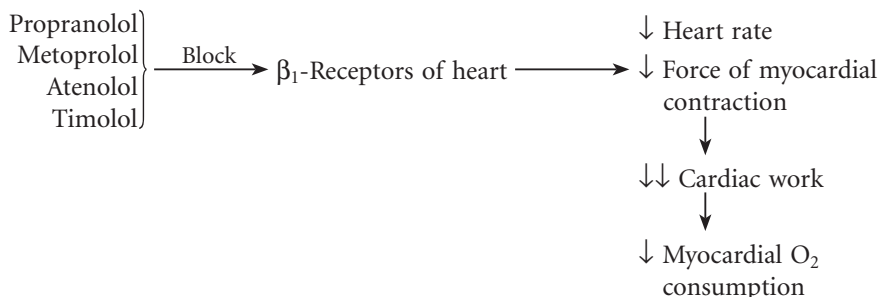
Step 2. Methaemoglobin combines with cyanide to form nontoxic cyanomethaemoglobin.

Step 3. Intravenous sodium thiosulphate converts cyanomethaemoglobin to sodium thiocyanate, which is rapidly excreted in urine.

Note. Hydroxocobalamin can be used in cyanide poisoning. It binds cyanide to form cyanocobalamin.

β-Adrenergic Blockers

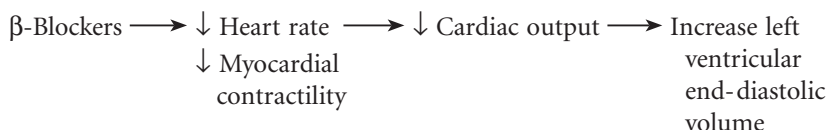
The beneficial effects of β-blockers in exertional angina are mainly due to negative chronotropic and negative inotropic effects.



β-Blockers have slow onset of action and are useful in anginal prophylaxis. β-Blockers improve exercise tolerance and reduce the frequency of anginal episodes. Use of β-blocker (those without intrinsic sympathomimetic activity) decreases mortality in patients with recent MI; hence, it should be started early and continued indefinitely. Cardiosselective β-blockers are preferred. β-Blockers with intrinsic sympathomimetic activity (e.g. pindolol) should be avoided as they may worsen angina.

Adverse Effects. They include bradycardia, heart block, bronchospasm in patients with bronchial asthma, etc.

β-Blockers can increase LV end-diastolic volume.



This disadvantage of β -blockers can be counteracted by combining them with nitrates. β -Blockers can exacerbate cardiac failure, peripheral vascular disease and may precipitate bronchospasm in patients with bronchial asthma.

β -Blockers should not be withdrawn abruptly because this may precipitate dangerous arrhythmias or MI.

β -Blockers are contraindicated in variant angina which occurs due to coronary vasospasm. Coronary artery has α_1 - and β_2 -adrenergic receptors. Blockade of β_2 -receptors results in unopposed α_1 -mediated vasoconstriction and aggravation of variant angina.

Calcium Channel Blockers

1. **Phenylalkylamine:** Verapamil.

2. **Benzothiazepine:** Diltiazem.

3. **Dihydropyridines (DHPs):** Nifedipine, amlodipine, cilnidipine, nicardipine, felodipine, isradipine, nisoldipine, lacidipine.

Mechanism of Action. Voltage-sensitive Ca^{2+} channels are of five subtypes: L, N, T, P and R. L-type is predominantly present in cardiac and smooth muscle cells.

CCBs block voltage-sensitive L-type Ca^{2+} channels by
binding to α_1 -subunit

Prevent entry of Ca^{2+} into the cell

No excitation–contraction coupling in the
heart and vascular smooth muscle

Pharmacological Actions. CCBs act mainly on cardiac and smooth muscles. They have little action on veins, hence do not alter preload.

1. **Verapamil:** It is a phenylalkylamine and has predominant action on heart.

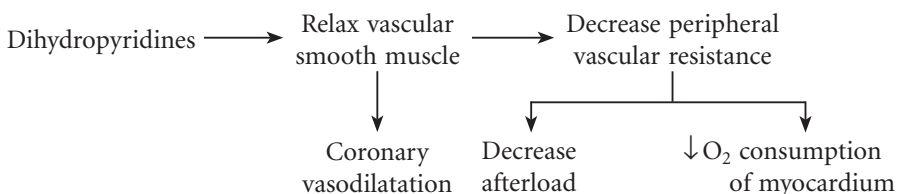
- It decreases force of contraction (negative inotropic effect) and decreases heart rate (negative chronotropic effect). This reduces oxygen requirement of the myocardium.

- It depresses SA node and slows AV conduction (negative dromotropic effect) by prolonging effective refractory period (ERP).

Verapamil is a less potent coronary and peripheral vasodilator than DHPs.

2. **Diltiazem:** It dilates peripheral and coronary arteries but its vasodilating property is less marked than DHPs and verapamil. It also causes negative inotropic, chronotropic and dromotropic effects. It is used in the treatment of angina, hypertension and supraventricular arrhythmias.

3. **DHPs:** These are potent arteriolar dilators and reduce peripheral vascular resistance. Higher doses are required for significant cardiac effects – cardiac depressant effect is less than verapamil and diltiazem.



- (a) **Nifedipine:** It is the prototype drug. It has a predominant action on vascular smooth muscle. Reflex tachycardia and palpitation are commonly seen with nifedipine. This can be minimized by using sustained-release preparation or counteracted by adding a β -blocker.
- (b) **Amlodipine:** It is absorbed slowly after oral administration. Palpitation and reflex tachycardia are less common with amlodipine. It is more potent and has a longer duration of action than nifedipine. It dilates both peripheral and coronary vessels. It has high oral bioavailability. It is mainly used in angina and hypertension. The common side effects are headache and ankle oedema. Reflex postcapillary constriction $\rightarrow$ $\uparrow$ hydrostatic pressure $\rightarrow$ ankle oedema.
S (–) Amlodipine: It is an active S (–) enantiomer of amlodipine. It is more potent and causes less adverse effects.
- (c) **Nicardipine:** Its antianginal effects are similar to nifedipine. It acts predominantly on coronary vessels.
- (d) **Felodipine:** It has greater vascular selectivity than nifedipine and amlodipine. Like nifedipine, it can also produce tachycardia and palpitation.
- (e) **Lacidipine, lercanidipine and benidipine:** They have long duration of action.
- (f) **Nimodipine:** It has high lipid solubility, freely crosses BBB and selectively dilates cerebral blood vessels. It is used to prevent cerebral vasospasm and subsequent neurological defects in patients with subarachnoid haemorrhage.
- (5) **Cilnidipine:** It blocks L-type and N-type calcium channels. Hence, reflex tachycardia and ankle oedema is less.

Pharmacokinetics. All CCBs are well absorbed through GI tract but they undergo varying degree of first-pass metabolism. All are highly bound to plasma proteins, metabolized in liver and excreted in urine.

Adverse Effects. They are mentioned in [Table 3.5](#).

Uses of CCBs

1. **Exertional angina** (for detailed explanation, see Pharmacological Actions): The beneficial effect in angina pectoris with CCBs is mainly due to a decrease in myocardial O_2 consumption (following $\downarrow$ HR, $\downarrow$ force of contraction or $\downarrow$ afterload), and dilatation of coronary arteries. Diltiazem, verapamil and DHPs (amlodipine, nifedipine SR and nicardipine) are used in stable angina. Felodipine, isradipine and nisoldipine are also effective in angina. Diltiazem and verapamil produce less reflex tachycardia. Diltiazem is preferred to verapamil, as it has fewer side effects. DHPs like nifedipine and felodipine may aggravate anginal symptoms because of reflex tachycardia, which can be counteracted by combining them with β -blockers.

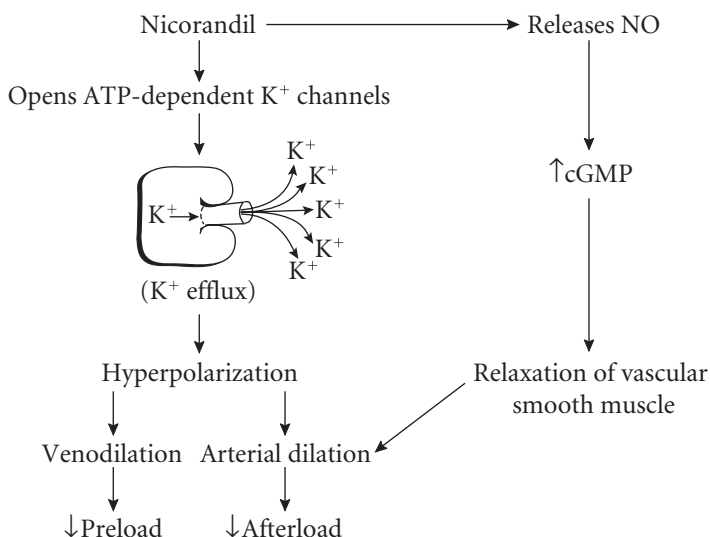
Table 3.5 ■ Adverse effects of calcium channel blockers

Nifedipine	Verapamil	Diltiazem
• Hypotension • Palpitation • Reflex tachycardia • Oedema • Flushing • Fatigue • Dizziness • Sedation	• Constipation • Sinus bradycardia • Oedema; may precipitate CCF in patients with low cardiac reserve • AV block and headache, rarely	• Headache • Hypotension • Bradycardia • Oedema • AV block occurs rarely

2. **Variant angina:** It is due to coronary spasm. Amlodipine, nifedipine SR and diltiazem can be used prophylactically. They relieve pain effectively by attenuating the coronary vasospasm. Combined use of DHPs and nitrates has shown increased efficacy in patients with variant angina.
3. **Unstable angina:** CCBs are used mainly when symptoms are not relieved by nitrates/ β -blockers or if these drugs are contraindicated.
4. **Supraventricular arrhythmias:** Verapamil is useful for supraventricular arrhythmias because of its depressant action on SA and AV nodes. It prolongs the refractory period and decreases the conduction velocity of AV node thereby reduces the ventricular rate in atrial flutter or atrial fibrillation. Diltiazem is also useful but is less effective than verapamil.
5. **Hypertension:** DHPs, diltiazem and verapamil are used in hypertension. They control blood pressure by their vasodilatory effect. They can be safely used in hypertensive patients with asthma, hyperlipidaemia and renal dysfunction.
6. **Hypertrophic cardiomyopathy:** Verapamil is the preferred CCB, as it improves diastolic function.
7. **Migraine:** Verapamil is useful for prophylaxis of migraine. Another CCB, flunarizine, is more effective than verapamil in reducing the frequency of migraine attacks.
8. **Raynaud's phenomenon:** It is a peripheral vasospastic condition. Nifedipine, amlodipine, felodipine or diltiazem are used to treat this condition.
9. Nifedipine is used as uterine relaxant in **premature labour**.
10. Nimodipine is used for prevention and treatment of **cerebral vasospasm** and subsequent neurological defects in patients with subarachnoid haemorrhage.

Potassium Channel Openers (Potassium Channel Activator)

Nicorandil is administered orally. It causes arteriolar and venodilation, and also improves coronary blood flow. Tolerance does not develop to its actions. The side effects are headache, hypotension, palpitation, flushing, nausea, vomiting, ulcers in the mouth, etc.



Other Drugs

Antiplatelet Agents. Antiplatelet agent, aspirin 162 mg or 325 mg, is administered orally in patients with suspected or definite MI; if the patient is allergic to aspirin, clopidogrel 300 mg is administered. Antiplatelet agent should be continued once daily.

Statins. See p. 139.

Ranolazine

- Ischaemia increases the late inward sodium current in myocardium resulting in calcium influx and overload. Ranolazine inhibits late inward Na^+ current $\rightarrow$ ↓ intracellular Ca^{2+} overload in myocardium, contractility and oxygen consumption without altering heart rate and BP.
- Used orally in chronic angina, it decreases the number of attacks and improves exercise tolerance.
- QT prolongation may occur.

Trimetazidine

- During ischaemia, the myocardium derives energy mainly from fatty acid oxidation which results in increased oxygen consumption. Trimetazidine $\rightarrow$ fatty acid oxidation inhibitor $\rightarrow$ partial inhibition of fatty acid oxidation in myocardium $\rightarrow$ increased use of glucose for energy $\rightarrow$ ↓ myocardial O_2 consumption.
- Improves exercise tolerance and decreases frequency of anginal episodes.
- Used orally in exertional angina in combination with other drugs.

Ranolazine is also an inhibitor of fatty acid oxidation.

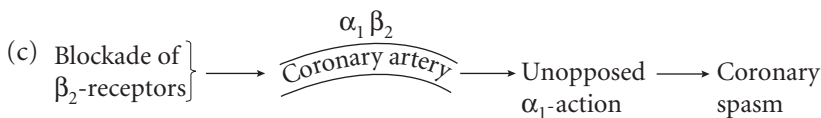
Ivabradine

- Site of action is SA node – heart rate is decreased $\rightarrow$ ↓ myocardial O_2 demand.
- Decreases frequency of anginal episodes. It can also be used in sinus tachycardia.

Dipyridamole. It dilates coronary blood vessels. It causes ‘coronary steal’ phenomenon by increasing blood flow to nonischaemic areas.

Combination Therapy

1. **Nitrates $\times$ β -blockers (propranolol):** This combination (used in exertional angina) increases the effectiveness and reduces the incidence of adverse effects (Fig. 3.6).
 - (a) Nitrates can counteract the increase in LV end-diastolic volume associated with propranolol.
 - (b) Nitrates $\rightarrow$ arteriolar dilatation $\rightarrow$ ↓ PVR $\rightarrow$ reflex tachycardia. Propranolol can block the reflex tachycardia that is associated with nitrates.



Nitrates can prevent the coronary spasm associated with β -blockers.

2. **Nifedipine (DHPs) $\times$ β -blockers:** β -Blockers can block the reflex tachycardia that is associated with nifedipine (Fig. 3.7). Coronary vasospasm by β -blockers is prevented. Slow-acting DHPs are also combined with β -blockers. The combination is useful in classical angina with associated coronary vasospasm.
3. **β -Blockers $\times$ verapamil/diltiazem:** This combination should not be used as it may cause additive depressant effect on SA node, AV node and cardiac contractility leading to heart block, heart failure or even cardiac arrest.
4. **CCBs $\times$ nitrates:** The net effect is an additive reduction in the myocardial O_2 demand and improved coronary blood flow (Fig. 3.8). This combination is useful in severe variant angina.
5. **Nitrates $\times$ β -blockers $\times$ CCBs:** This combination is especially useful in severe and resistant cases of exertional angina and also in unstable angina (Fig. 3.9).

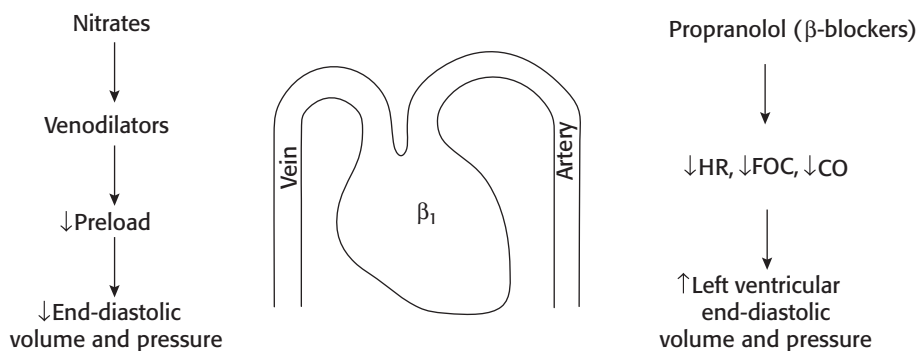


Fig. 3.6 Effects of nitrates $\times$ β -blockers (propranolol).

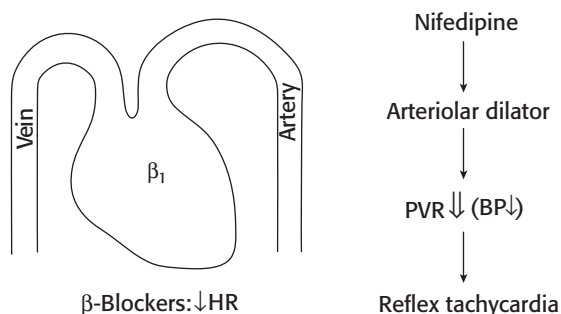


Fig. 3.7 Effects of nifedipine (DHPs) $\times$ β -blockers.

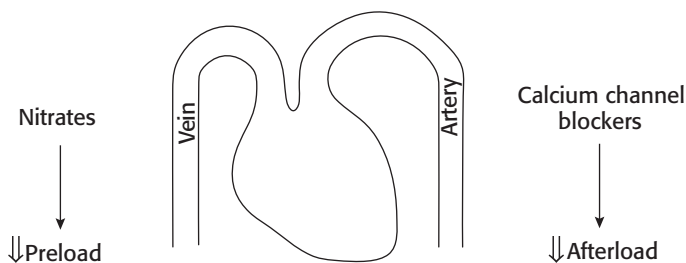


Fig. 3.8 Effects of calcium channel blockers + nitrates.

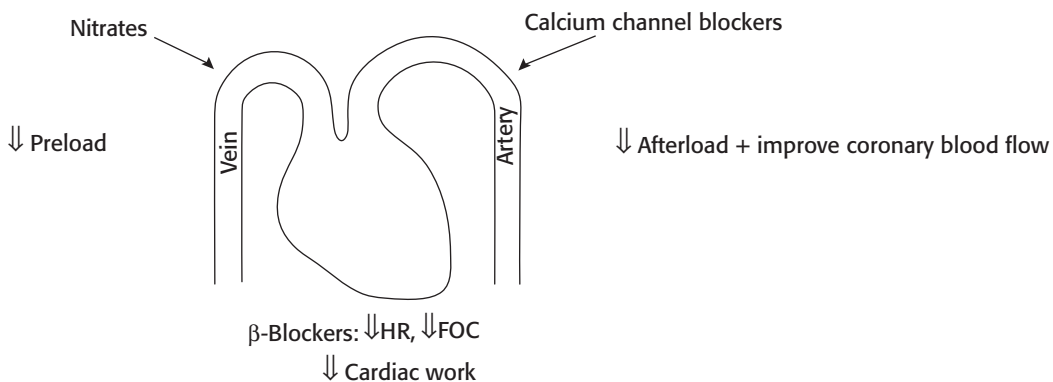


Fig. 3.9 Effects of nitrates + β -blockers + CCBs.

- 6. Sildenafil/tadalafil (PDE-5 inhibitors) × nitrates:** Sildenafil potentiates vasodilator action of nitrates; can cause MI and sudden death. Nitrates should be avoided for 24 hours after sildenafil intake.

PHARMACOTHERAPY OF ACUTE MYOCARDIAL INFARCTION

1. Antiplatelet agent: Aspirin, 162 mg or 325 mg orally (chewed and swallowed), is administered at once to a patient with suspected or definite MI. If the patient is allergic to aspirin, clopidogrel 300 mg is administered. Antiplatelet agent should be continued once daily.
2. Analgesia: Intravenous morphine 10 mg for relief of pain. Antiemetics like promethazine 25–50 mg slow i.v. to prevent opioid-induced vomiting.
3. Nitrates: Intravenous nitroglycerin for recurrent or persistent pain and to treat LV failure.
4. Low flow oxygen therapy (2–4 L/minute) if there is decreased oxygen saturation.
5. Reperfusion therapy: Primary percutaneous coronary intervention (PCI) or thrombolytic therapy.
 - Primary PCI, if facilities are available.
 - Thrombolytic therapy: Streptokinase, alteplase, tenecteplase, reteplase or urokinase is used to restore coronary patency and reperfusion of infarcted area.
6. Anticoagulants: Low-molecular-weight heparin or unfractionated heparin is given to prevent reinfarction and thromboembolic complications.
7. β -Blockers should be administered during first 24 hours unless contraindicated. They prevent reinfarction, arrhythmias and reduce mortality.
8. ACE inhibitors (e.g. ramipril) or angiotensin receptor blockers (e.g. valsartan) are administered early to improve survival.
9. Statins (e.g. atorvastatin) should be started (secondary prevention) to reduce thrombotic events and reinfarction.
10. Acidosis is treated with intravenous sodium bicarbonate.

Drugs Used in Congestive Cardiac Failure

PH1.29

The function of the heart is to pump an adequate amount of blood to various tissues. In CCF, there is an inadequate or inefficient contraction of the heart leading to reduced CO. In initial stages of CCF, the compensatory mechanisms that try to maintain the CO (Fig. 3.10) are as follows:

- Increased sympathetic activity.
- Increased renin–angiotensin–aldosterone activity.
- Myocardial hypertrophy and remodelling.

As time progresses, the compensatory mechanisms fail and gradually clinical symptoms of failure appear. The basic haemodynamic disturbances seen in CCF are as follows:

- Increased pulmonary capillary pressure termed as backward failure, which is characterized by dyspnoea and orthopnoea.
- Decreased CO termed as forward failure, leading to decreased oxygen supply to the peripheral tissues (tissue hypoxia).

The goal of therapy is to provide relief from symptoms, slow the progression of disease and decrease mortality. The treatment strategies for CCF include preload reduction, afterload reduction and enhancement of contractile state of the heart.

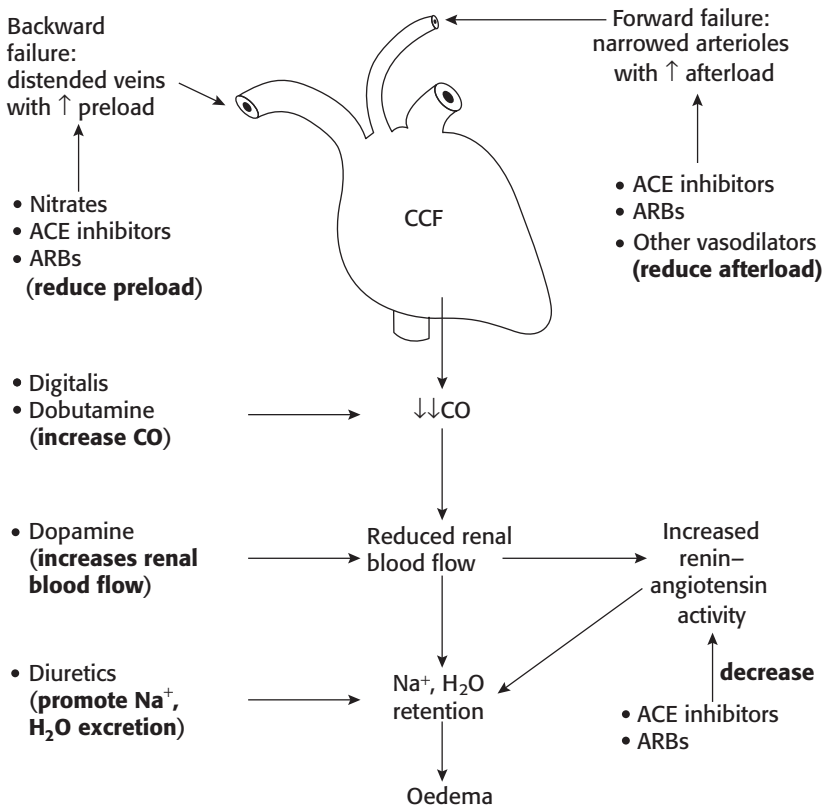


Fig. 3.10 Pathophysiology of CCF and mechanism of action of some drugs used in its treatment. ARBs, angiotensin receptor blockers; CCF, congestive cardiac failure; CO, cardiac output.

Classification

1. Diuretics:

- Loop diuretics:* Furosemide, bumetanide, torsemide.
- Thiazide diuretics:* Chlorothiazide, hydrochlorothiazide, metolazone.
- Aldosterone antagonists:* Spironolactone, eplerenone.

2. Vasodilators:

- Arteriolar and venodilators:*
 - ACE inhibitors: Enalapril, lisinopril, ramipril, fosinopril, trandolapril.
 - Angiotensin receptor blockers (ARBs): Losartan, candesartan, valsartan, telmisartan.
 - Direct renin inhibitor: Aliskiren.
 - Sodium nitroprusside.
- Venodilators:* Nitroglycerin, isosorbide dinitrate.
- Arteriolar dilators:* Hydralazine, minoxidil, nicorandil.

3. β -Adrenergic blockers: Metoprolol, bisoprolol, carvedilol, nebivolol.

4. Sympathomimetic amines: Dopamine, dobutamine.

5. Cardiac glycosides: Digoxin.

6. Phosphodiesterase 3 inhibitors: Inamrinone, milrinone.

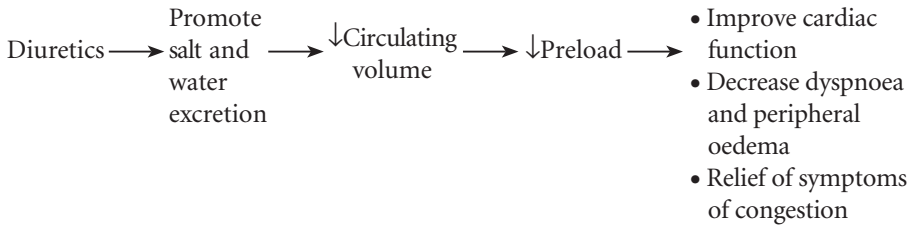
7. Vasopressin-receptor antagonists: Tolvaptan, conivaptan.

8. Neprilysin inhibitor: Sacubitril

9. Brain natriuretic peptide (BNP): Nesiritide.

Diuretics

A majority of patients with CHF are started on diuretics.

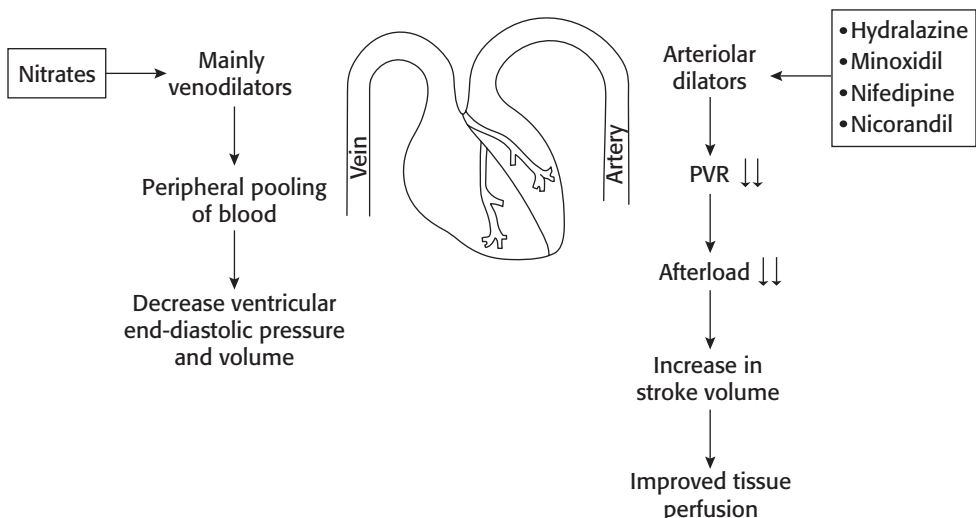


Therapy is initiated with a loop diuretic – oral furosemide/torsemide/bumetanide. Furosemide is the commonly used loop diuretic. Torsemide and bumetanide are better absorbed than furosemide. In severe HF, i.v. diuretic is required. Thiazides can be added to loop diuretics in advanced cases of HF for synergistic effect. Serum K^+ levels should be monitored. Volume contraction should be avoided. Aldosterone antagonist can be added to loop diuretic in moderate to severe HF to increase diuretic efficacy, counteract K^+ loss and improve survival. Long-term treatment with diuretics may be required to prevent fluid retention and recurrent oedema.

Vasodilators

The vasodilators may be classified according to the distribution of their effect:

1. **Mixed arteriolar and venodilators:** ACE inhibitors, ARBs, sodium nitroprusside, reduce both preload and afterload.
2. **Drugs with predominant venodilatory effect (Fig. 3.11):** Nitrates reduce preload; they also have some effect on arterioles.
3. **Drug with predominant arteriolar dilating effect (Fig. 3.11):** Hydralazine, minoxidil, etc. reduce afterload.



Note: ACE inhibitors, ARBs, sodium nitroprusside reduce both preload and afterload.

Fig. 3.11 Effects of vasodilators in congestive cardiac failure.

ACE Inhibitors. They are the standard therapy for all grades of CHF and asymptomatic LV systolic dysfunction. They inhibit conversion of angiotensin I to angiotensin II. ACE inhibitors inhibit the generation of angiotensin II resulting in the following:

- Decrease in peripheral vascular resistance → increase in stroke volume → improved tissue perfusion. Increase in renal blood flow → diuresis → ↓ circulating blood volume.
- Decrease in aldosterone production → decrease in sodium and water retention → ↓ preload.
- Venodilation → ↓ preload.
- There is decrease in pressure in atria and pulmonary circuit.
- Retard/reverse ventricular hypertrophy and remodelling by decreasing angiotensin II and aldosterone levels.

Therapy with ACEIs leads to symptomatic improvement, decreased hospitalization and mortality and slowing down of disease progression.

For mechanism of action, adverse effects and contraindications, see pp. 100–102.

Angiotensin Receptor Blockers (p. 103). Losartan, candesartan, etc. competitively block AT₁-receptors on the heart, peripheral vasculature and kidney. They prevent the effects of angiotensin II and produce effects similar to those of ACE inhibitors. Angiotensin receptor blockers are mainly used in patients who cannot tolerate ACE inhibitors because of cough, angioedema and neutropenia.

Direct Renin Inhibitor. Aliskiren, a direct renin inhibitor, produces a decrease in plasma renin, angiotensin I and II levels. This decreases BP, LV mass and may produce beneficial effects in heart failure.

Other vasodilators (Fig. 3.11):

Sodium nitroprusside (i.v.) and **nitroglycerin** (i.v.) are used for severe heart failure. **Hydralazine**, an arteriolar dilator, increases CO in patients with heart failure. The disadvantages with the use of arteriolar dilators are reflex tachycardia and fluid retention. Tachycardia is rare with mixed arteriolar and venodilators.

β-Adrenergic Blockers

β-Blockers like metoprolol, bisoprolol, carvedilol and nebivolol are useful in mild to moderate heart failure. Long-term therapy with these β-blockers improves symptoms, reduces hospitalization and decreases mortality in patients with mild to moderate heart failure. The exact mechanism of action is not clear. They block β-receptor-mediated effects of catecholamines on the heart. This improves LV structure and function, decreases wall stress, increases ejection fraction and decrease LV size. They decrease apoptosis and ventricular remodelling. They also decrease frequency of arrhythmias. The antioxidant effect of carvedilol also contributes to its beneficial effects. Therapy with β-blockers in heart failure should be under careful supervision.

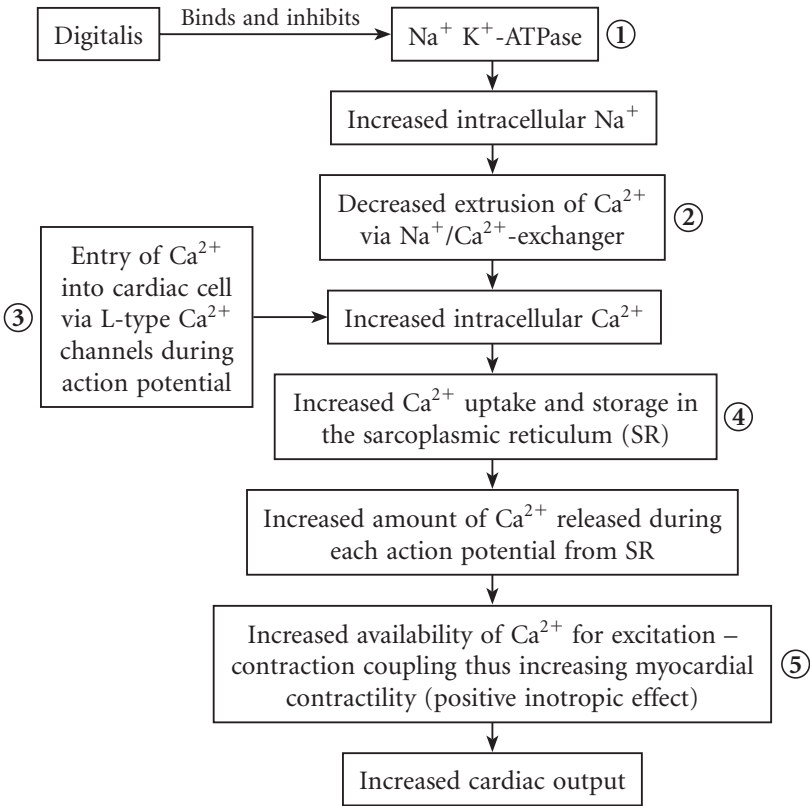
Cardiac Glycosides

Chemistry. The glycosides consist of an aglycone (steroid nucleus with an attached lactone ring) with one or more sugar moieties attached to it. They have a potent action on the heart, hence are referred to as cardiac glycosides. The utility of digitalis in the treatment of heart failure was shown by William Withering.

Sources

Source	Glycosides
<i>Digitalis purpurea</i> (leaf)	Digitoxin
<i>Digitalis lanata</i> (leaf)	Digoxin, digitoxin
<i>Strophanthus gratus</i> (seed)	Strophanthin-G (ouabain)

Mechanism of Action of Cardiac Glycosides (Digitalis; Fig. 3.12). $\text{Na}^+\text{K}^+\text{-ATPase}$ is a membrane-bound enzyme which is called digitalis receptor. It is also called sodium pump.



Pharmacological Actions

- 1. Cardiac
- 2. Extracardiac

Cardiac Actions. Digitalis has direct and indirect actions on the heart.

- Direct action by inhibiting $\text{Na}^+\text{K}^+\text{-ATPase}$
- Indirect action by stimulating vagus (vagomimetic effect)

- 1. **Myocardial contractility:** Digitalis increases the force of contraction of the myocardium (positive inotropic effect). This effect is more prominent in the failing heart. Digitalized heart contracts more forcibly and completely. The positive inotropic effect causes complete emptying of the ventricles during systole and increases the CO. This decreases pulmonary congestion and systemic venous pressure. The diastolic size of the heart is reduced. When the size of the heart is reduced, muscle fibre length is also reduced, thereby,

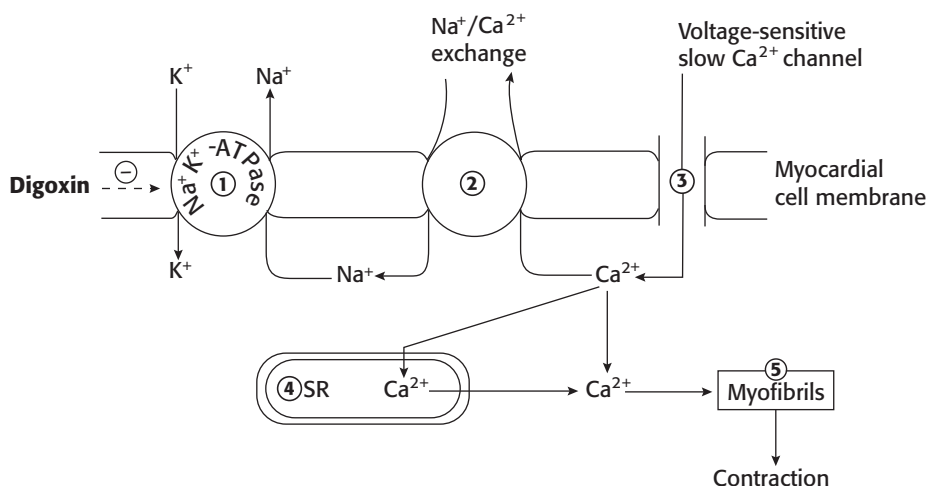


Fig. 3.12 Mechanism of action of cardiac glycosides: SR, sarcoplasmic reticulum.

decreasing the oxygen requirement of myocardium. The digitalized heart, thus, can do more work for the same energy. Therefore, digitalis is called a 'cardiotonic'.

- Heart rate:** In patients with CCF, digitalis reduces the heart rate (negative chronotropic effect) by direct and indirect actions. In small doses, digitalis decreases heart rate by stimulation of vagus. In toxic doses, it can increase sympathetic activity thus increasing heart rate.
- Electrophysiological actions:** At therapeutic concentrations, digoxin decreases automaticity and increases resting membrane potential by vagal action in atria and AV node. It also prolongs ERP and decreases conduction velocity in AV node. This may lead to bradycardia and AV block. At higher concentrations, digoxin can increase automaticity in cardiac tissue by direct action as well as by increasing sympathetic activity. This can result in atrial and ventricular arrhythmias.
- ECG:** Digitalis produces prolongation of P-R interval, inversion of T wave and depression of ST segment.

Extracardiac Actions

- Gastrointestinal tract (GIT):** Digitalis can produce anorexia, nausea, vomiting and occasionally diarrhoea. Nausea and vomiting are due to stimulation of chemoreceptor trigger zone (CTZ) and a direct action on the gut.
- Kidney:** In patients with CCF, digitalis causes diuresis (increased urine output).
- Central nervous system (CNS):** In high doses, it can cause central sympathetic stimulation, confusion, blurring of vision, disorientation, etc.

Pharmacokinetics. Digoxin is the commonly used glycoside and is usually administered by oral route; food delays the absorption of digoxin. It is widely distributed in the body, concentrated in the heart, liver, kidney and skeletal muscle. It crosses BBB and is mainly excreted unchanged in urine. Dosage adjustment of digoxin is necessary in patients with renal failure.

Adverse Effects. Digoxin has a narrow margin of safety. Monitoring of serum digoxin, electrolyte levels and electrocardiogram (ECG) are important during digitalis therapy.

1. Extracardiac

- GIT:** Early symptoms of toxicity are anorexia, nausea and vomiting, which are due to GI irritation and CTZ stimulation.

- (b) **CNS** effects include headache, confusion, restlessness, disorientation, weakness, visual disturbances, altered mood and hallucinations.
- (c) **Skin rashes and gynaecomastia** can occur occasionally.
- 2. **Cardiac:** Digitalis can cause any type of arrhythmias. The most common are ventricular premature beats, pulsus bigeminy and ventricular tachycardia. It can also cause AV block, atrial tachycardia, atrial fibrillation, atrial flutter and even severe bradycardia.

Factors Affecting Digitalis Toxicity

1. **Age:** Elderly patients are more susceptible to digitalis toxicity due to declining renal and hepatic function.
2. **Route:** Intravenous digitalization carries more risk than oral route.
3. **Hypokalaemia** increases the binding of digoxin to Na^+K^+ -ATPase and enhances its toxicity.
4. **Hypercalcaemia** and **hypomagnesaemia** enhance digoxin toxicity.
5. **Hypothyroidism**, **hyperthyroidism**, **hypoxia**, **renal failure** and **myocarditis** are predisposing factors to digitalis toxicity.

Treatment of Digoxin Toxicity

1. Shift the patient to intensive care unit (ICU).
2. Stop digoxin and potassium-depleting diuretics (thiazides/loop diuretics).
3. Potassium chloride (KCl) orally or intravenously is the drug of choice for tachyarrhythmias, when serum K^+ level is normal/low.
4. Supraventricular arrhythmias are treated with oral or intravenous propranolol.
5. Intravenous lignocaine is the drug of choice for ventricular arrhythmias because it has:
 - Relatively low incidence of toxicity.
 - A rapid onset and short duration of action, so its action wears off immediately after stopping the infusion.
 - No action on AV nodal conduction velocity, hence, does not intensify the AV block in digitalis toxicity.
6. AV block and bradyarrhythmias are treated with atropine and cardiac pacing.
7. **Digoxin antibodies (Digibind):** It is used only in case of serious digitalis toxicity. It neutralizes circulating digoxin/digitoxin and rapidly reverses the toxicity, but it is expensive.

Drug Interactions

1. **Cholestyramine/colestipol × digoxin:** Cholestyramine and colestipol (bile acid binding resins) bind to cardiac glycosides in the gut and reduce its absorption.
2. **β -blocker/verapamil × digoxin:** These drugs have additive depressant effect on SA and AV nodes and may precipitate AV block.
3. **Thiazides/loop diuretics × digoxin:** Hypokalaemia caused by diuretics, may potentiate digoxin toxicity. Hypokalaemia increases the binding of digoxin to Na^+K^+ -ATPase.
4. **Calcium × digoxin:** Calcium increases the incidence of digoxin toxicity.
5. **Digoxin × sympathomimetic/succinylcholine:** The chances of cardiac arrhythmias are more with sympathomimetic/succinylcholine in patients on digoxin.

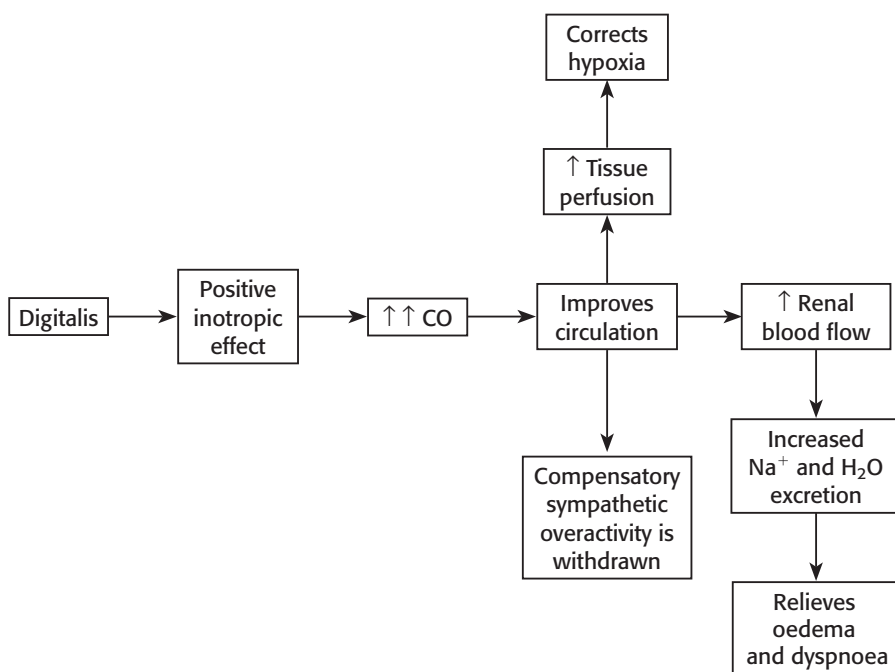


Fig. 3.13 Beneficial effects of digitalis in CCF. CO, cardiac output.

Uses of Digitalis

1. **CCF:** Digitalis is useful in patients with low output failure, especially when associated with atrial fibrillation. It is ineffective in high output failure associated with severe anaemia, thyrotoxicosis and AV shunt.

The beneficial effects of digoxin in case of heart failure are due to its action on myocardium (positive inotropic effect), venous system and kidney (Fig. 3.13).

For explanation, see Pharmacological Actions.

2. **Atrial fibrillation:** It is the most common cardiac arrhythmia. In atrial fibrillation, the atria beat at a rate of 350–600/minute. Digitalis has both direct and indirect (vagomimetic) actions on AV node. It depresses AV node by increasing ERP and decreasing conduction velocity, thus reduces the ventricular rate. Verapamil and propranolol can be used in atrial fibrillation.
3. **Atrial flutter:** In atrial flutter, the atria beat rapidly at a rate of about 300/minute. Digitalis controls ventricular rate by depressing AV conduction.
4. **Paroxysmal supraventricular tachycardia (PSVT):** In PSVT, the heart rate is about 140–220/minute. The preferred drug for PSVT is adenosine. Propranolol or verapamil can also be used. Digoxin has a slower onset of action hence it is not suitable for acute therapy. Digoxin is preferred in PSVT, if there is associated heart failure. It terminates the arrhythmia by increasing the vagal tone.

Sympathomimetic Amines

Dopamine and dobutamine are used in acute heart failure. They have positive inotropic effect and provide symptomatic relief in patients with ventricular dysfunction.

Dopamine. It is a catecholamine and has dose-dependent haemodynamic effects. At low doses (<2 mcg/kg/minute), dopamine selectively dilates renal, mesenteric and coronary blood vessels by acting on D_1 -receptors. Thus, dopamine increases GFR and urine output. At moderate doses ($2\text{--}5$ mcg/kg/minute), dopamine stimulates β_1 -receptors of heart, increases myocardial contractility and CO but tachycardia is less prominent. It also stimulates dopaminergic receptors resulting in an increase in GFR. Dopamine (i.v. infusion) is used in cardiogenic shock and acute heart failure with renal impairment. It improves both cardiac and renal function. At high concentration (>10 mcg/kg/minute), it causes generalized vasoconstriction. This increases afterload and reduces blood flow to renal, mesenteric and other vital organs. So the beneficial effects seen with low to moderate doses of dopamine are lost at higher concentrations.

Dobutamine. It is a synthetic catecholamine and acts on β_1 -, β_2 - and α_1 -receptors. It has selective inotropic effect and increases CO. In therapeutic doses, it has little effect on BP and heart rate. Total peripheral resistance is generally not affected. This is due to counterbalancing of α_1 -receptor-mediated vasoconstriction and β_2 -receptor-mediated vasodilatation. It is administered by i.v. infusion for short-term treatment of acute heart failure (due to MI or cardiac surgery) and cardiogenic shock. The side effects are tachycardia, rise in BP and development of tolerance.

Aldosterone Antagonists

Increased aldosterone levels in CHF causes salt and water retention $\rightarrow$ increased preload; potassium excretion can cause hypokalaemia $\rightarrow$ increased risk of arrhythmias. Aldosterone also causes ventricular remodelling and hypertrophy. Spironolactone/eplerenone blocks action of aldosterone on its receptor and blocks these effects. They slow disease progression and decrease mortality. They are used in combination with other drugs in moderate to severe heart failure.

Phosphodiesterase 3 inhibitors

Inamrinone and milrinone are selective phosphodiesterase 3 (PDE-3) inhibitors and increase cAMP level. They exert both positive inotropic and vasodilator actions (inodilators). They are administered intravenously. They increase CO and decrease afterload. They are used for short-term treatment of severe heart failure. The adverse effects of inamrinone include nausea, vomiting, arrhythmias, thrombocytopenia and hepatotoxicity. Milrinone is more potent than inamrinone and does not produce thrombocytopenia.

Vasopressin-Receptor Antagonists

Short-term therapy with tolvaptan may improve symptoms in CHF with volume overload and severe hyponatraemia.

Natriuretic Peptide

Nesiritide, recombinant form of brain natriuretic peptide (BNP), is useful in acute decompensated heart failure. Dyspnoea is reduced. It is a vasodilator and is administered intravenously. Hypotension is a common adverse effect.

Sacubitril

It inhibits neprilysin $\rightarrow$ inhibits metabolism of ANP (atrial natriuretic peptide) and BNP $\rightarrow$ vasodilation and diuresis. It is used in combination with valsartan for severe heart failure

Management of CCF include Diet (salt restriction), Diuretics, Dilators (vasodilators-ACEIs, ARBs), Digoxin, Dopamine, Dobutamine, PDE-3 inhibitors, etc. (note the 'Ds') and beta-blockers. ACEIs, ARBs, aldosterone antagonists, sacubitril and β -blockers slow

down the progression of disease. Symptoms of congestion are relieved by vasodilators, diuretics, dobutamine, dopamine, digoxin, milrinone and inamrinone.

Antiarrhythmic Drugs

PH1.30

CARDIAC ELECTROPHYSIOLOGY

The transmembrane potential of a cardiac cell at rest is about -90 mV negative to the exterior. This is determined mainly by sodium, potassium, calcium and chloride ions.

Ionic Distribution

Normally

- K^+ is more in the intracellular fluid (ICF) than extracellular fluid (ECF).
- Na^+ , Ca^{2+} and Cl^- are more in the ECF.

Cardiac Action Potential

Normally, an impulse is generated in the SA node. From SA node $\rightarrow$ atria $\rightarrow$ AV node (slowly) $\rightarrow$ bundle of His $\rightarrow$ ventricles.

The action potential of Purkinje system has five phases (Fig. 3.14):

- **Phase 0 (rapid depolarization):** It is mainly due to rapid influx of Na^+ through open sodium channels. The upstroke stops following inactivation of sodium channels.
- **Phase 1 (period of early fast repolarization):** It occurs due to stoppage of inward flow of Na^+ and start of K^+ outflow from the cell. It lasts for a brief period.
- **Phase 2 (plateau phase):** During this phase, Ca^{2+} enters the myocardial cell through voltage-dependent slow Ca^{2+} channels whereas K^+ moves out of the cells through potassium channels.
- **Phase 3 (phase of repolarization):** Calcium channel closes; efflux of K^+ occurs throughout this phase.
- **Phase 4 (spontaneous depolarization):** The membrane potential returns to the resting value. In the Purkinje fibres, there is spontaneous depolarization.

In the SA and AV node, phase 0 is due to slow inflow of Ca^{2+} ions through activated Ca^{2+} channels. These cells also undergo spontaneous depolarization like Purkinje fibres. Spontaneous depolarization results from depolarizing currents due to flow of Na^+ , Ca^{2+} and K^+ ions.

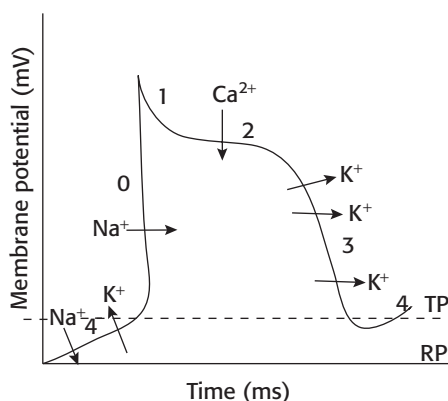


Fig. 3.14 Cardiac action potential. TP, threshold potential. RP, resting potential; PHASE 0, rapid depolarization; PHASE 1, early fast repolarization; PHASE 2, plateau phase; PHASE 3, repolarization; PHASE 4, spontaneous depolarization.

In atria and ventricles, the membrane potential is steady during diastole. The duration of atrial action potential is shorter than that of ventricles.

Properties of a Cardiac Cell

- **Automaticity:** It is the ability of the cardiac cell to undergo spontaneous depolarization. Normally, the rate of spontaneous depolarization is fastest in SA node; hence, it is the pacemaker of the heart.
- **Excitability:** It is the ability of a cell to undergo depolarization in response to a stimulus.
- **Threshold potential:** It is the potential at which sudden, rapid and complete depolarization occurs resulting in the generation of an action potential.
- **Conduction velocity:** It depends mainly on the slope of action potential and phase 0 depolarization.
- **Effective refractory period (ERP):** It is the minimal interval between two successive, propagated action potentials.

ARRHYTHMIAS

Arrhythmias are disturbances in cardiac rhythm (i.e. abnormality in site of origin of impulse, its rate, regularity or conduction). Arrhythmias can be either tachyarrhythmias or bradyarrhythmias.

- Bradyarrhythmias may be due to reduced automaticity or abnormal slowing/blockade of impulse conduction.
- Tachyarrhythmias are due to either increased automaticity, after depolarization or re-entry of an impulse.

Various cardiac arrhythmias are atrial flutter, atrial fibrillation, PSVT, ventricular tachycardia, ventricular fibrillation, *torsades de pointes*, AV block, etc.

Drugs used to restore normal rhythm are known as antiarrhythmic drugs.

Classification of Antiarrhythmic Drugs (Vaughan–Williams)

- **Class I: Na⁺ channel blockers** (membrane stabilizing agents)
 - IA: Drugs that moderately depress phase 0 depolarization – quinidine, procainamide, disopyramide.
 - IB: Drugs that have minimal effect on phase 0 depolarization – lignocaine, mexiletine.
 - IC: Drugs that markedly depress phase 0 depolarization – flecainide, propafenone.
- **Class II (β -adrenergic blockers):** Propranolol, atenolol, esmolol, metoprolol, sotalol.
- **Class III (drugs that prolong duration of action potential):** Amiodarone, dronedarone, sotalol, dofetilide, ibutilide, bretylium.
- **Class IV (CCBs):** Verapamil, diltiazem.

Other antiarrhythmic agents are digoxin, adenosine, atropine, isoprenaline, etc.

Class I: Na⁺ Channel Blockers

Quinidine. It is a class IA antiarrhythmic drug. It is an alkaloid obtained from cinchona bark.

Pharmacological Actions of Quinidine

1. Cardiovascular system

(a) **Heart:**

- Quinidine blocks Na⁺ channels in the open state → decreases automaticity, excitability, rate of phase 0 depolarization and conduction velocity.

- It blocks potassium channels → increases duration of action potential.
- It prolongs ERP as a result of blockade of both Na^+ and K^+ channels.

It suppresses ectopic foci and blocks re-entry of impulses.

- (b) **AV node:** Effect on AV node conduction is variable. It has vagolytic (increases AV node conduction) and direct depressant action on AV node.
- (c) **ECG:** Quinidine prolongs QRS complex and QT interval.
- (d) **BP:** Quinidine causes fall in blood pressure due to α -adrenergic blocking and direct myocardial depressant effects.

2. Skeletal muscles: Quinidine reduces skeletal muscle contraction.

3. Others: It also has antimalarial, antipyretic and oxytocic activities.

Pharmacokinetics. Quinidine is well absorbed from GI tract, highly bound to plasma proteins, metabolized in liver, and about 20% is excreted unchanged in urine.

Adverse Effects. The important adverse effects are diarrhoea, thrombocytopenia and fall in BP and *torsades de pointes*. Hepatitis and fever can rarely occur. Large doses of quinidine may produce a syndrome called ‘cinchonism’. The manifestations are tinnitus, deafness, headache, blurring of vision, diplopia, photophobia, confusion, delirium, disorientation and psychosis.

Drug Interactions

- 1. Quinidine** may potentiate the effects of neuromuscular blocking drugs.
- 2. Quinidine $\times$ β -blockers/verapamil/potassium salts:** Additive cardiac depressant effect may lead to cardiac arrest.

Uses. Quinidine has a broad spectrum of antiarrhythmic activity but it is not the drug of choice in any type of arrhythmias. Its use has declined because of its adverse effects and availability of better antiarrhythmic drugs. It is useful in maintaining normal sinus rhythm in patients with atrial fibrillation or atrial flutter and occasionally to treat ventricular tachycardia.

Procainamide. Like quinidine, procainamide is also a class IA antiarrhythmic drug. Its effects are similar to those of quinidine but it has no anticholinergic and α -adrenergic blocking effects.

Pharmacokinetics. Procainamide is well absorbed after oral administration. It can also be given by i.v. and i.m. routes. It is metabolized in liver by acetylation. The major metabolite is *N*-acetyl procainamide (NAPA) that has K^+ channel-blocking activity. NAPA is excreted in urine; hence dosage adjustment may be needed in patients with renal failure.

Adverse Effects

- 1. CVS:** Hypotension (due to ganglion blockade) and heart block are the main adverse effects following i.v. administration. *Torsades de pointes* can also occur.
- 2. GIT:** Nausea and vomiting.
- 3. CNS:** Mental confusion, depression, hallucinations and psychosis. Long-term procainamide therapy often produces lupus-like syndrome with arthralgia and arthritis.

Uses. It is useful in ventricular arrhythmias associated with acute MI. It is not used for long-term oral therapy due to need for frequent dosing and risk of lupus syndrome.

Disopyramide. It is a class IA antiarrhythmic drug. Its actions are similar to those of quinidine but it has more marked anticholinergic action.

Pharmacokinetics. Disopyramide is well absorbed after oral administration. It is partly metabolized in liver and partly excreted in urine in the unchanged form.

Uses. Disopyramide is mainly used for the treatment of ventricular arrhythmias. It can also be used to maintain sinus rhythm in patients with atrial fibrillation or atrial flutter.

Adverse Effects. Anticholinergic side effects are urinary retention especially in benign prostatic hyperplasia (BPH), dryness of mouth, blurring of vision, constipation, precipitation of an attack of glaucoma, etc.

Lignocaine. Lignocaine is a local anaesthetic having antiarrhythmic activity. It is a class IB antiarrhythmic drug. Local anaesthetic preparation of lignocaine contains methylparaben, a preservative, hence not used as antiarrhythmic agent.

Pharmacological Actions. It blocks sodium channels in the inactivated (predominantly) and the active states. It has minimal effect on normal cardiac tissues. Its effect is prominent in depolarized (ischaemic) tissues. It decreases automaticity of ectopic foci by reducing the slope of phase 4 depolarization and depresses conduction in depolarized (diseased) tissue. Action potential duration is usually unaffected or may be shortened.

Pharmacokinetics. Lignocaine is orally not effective because of extensive first-pass metabolism. Lignocaine is, therefore, commonly administered by intravenous route as an antiarrhythmic. It is widely distributed in the body, readily crosses BBB, is poorly bound to plasma proteins, rapidly metabolized in liver and has short plasma half-life of 1–2 hours. The volume of distribution and hepatic clearance of lignocaine are reduced in patients with heart failure; hence, both the loading and maintenance dose should be decreased. In hepatic disease, the clearance of lignocaine is reduced; hence, it requires a reduction in the maintenance dose.

Drug Interactions. **Lignocaine × propranolol:** Propranolol reduces lignocaine elimination by reducing the hepatic blood flow, thus increases the risk of lignocaine toxicity.

Adverse Effects. These are mainly related to the central nervous system – headache, drowsiness, nystagmus, blurred vision, confusion, muscle twitchings and convulsions. In high doses, lignocaine may cause hypotension due to myocardial depression. Side effects are potentiated in renal and hepatic failure.

Uses

- Lignocaine is used for emergency treatment of ventricular arrhythmias associated with MI, digitalis toxicity and cardiac surgery.
- Lignocaine is preferred in ventricular arrhythmias because it:
 - Is relatively less toxic.
 - Has a rapid onset and short duration of action, so its action wears off immediately after stopping the infusion.
 - Has no action on AV nodal conduction velocity, hence does not intensify the AV block during treatment of ventricular arrhythmias in digitalis toxicity.
- Lignocaine is administered intravenously initially as bolus 1–2 mg/kg and later 1–4 mg/minute i.v. infusion as maintenance dose.
- Lignocaine is not useful in atrial arrhythmias because atrial action potentials are of very short duration – so the Na⁺ channels are in the inactivated state for a very brief period of time.

Mexiletine. It is an analogue of lignocaine and has similar actions. It is used orally and parenterally in the treatment of ventricular arrhythmias. The common adverse effects are nausea, dizziness and tremors.

Flecainide and Propafenone. These are class IC antiarrhythmic drugs. They block sodium channels in the open state. Class IC drugs have the most potent blocking effect on sodium channels. They markedly depress phase 0 depolarization, slow conduction and prolong PR interval. Propafenone also blocks β receptors.

Adverse Effects. Both the drugs can exacerbate arrhythmias and CCF. Other adverse effects seen with propafenone are metallic taste, constipation, bradycardia and bronchospasm. Blurring of vision is common with flecainide.

Uses. Propafenone and flecainide are primarily used for the treatment of supraventricular arrhythmias; can also be used in ventricular arrhythmias. Both the drugs are administered orally.

Class II: β -Blockers. Propranolol, atenolol, esmolol, metoprolol, etc. are class II antiarrhythmic agents. They block the effects of catecholamines on the heart. They:

- Depress the phase 4 depolarization – decrease automaticity in SA node and ectopic foci (when increased by adrenergic stimulation).
- Prolong the refractory period and decrease the conduction velocity in AV node which makes them useful:
 - In the treatment of re-entrant arrhythmias involving the AV node (PSVT).
 - To control ventricular rate in atrial flutter and atrial fibrillation.

In high doses, propranolol has ‘quinidine-like’ membrane stabilizing effect.

Pharmacokinetics, adverse effects and contraindications are discussed on pp. 93–95.

Esmolol. It is a cardioselective β_1 -blocker with a rapid onset and short duration of action. Intravenous esmolol is used for emergency control of ventricular rate in atrial flutter and atrial fibrillation. Intravenous esmolol is also highly effective for terminating an attack of PSVT. Side effects are hypotension, dizziness and bronchospasm in asthmatics.

Sotalol. It is a nonselective β -adrenergic blocker with additional K^+ channel-blocking (class III) property, thus prolonging the duration of action potential. It decreases automaticity, slows AV conduction and prolongs ERP. Sotalol is used to treat life-threatening ventricular tachyarrhythmias and to maintain sinus rhythm in atrial fibrillation. Adverse effects and contraindications are same as propranolol. Sotalol can cause *torsades de pointes*.

Class III: Drugs that Prolong Duration of Action Potential

Amiodarone. It is an iodine-containing compound and structurally related to thyroid hormone. It has a broad spectrum of antiarrhythmic activity.

- Amiodarone blocks potassium channels $\rightarrow$ increases duration of action potential $\rightarrow$ prolongs refractory period and suppresses abnormal automaticity (Fig. 3.15).
- Blocks sodium channels in the inactivated state $\rightarrow$ decreases conduction mainly in the partially depolarized tissue.
- Blockade of sodium and potassium channels prolongs refractory period in the cardiac tissue.
- It also has weak β -adrenergic blocking and calcium channel-blocking actions. It decreases heart rate and AV conduction.

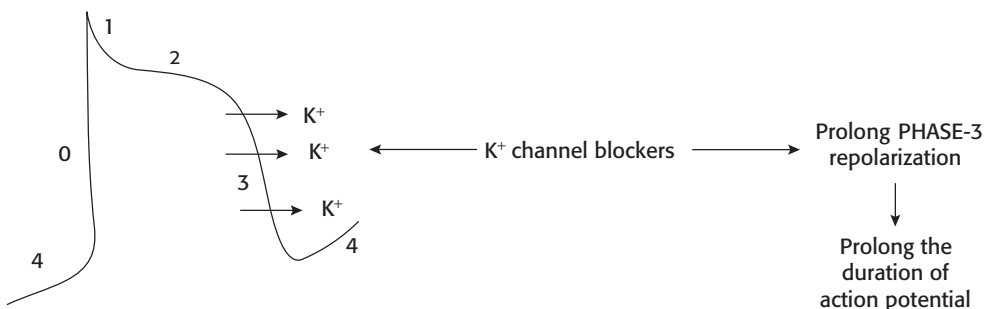


Fig. 3.15 Mechanism of action of amiodarone and other class III drugs.

Pharmacokinetics. Following oral administration, bioavailability is about 30%. It can be given intravenously for rapid effect. It accumulates in fat, muscle, lungs, liver, skin, etc. and has a long half-life (1–2 months). Amiodarone is metabolized in the liver.

Uses. Amiodarone has a broad spectrum of antiarrhythmic actions with a low incidence of *torsades de pointes*. It is effective in the treatment of atrial and ventricular arrhythmias. It is used to maintain normal sinus rhythm in atrial fibrillation and prevent recurrent ventricular tachycardia.

Adverse Effects

1. **CVS:** Hypotension (due to vasodilation), CHF and exacerbation of arrhythmias.
2. **Neurological:** Peripheral neuropathy.
3. **Respiratory:** Pulmonary fibrosis.
4. **GIT:** Nausea and hepatitis.
5. **Photosensitivity and pigmentation** of the skin.
6. **Eye:** Corneal deposits.
7. **Thyroid:** Hypothyroidism and hyperthyroidism; hence TSH, T₃ and T₄ levels should be monitored during long-term therapy with amiodarone.
(Note the 'Ps'.)

Drug Interactions. Amiodarone × β -blockers/verapamil: Additive depressant action on SA and AV node lead to SA block and AV block, respectively.

Amiodarone inhibits the renal clearance of digoxin, thereby increases serum digoxin levels.

It also increases concentration of quinidine and procainamide. Amiodarone potentiates the anticoagulant effect of warfarin.

Note: Amiodarone is a broad-spectrum antiarrhythmic agent with long half-life, causes multiple effects, may cause wide range of adverse effects, but does not require dose adjustment in patients with hepatic or renal disease.

Dofetilide and *ibutilide* are pure potassium channel blockers. They are useful in maintaining normal sinus rhythm in atrial fibrillation.

Class IV: Calcium Channel Blockers

Verapamil. It blocks both activated and inactivated L-type Ca²⁺ channels – depresses calcium-mediated depolarization. Verapamil decreases conduction velocity and increases refractory period of AV node; useful in

- Terminating re-entry involving AV node (PSVT)
- Reducing ventricular rate in atrial flutter and fibrillation

It decreases slope of phase 4 depolarization in the SA node (bradycardia) and in the ectopic foci.

Pharmacokinetics, adverse effects, drug interactions and uses are discussed on pp. 117–119.

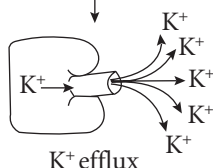
Diltiazem. All features are similar to verapamil but it is comparatively less potent than verapamil.

Miscellaneous Agents

Adenosine. It is a purine nucleoside that is administered as a rapid i.v. bolus for rapid control of PSVT. The duration of action of adenosine is less than 1 minute because it is rapidly transported into red blood corpuscles (RBCs) and endothelial cells.

Mechanism of Action

Intravenous adenosine
↓
Binds to specific G-protein-coupled adenosine (A_1)-receptors
↓
Activates ACh-sensitive K^+ channels in the atrium, SA and AV nodes



- Hyperpolarization and decreased automaticity of SA node → decreased sinus rate
- Reduced duration of action potential in atria, reduced excitability
- Increased refractory period and slowing of conduction in AV node

Adenosine also decreases Ca^{2+} currents in AV node → depresses AV node.

Through its action on AV node, it blocks re-entry of impulses involving AV node and terminates an attack of PSVT. It is the preferred drug for rapid termination of PSVT because it has:

- (1) High efficacy.
- (2) A short duration of action – adverse effects last for brief period.
- (3) Minimal negative inotropic action.

Adverse Effects and Disadvantages. These include **Asystole**, **Bronchospasm**, **Chest pain**, **Dyspnoea**, **Expensive**, **Flushing**, **Hypotension** and **Headache**. Side effects are transient due to its short duration of action.

Drug Interactions. **Adenosine × methylxanthines:** Methylxanthines antagonize the effects of adenosine by blocking its receptors.

Adenosine × dipyridamole: Dipyridamole inhibits uptake of adenosine into cells and potentiates its actions.

Magnesium. Intravenous magnesium sulphate is useful in *torsades de pointes* (even if serum magnesium levels are normal). It can be used in digitalis-induced arrhythmias if there is hypomagnesaemia.

Atropine. It is used in the treatment of bradycardia and AV block due to vagal overactivity (e.g. acute MI and digitalis toxicity). It has vagolytic action.

Isoprenaline. Intravenous isoprenaline can be used in second degree or complete heart block following acute MI.

Some of the important drugs used in different types of cardiac arrhythmias are listed in [Table 3.6](#).

Table 3.6 ■ Drugs used in cardiac arrhythmias

Type of arrhythmia	Drugs used
Paroxysmal supraventricular tachycardia (PSVT)	• Adenosine • Verapamil • Esmolol
Atrial fibrillation	• Amiodarone • Verapamil • Propafenone • Digoxin
Atrial flutter	• Esmolol • Verapamil • Amiodarone • Propafenone
Ventricular tachycardia	• Amiodarone • Propranolol
Ventricular fibrillation	• Amiodarone • Lignocaine

Hypolipidaemic Drugs

PH1.31

Lipoproteins are necessary for the transport of cholesterol and triglycerides in blood. The plasma lipoproteins are chylomicrons, very low density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL). The HDL transports excess cholesterol from the peripheral tissues to liver for excretion in bile. In hyperlipoproteinaemias, the concentration of lipoproteins in plasma is elevated.

Normal plasma lipid levels (mg/dL)

Total cholesterol _____	<200
LDL cholesterol _____	<100
HDL cholesterol _____	
Men _____	>40
Women _____	>50
Triglycerides _____	<150

Hyperlipoproteinaemias may be *primary* (genetically determined) or *secondary* to diabetes mellitus, hypothyroidism, chronic renal disease, chronic alcoholism and drugs (β -blockers, corticosteroids, diuretics, oral contraceptives, etc.).

Classification of Hypolipidaemic Drugs

1. **HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors (statins):** Atorvastatin, pravastatin, pitavastatin, lovastatin, simvastatin, rosuvastatin.
2. **Fibric acid derivatives:** Gemfibrozil, fenofibrate, bezafibrate, clofibrate.
3. **Bile acid-binding resins:** Cholestyramine, colestipol, colesevelam.
4. **Inhibitor of triglyceride production and lipolysis:** Nicotinic acid.
5. **Dietary cholesterol absorption inhibitor:** Ezetimibe.

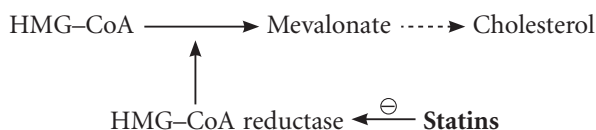
6. **Monoclonal antibodies:** Alirocumab, evolocumab.

7. **Others:** Gugulipid, omega-3 fatty acids.

HMG-CoA Reductase Inhibitors (Statins)

Statins are the most effective agents for treating hyperlipidaemias. They include rosuvastatin, atorvastatin, pravastatin, pitavastatin, lovastatin and simvastatin.

Mechanism of Action. Statins competitively inhibit HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis (i.e. the conversion of HMG-CoA to mevalonate). This results in a decrease in blood LDL and VLDL levels. ↓Cholesterol synthesis → ↑LDL receptors in the liver → ↑LDL uptake and degradation. Thus, statins are very effective in reducing plasma LDL levels. They also reduce triglycerides (TGs) and increase HDL-cholesterol levels in plasma. Statins (those with short half-life) are usually given once daily in the evening because cholesterol biosynthesis occurs mainly at night. Atorvastatin and rosuvastatin have long half-life.



Among statins, lovastatin and simvastatin are prodrugs and are converted to their active forms in the liver. All statins undergo extensive first-pass metabolism in liver and most of the absorbed dose is excreted in bile. Pitavastatin is the most potent statin.

Other actions of statins – atherosclerotic plaque stability, antioxidant and antiinflammatory actions; decrease platelet aggregation; increase production of NO by endothelium. These actions also contribute to the cardioprotective effects of statins.

Adverse Effects*

1. Hepatotoxicity (dose related) with increase in serum transaminase levels.
2. Headache and sleep disturbances.
3. Myopathy: Muscle pain and weakness with raised plasma creatinine kinase activity. Rhabdomyolysis may occur.
4. Gastrointestinal: Anorexia, nausea, vomiting and diarrhoea.

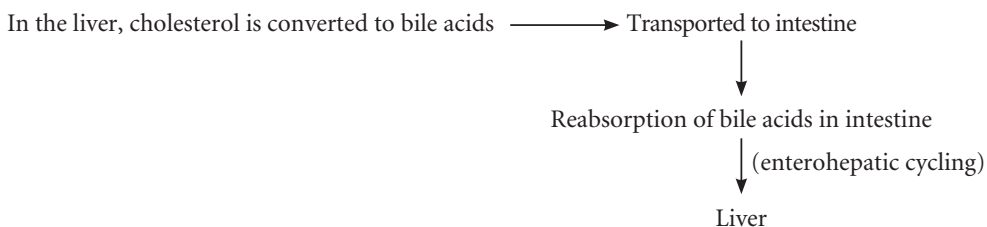
Statins should not be taken in pregnancy.

Uses. Statins are the commonly used drugs for treatment of primary hyperlipidaemias with increased LDL and cholesterol levels. They are also used in secondary hyperlipidaemias due to diabetes or nephrotic syndrome.

Drug interactions. Statins × cyclosporine/erythromycin/azoles: They inhibit the metabolism of statins (except pravastatin) → increased blood levels of statins → increased incidence of myopathy.

Bile Acid-Binding Resins (Bile Acid Sequestrants)

They are cholestyramine, colestipol and colesevelam.



*Mnemonic for adverse effects of statins – HMG

Resins bind bile acids in the gut and interrupt their enterohepatic circulation, thus promote conversion of cholesterol to bile acids in the liver. They also stimulate the formation of hepatic LDL-receptors which take up more LDL-cholesterol from the circulation. The net effect is reduction of LDL levels with little effect on HDL level.

Uses. Resins are used in the treatment of primary hypercholesterolaemia. Resins should be taken orally with water or fruit juice before meals. They are also useful to relieve itching of obstructive jaundice.

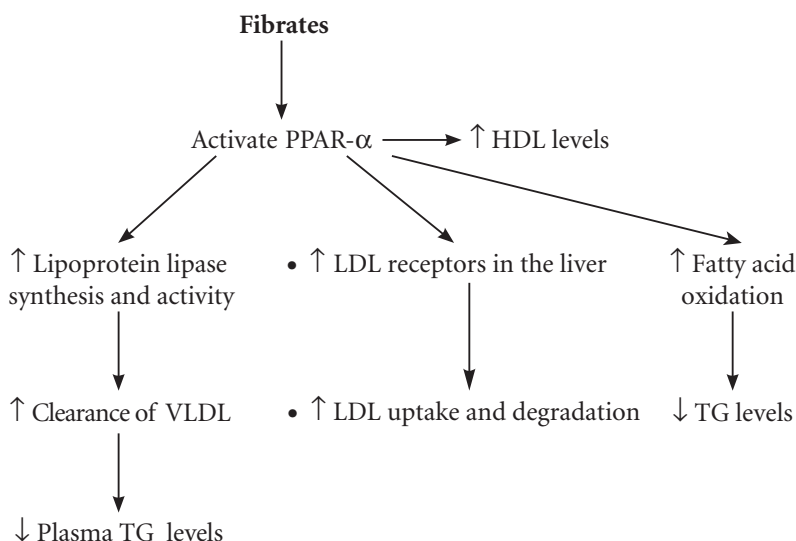
Adverse Effects. Since resins are not absorbed through the gut, systemic adverse effects are not seen. The common adverse effects are unpalatability, bloating, nausea, flatulence and constipation. They also bind to other drugs (thiazides, digitalis, anticoagulants, propranolol, thyroxine, fat-soluble vitamins, etc.) in the gut and reduce their absorption.

Fibrates (Fibric Acid Derivatives)

Some of the fibrates are clofibrate, gemfibrozil, bezafibrate and fenofibrate.

They activate peroxisome proliferator-activated receptor α (PPAR- α) present in the liver, adipose tissue and skeletal muscle.

Mechanism of Action



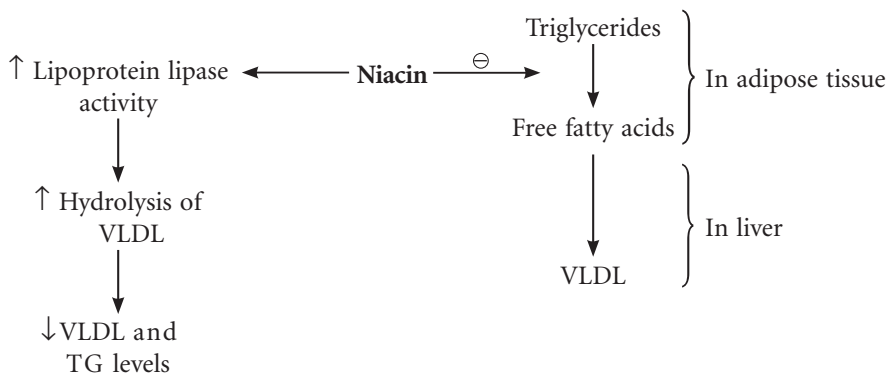
Fibrates also inhibit TG synthesis in liver. Fibrates are well absorbed after oral administration, widely distributed and concentrated in liver, kidney and intestine; metabolized in liver and excreted in urine.

Uses. Fibrates are very effective in type III hyperlipoproteinaemia and severe hypertriglyceridaemia.

Adverse Effects. Fibrates are usually well tolerated. The common side effects are dyspepsia, nausea, vomiting, diarrhoea, muscle pain and headache. There is an increased incidence of gallstones with clofibrate. Fibrates can potentiate the effect of warfarin and oral hypoglycaemic drugs. Use of combination of gemfibrozil with statins increases the risk of myopathy. (Fenofibrate/bezafibrate can be combined with statins.) Fibrates are contraindicated in pregnancy.

Nicotinic Acid (Niacin)

Niacin is a B-complex vitamin. In larger doses, it has a hypolipidaemic effect; it reduces plasma TGs, VLDL, LDL, and increases HDL levels. Lipoprotein(a) is decreased.



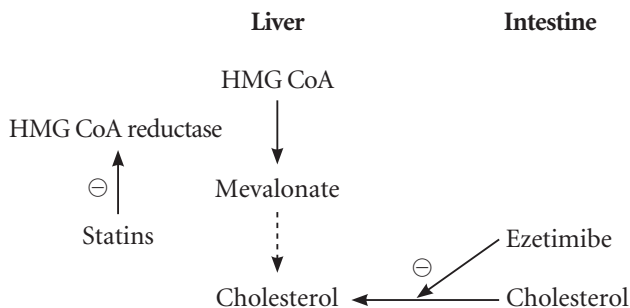
Niacin inhibits lipolysis in adipose tissue, thus reduces hepatic TG and VLDL synthesis. Niacin is the most effective agent for increasing HDL level. It should be started at a low dose and taken with meals to delay absorption. Niacin is mainly used in patients with both hypertriglyceridaemia and low HDL levels.

Adverse Effects. The main adverse effects are flushing and dyspepsia. Flushing (prostaglandin-mediated vasodilation) can be reduced either by combining niacin with aspirin or starting with a low dose of niacin. The other side effects are itching, headache, hyperpigmentation, peptic ulcer, hyperuricaemia, hepatotoxicity, hyperglycaemia and rarely atrial arrhythmias. Niacin may potentiate the effects of warfarin. It is contraindicated in pregnancy.

Ezetimibe (Cholesterol Absorption Inhibitor)

It inhibits the absorption of dietary and biliary cholesterol in the intestine. It reduces LDL cholesterol.

Uses. Ezetimibe is mainly used with a statin, when the LDL levels are not controlled with statin monotherapy. The combination of ezetimibe and statins has a beneficial effect. Statins inhibit cholesterol synthesis but increase intestinal cholesterol absorption. Ezetimibe inhibits intestinal cholesterol absorption but increases cholesterol synthesis. Combined use of these drugs prevents the increase in cholesterol absorption caused by statins and increased cholesterol synthesis caused by ezetimibe. The combination produces an additive reduction in LDL cholesterol levels.



Adverse Effects. There is a low incidence of hepatic dysfunction with ezetimibe.

Monoclonal antibodies: Alirocumab and evolocumab inhibit antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9), thus increasing hepatic clearance of LDL and lower plasma LDL levels. They are used as adjunct to statin therapy. They are administered parenterally; should be avoided in pregnancy and lactating mother.

Omega-3 Fatty Acids

They are effective in the treatment of hypertriglyceridaemia. They are present in fish oils. Omega-3 fatty acids activate PPAR- α and reduce triglyceride levels. Nausea and belching may occur.

Plasma Volume Expanders

PH1.25

Plasma volume expanders are solutions used for temporary maintenance of blood volume in emergency situations. Colloidal solutions are commonly used as plasma expanders. Colloidal solutions have a high-molecular weight and exert a high oncotic pressure. The important colloidal solutions are human albumin, dextran, polyvinylpyrrolidone, hetastarch and degraded gelatin polymer.

Requirements of an Ideal Plasma Expander

1. The oncotic pressure, pH and viscosity of the solution should be same as that of plasma.
2. It should be retained in the circulation for an adequate period.
3. It should be nonpyrogenic and nonantigenic.
4. It should be stable and cheap.
5. It should not interfere with blood grouping and cross-matching of blood.

HUMAN ALBUMIN

Albumin and plasma protein fraction, which are prepared from pooled human plasma are the commonly used plasma expanders. About 25 g of 5% albumin is osmotically equivalent to about 500 mL of fresh frozen plasma. This is valuable to restore colloidal osmotic pressure in hypovolaemic states, such as burns, haemorrhage and surgical procedures. There is no risk of hepatitis B/hepatitis C/HIV infections. It can cause hypersensitivity and overloading of circulation. Plasma protein fraction contains globulin in addition to albumin.

DEXTRAN

Dextran is a water-soluble glucose polymer produced by bacteria grown on sucrose media. It is available as dextran 40 and dextran 70. Dextrans increase plasma colloidal oncotic pressure similar to that of plasma proteins.

Dextran 40. It is given by i.v. infusion as a 10% solution. It acts rapidly but has a relatively transient effect. It reduces blood viscosity and inhibits sludging of RBCs in small blood vessels. It also improves microcirculation.

Dextran 70. It is infused as a 6% solution and is preferred when small volumes are required. It produces less expansion of plasma volume than dextran 40. It has a longer duration of action because of its slow renal excretion. It also reduces blood viscosity and inhibits sludging of RBCs.

Dextrans may induce rouleaux formation and this interferes with blood grouping and cross-matching. They can interfere with platelet function and coagulation. The adverse effects of dextran are hypersensitivity, fever, joint pain, urticaria, hypotension, bronchospasm and rarely anaphylactic reaction. The anticoagulant effect of heparin may be enhanced by dextran.

HYDROXYETHYL STARCH OR HETASTARCH

It is derived from starch. It acts by increasing oncotic effect similar to that of plasma albumin. It is stable at room temperature and has a long duration of action. Hetastarch has also been used to improve granulocyte harvesting during leukapheresis procedures. It does not interfere with blood grouping and cross-matching of blood. The adverse effects are flu-like syndrome (headache, fever and myalgia), itching, urticaria and anaphylactoid reactions.

DEGRADED GELATIN POLYMER

Gelatin is a polypeptide obtained from ox collagen. Gelatin in degraded form is used commonly as a plasma expander. It exerts oncotic pressure similar to that of albumin. Plasma expansion lasts for about 12 hours. It does not interfere with blood grouping and cross-matching of blood. Gelatin has also been used as a haemostatic in surgical procedures. It can cause flushing, itching, urticaria, bronchospasm and hypotension. Severe reactions can occur with urea-linked gelatin, e.g. Haemaccel.

POLYVINYLPYRROLIDONE

This is a synthetic polymer. It interferes with blood grouping and cross-matching of blood. It binds to drugs such as insulin and penicillin in circulation and reduces their effect. It is rarely used now.

Uses of Plasma Expanders. They are used to maintain circulating volume in burns, haemorrhage, severe trauma, etc. when blood/plasma is not readily available.

Contraindications. They are severe anaemia, bleeding disorders, CHF, renal failure and hepatic failure.

Summary of selected important cardiovascular drugs

Drug	Actions	Cardiovascular uses	Adverse effects
ACE inhibitors (captopril, enalapril, lisinopril, ramipril)	Inhibit the conversion of angiotensin I to angiotensin II resulting in: • Dilatation of arterioles $\rightarrow \downarrow$ PVR $\rightarrow \downarrow$BP, $\downarrow$ afterload $\rightarrow \uparrow$CO $\rightarrow$ improve tissue perfusion • Decrease in aldosterone production $\rightarrow$ decreases Na^+, water retention $\rightarrow \downarrow$ preload • Venodilatation $\rightarrow \downarrow$ preload • Inhibit the degradation of bradykinin • Stimulate synthesis of vasodilating PGs • Retard/reverse cardiac hypertrophy and remodelling	• Hypertension • Congestive cardiac failure • Acute myocardial infarction <i>Other uses:</i> Diabetic nephropathy Scleroderma renal crisis	Cough, angioedema, proteinuria, teratogenic effect, hypotension (first dose phenomenon), neutropenia, rashes, itching, and loss of taste sensation (Mnemonic: CAPTOPRIL)
Angiotensin receptor blockers (ARBs) (losartan)	• They competitively block binding of angiotensin II to AT_1 receptors on heart, peripheral vasculature and kidney • ARBs produce effects similar to those of ACE inhibitors	• Hypertension • Congestive cardiac failure • Myocardial infarction <i>Other uses:</i> Diabetic nephropathy	Headache, hypotension, rashes, nausea, vomiting and teratogenic effects; cough and angioedema less likely than ACE inhibitors
Direct renin inhibitor (aliskiren)	By inhibiting renin, decreases levels of angiotensin I and angiotensin II	Hypertension	Headache, hypotension, diarrhoea, angioedema and abdominal pain

β-Adrenergic blockers

- Decrease HR, FOC, CO → ↓ BP
- Decrease renin release → ↓ BP
- Decrease sympathetic outflow from CNS → ↓ BP
- Depress SA node and AV nodal activity
- Decrease conduction in atria and AV node
- Decrease automaticity of ectopic foci
- Increase refractory period of AV node
- Decrease cardiac work, thus reduce O₂ requirement of myocardium

- Hypertension
- Prophylaxis of stable angina
- Cardiac arrhythmias (AF, AFI, PSVT)
- Myocardial infarction
- Congestive cardiac failure (metoprolol, nebivolol, carvedilol)
- Pheochromocytoma
- Hypertrophic obstructive cardiomyopathy
- Dissecting aortic aneurysm

Bradycardia, AV block, bronchospasm, sedation, fatigue, muscular weakness, mental depression and masking of symptoms and signs of hypoglycaemia especially in diabetes patients

Other uses:

- Glaucoma (timolol, levobunolol, betaxolol, etc.)
- Hyperthyroidism
- Prophylaxis of migraine
- Essential tremors
- Acute anxiety states
- Alcohol withdrawal

Calcium channel blockers (CCBs)**Dihydropyridines**
(nifedipine, amlodipine)

- Potent arteriolar dilators → ↓ PVR → ↓ BP, ↓ Afterload
- Coronary vasodilatation
- Minimal direct effect on the heart
- Reflex tachycardia and palpitation are commonly seen with nifedipine; this can be minimized by using sustained release preparation or counteracted by adding a β-blocker

- Stable angina
- Variant angina
- Unstable angina
- Hypertension
- Raynaud's phenomenon
- Subarachnoid haemorrhage (nimodipine)

Postural hypotension, palpitation, reflex tachycardia, ankle oedema, flushing, fatigue, sedation

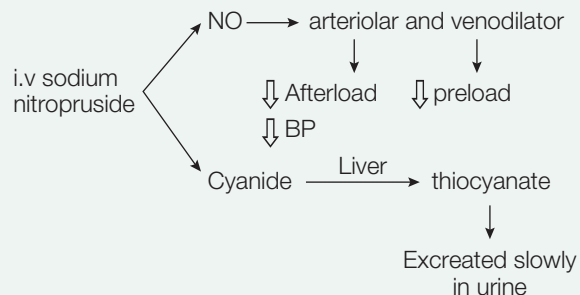
Other uses:

Premature labour

Continued

Summary of selected important cardiovascular drugs—cont'd

Drug	Actions	Cardiovascular uses	Adverse effects
Phenylalkylamine (verapamil)	- Has predominant action on heart than arterioles - Decreases HR - Decreases FOC - Depresses SA node and slows AV conduction - Prolongs effective refractory period - Less potent coronary and peripheral vasodilator than DHPs	- Prophylaxis of stable angina - Variant angina - Unstable angina - Hypertension - Supraventricular arrhythmias (AF, AFI, PSVT) - Hypertrophic cardiomyopathy <i>Other uses:</i> Prophylaxis of migraine	Constipation, bradycardia, AV block, oedema, may precipitate CCF in patients with low cardiac reserve
Benzothiazepine (diltiazem)	- Dilates peripheral and coronary arteries – less marked than nifedipine and verapamil - Decreases force of contraction - Decreases HR - Depresses SA node and slows AV conduction	- Prophylaxis of stable angina - Variant angina - Hypertension - Supraventricular arrhythmias (AF, AFI, PSVT)	Headache, hypotension, bradycardia, oedema, AV block
Organic nitrates (Nitroglycerin, isosorbide mononitrate, isosorbide dinitrate)	- Mainly venodilators →↓ Preload - Arteriolar dilators →↓ Afterload - Dilate large coronary vessels and collateral vessels - Have no direct action on heart	- Acute attack of angina - Prophylaxis of angina (isosorbide mononitrate orally, isosorbide dinitrate orally, nitroglycerin-oral SR preparation/ointment/disc/patch) - Variant angina (nitrates) - Unstable angina (NTG: s.l./i.v.) - Acute MI (NTG: i.v. infusion) - Acute heart failure (i.v. NTG) - Hypertensive emergency (i.v. NTG infusion) <i>Other uses:</i> - Biliary colic - Cyanide poisoning	Headache, postural hypotension, reflex tachycardia, palpitation, flushing, weakness, syncope, methaemoglobinaemia, nitrate tolerance and dependence

Sodium nitroprusside

- Hypertensive emergencies
- Severe heart failure

Anorexia, nausea, vomiting, fatigue; disorientation, psychosis and convulsion (due to cyanide)

Potassium channel openers

Minoxidil
Diazoxide

}

Arteriolar dilators → ↓ PVR → ↓ BP

Hypertensive emergencies (were used)

Reflex tachycardia, Na⁺ and water retention, headache, flushing

Other uses:

Topical minoxidil – promotes hair growth in male type of baldness

Angina

Headache, hypotension, flushing, palpitation, nausea, vomiting, ulcers in the mouth

Nicorandil

Arterial dilator } ↓ Afterload
Venodilator } ↓ Preload

Releases NO

Cardioprotective effect

Dilates coronary vessels and improves blood flow to myocardium

Hydralazine

Arteriolar dilator → ↓ PVR → ↓ BP

Hypertension

Headache, hypotension, flushing, angina, MI and immunological reactions (lupus syndrome) may occur

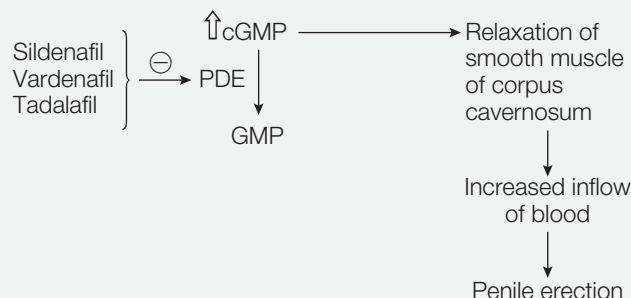
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Summary of selected important cardiovascular drugs—cont'd

Drug	Actions	Cardiovascular uses	Adverse effects
α-Adrenergic blockers			
Phenoxybenzamine	Nonselective, irreversible α-receptor blocker; also inhibits the reuptake of NA into the adrenergic nerve endings In addition, it blocks histamine (H_1), cholinergic and serotonergic receptors - Mainly venodilator - Arteriolar dilator } $\downarrow$ Preload, $\downarrow$ Afterload, $\downarrow$ BP	Pheochromocytoma - Preoperatively - Inoperable cases	Postural hypotension, tachycardia, palpitation, diarrhoea, nasal stuffiness, giddiness, impotence
Phentolamine	Nonselective, reversible α-blocker; has rapid onset but short duration of action on i.v. administration - Mainly venodilator - Arteriolar dilator } $\downarrow$ BP	- i.v. Phentolamine is used: - To control hypertensive crisis due to clonidine withdrawal, cheese reaction - To control hypertensive episodes intraoperatively during surgery of pheochromocytoma - Local infiltration to prevent tissue necrosis due to extravasation of α agonists.	Tachycardia, palpitation, arrhythmias, angina and MI
Prazosin	Selective α_1 -receptor blockers	Hypertension	
Terazosin	Arteriolar and venodilators; arteriolar dilatation is more marked	Benign prostatic hyperplasia (BPH)	First dose postural hypotension, nasal congestion, tachycardia, impaired ejaculation, impotence
Doxazosin			
Tamsulosin	Uroselective α_1 (α_{1A}) receptor blocker	Benign prostatic hyperplasia (BPH)	Retrograde ejaculation, postural hypotension

Phosphodiesterase 5 inhibitors (PDE-5)

Sildenafil
Vardenafil
Tadalafil



- Pulmonary hypertension (sildenafil)
- Erectile dysfunction

Headache, flushing, hypotension, colour vision defects and diarrhoea

Adenosine

i.v. adenosine, acts rapidly, depresses SA node, atrial and AV nodal conduction

To terminate an attack of PSVT

Assystole, **B**ronchospasm, **C**hest pain, **D**yspnoea, **E**xpensive, **F**lushing, hypotension, headache

Amiodarone

Has broad spectrum of antiarrhythmic activity

- Blocks potassium channels
- Blocks Na^+ channel in inactivated state
- Has β -adrenergic blocking action
- Has calcium channel-blocking action

Ventricular and supraventricular arrhythmias

Hypotension, peripheral neuropathy, pulmonary fibrosis, nausea, hepatitis, photosensitivity, corneal deposits, hypothyroidism and hyperthyroidism

Lignocaine

- Class IB antiarrhythmic drug
- Blocks Na^+ channels in the inactivated (predominantly) and the active states
- Decreases automaticity of ectopic foci
- Depresses conduction in depolarized tissue
- Action potential duration is usually unaffected or may be shortened

- Ventricular arrhythmias associated with MI, digitalis toxicity and cardiac surgery
- As local anaesthetic

Headache, drowsiness, nystagmus, blurred vision, confusion, convulsion

Continued

Summary of selected important cardiovascular drugs—cont'd

Drug	Actions	Cardiovascular uses	Adverse effects
Digoxin	• Has direct and indirect actions on the heart • Direct action by inhibiting $\text{Na}^+ \text{K}^+ \text{-ATPase}$ • Indirect action by stimulating vagus (vagomimetic effect) • Has positive inotropic effect • Decreases heart rate by direct and indirect actions • At therapeutic concentration, decreases automaticity, prolongs ERP and decreases conduction velocity in AV node • At higher concentration, increases automaticity in cardiac tissue by direct action as well as by increasing sympathetic activity	• CCF (low output failure) • Atrial fibrillation • Atrial flutter • PSVT	• Cardiac: Digitalis can cause any type of arrhythmias • Ventricular premature beats, pulsus bigeminy, ventricular tachycardia, AV block, atrial tachycardia, atrial fibrillation, atrial flutter, severe bradycardia, anorexia, nausea, vomiting, headache, confusion, restlessness, disorientation, weakness, visual disturbance
Endothelin (ET) receptor antagonists Bosentan, macitentan (block ET_A and ET_B receptors); Ambresentan (blocks ET_A receptors)	Vasodilation mainly pulmonary, coronary, renal blood vessels	Pulmonary arterial hypertension	Increase in hepatic aminotransferases, headache, flushing due to vasodilation
Pentoxifylline	Decreases viscosity of blood, improves microcirculation	Peripheral vascular disease	Nausea, vomiting
Cilostazol	Inhibits PDE 3, causes vasodilation and inhibits platelet aggregation	Peripheral vascular disease	Nausea, vomiting, headache

Renal Pharmacology

Kidney is mainly a regulatory organ; it also has excretory function. The functional unit of kidney is nephron. Each kidney contains about 1 million nephrons. The functions of kidney are as follows:

1. *Regulatory*: Acid–base, fluid and electrolyte balance.
2. *Excretory*: Excretion of nitrogenous waste products.
3. *Hormonal*: Activation of vitamin D, production of renin and erythropoietin.

Mechanism of Urine Formation

PH1.24

It consists of the following steps

1. Glomerular filtration
2. Tubular reabsorption
3. Active tubular secretion

Urine formation begins with glomerular filtration. The volume of fluid filtered is about 180 L/day, of which more than 99% gets reabsorbed in the renal tubules; urine output is about 1–1.5 L/day. After filtration, fluid traverses in the renal tubules. The tubular fluid contains Na^+ , K^+ , Cl^- , HCO_3^- , amino acids, glucose, etc.

PROXIMAL CONVOLUTED TUBULE: SITE 1 (Fig. 4.1)

Most of the filtered Na^+ is actively reabsorbed; chloride is reabsorbed passively along with sodium. Carbonic anhydrase plays an important role in the reabsorption of bicarbonate and secretion of H^+ . The Na^+-H^+ exchanger in the proximal tubular cells transports Na^+ from the lumen into the cell and H^+ from the cell into the tubular fluid. Potassium, glucose, amino acids, etc. are also reabsorbed in proximal convoluted tubule (PCT). Proportionately, water also gets reabsorbed, so tubular fluid in the PCT remains isotonic.

DESCENDING LIMB OF LOOP OF HENLE

The descending limb is impermeable to Na^+ and urea and highly permeable to water. Hence, fluid in this segment becomes hypertonic.

THICK ASCENDING LIMB OF LOOP OF HENLE: SITE 2 (Fig. 4.1)

The thick ascending limb is impermeable to water but highly permeable to Na^+ and Cl^- . Active reabsorption of sodium and chloride occurs by $\text{Na}^+-\text{K}^+-2\text{Cl}^-$ cotransporter. This is selectively blocked by loop diuretics. Ca^{2+} and Mg^{2+} are also reabsorbed at this site. The tubular fluid becomes hypotonic.

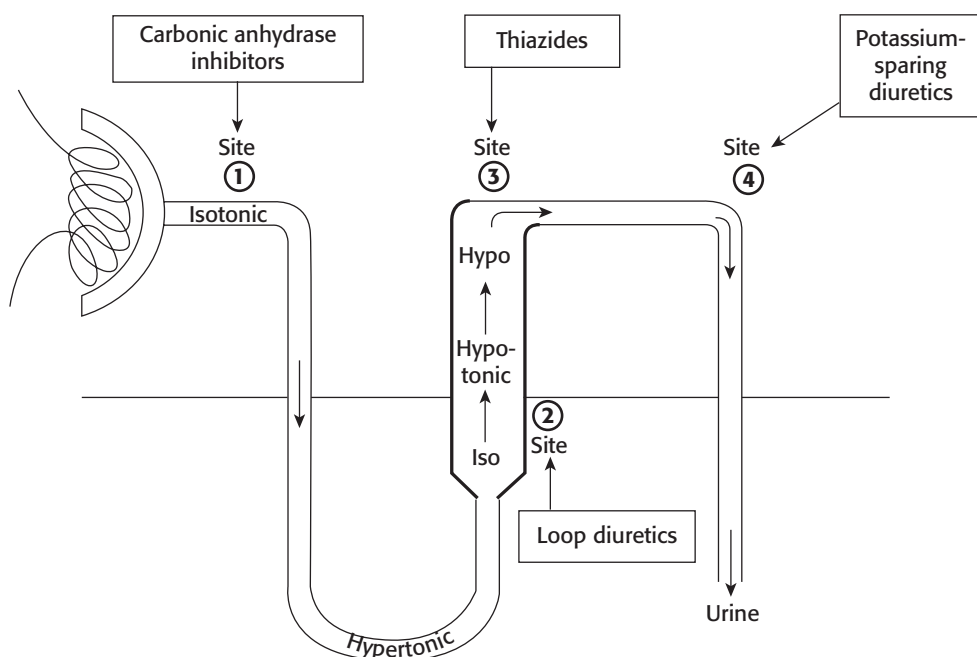


Fig. 4.1 Nephron showing various sites of action of diuretics.

EARLY DISTAL TUBULE: SITE 3 (Fig. 4.1)

It is impermeable to water, but sodium and chloride are reabsorbed with the help of Na^+-Cl^- symporter. This is blocked by thiazides.

LATE DISTAL TUBULE AND COLLECTING DUCT: SITE 4 (Fig. 4.1)

Sodium is actively reabsorbed; chloride and water diffuse passively. Exchange of Na^+-K^+ , H^+ ions occur. The Na^+-K^+ exchange is under the influence of aldosterone (aldosterone promotes Na^+ absorption and K^+ depletion). Absorption of water in collecting duct (CD) is under the influence of antidiuretic hormone (ADH). In the absence of ADH, the CD becomes impermeable to water and a large amount of dilute urine is excreted. Normally, H^+ ions present in urine convert NH_3 to NH_4^+ , which is excreted.

Diuretics

PH1.24

Diuretics are drugs that promote excretion of Na^+ and water in urine.

CLASSIFICATION ACCORDING TO PRIMARY SITE OF ACTION IN THE NEPHRON (Fig. 4.1)

- 1. Drugs acting at PCT (site 1)**
Carbonic anhydrase inhibitor: Acetazolamide.
- 2. Drugs acting at thick ascending limb of loop of Henle (site 2)**
Loop diuretics: Furosemide, bumetanide, torsemide.
- 3. Drugs acting at early distal tubule (site 3)**
Thiazides: Chlorothiazide, hydrochlorothiazide, hydroflumethiazide, bendroflumethiazide, benzthiazide.

Thiazide-related diuretics: Chlorthalidone, indapamide, metolazone, xipamide.

4. Drugs acting at late distal tubule and CD (site 4)

Aldosterone antagonists: Spironolactone, eplerenone.

Direct inhibitors of renal epithelial Na^+ channels: Amiloride, triamterene.

5. Drugs acting on entire nephron (main site of action is loop of Henle)

Osmotic diuretics: Mannitol, glycerol, isosorbide.

Carbonic Anhydrase Inhibitors

Mechanism of Action. CO_2 and H_2O from the tubular lumen diffuse into tubular cell where H_2CO_3 is formed under the influence of carbonic anhydrase (Fig. 4.2). Carbonic acid (H_2CO_3) dissociates into H^+ and HCO_3^- . The bicarbonate ions are transported into the interstitium. The H^+ ions exchange with luminal Na^+ (Na^+-H^+ antiporter). In the lumen, H^+ ions combine with the filtered HCO_3^- to form H_2CO_3 . The H_2CO_3 dissociates into CO_2 and H_2O with the help of carbonic anhydrase, which is present near the brush border. The main site of action of acetazolamide is proximal tubule (site 1); it also acts in the CD. Acetazolamide, by inhibiting carbonic anhydrase enzyme, prevents the formation of H^+ ions. Thus, Na^+-H^+ exchange is prevented. Na^+ is excreted along with HCO_3^- in urine.

In the DCT, increased Na^+-K^+ exchange leads to loss of K^+ . The net effect is loss of Na^+ , K^+ and HCO_3^- in urine resulting in alkaline urine.

Uses. Acetazolamide is not used as diuretic because of its low efficacy. It is used in the following:

1. Glaucoma: Carbonic anhydrase inhibitors decrease intraocular pressure (IOP) by reducing the formation of aqueous humour. Acetazolamide is used in acute congestive glaucoma by oral and i.v. routes. Topical carbonic anhydrase inhibitors (dorzolamide and brinzolamide) are used in chronic simple glaucoma (see p. 58).
2. To alkalinize urine in acidic drug poisoning.
3. Acute mountain sickness: Acetazolamide can be used both for symptomatic relief and prophylaxis of acute mountain sickness. It is better to administer it prophylactically. The beneficial effect may be due to a decrease in pH and formation of cerebrospinal fluid.

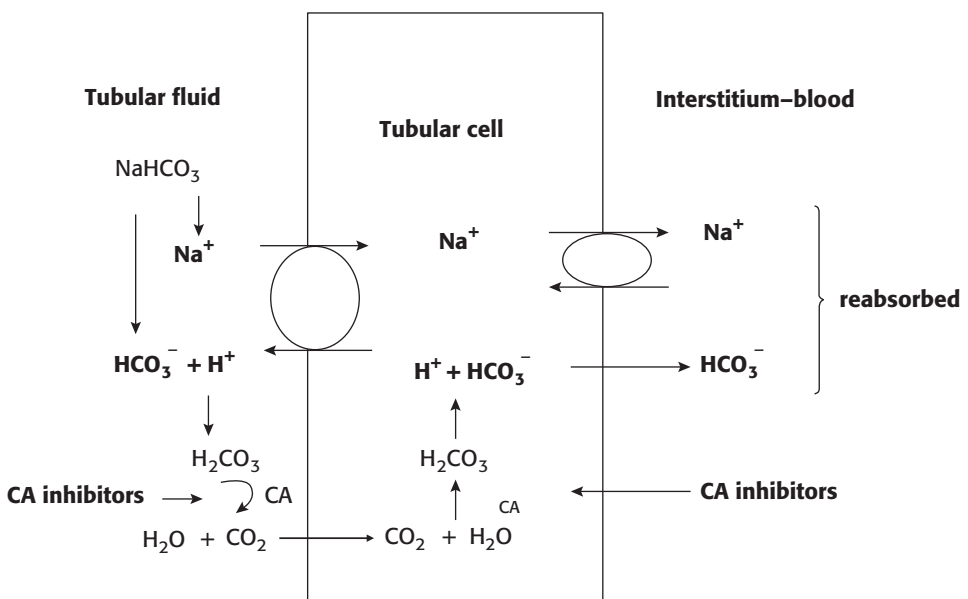


Fig. 4.2 Mechanism of action of carbonic anhydrase (CA) inhibitors.

4. **Miscellaneous:** As an adjuvant in familial periodic paralysis – benefit results from lowering of pH.

Adverse Effects. These include hypersensitivity reactions (skin rashes, fever, nephritis, etc.), drowsiness, paraesthesia, hypokalaemia, metabolic acidosis, headache and renal stones.

Contraindications

1. **Liver disease:** Hepatic coma may be precipitated in patients with cirrhosis due to decreased excretion of NH_3 in alkaline urine.
2. **Chronic obstructive pulmonary disease (COPD):** Worsening of metabolic acidosis is seen in patients with COPD.

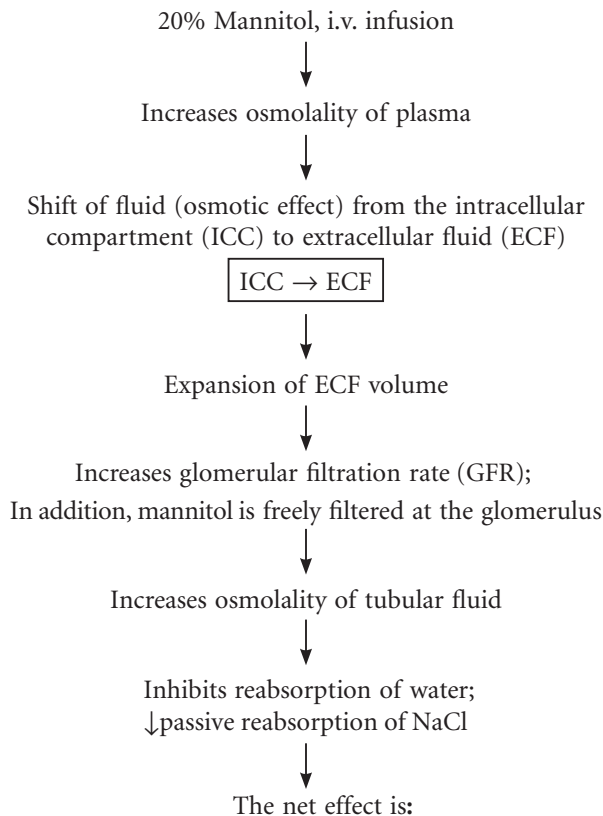
Osmotic Diuretics

These include mannitol, glycerol and isosorbide.

Mannitol: Mannitol is administered intravenously. It is neither metabolized in the body nor significantly reabsorbed from the renal tubules. It is pharmacologically inert and is freely filtered at the glomerulus.

Glycerol: Glycerol can be used orally to reduce IOP in acute congestive glaucoma.

Mechanism of Action. Osmotic diuretics draw water from tissues by osmotic action. This results in increased excretion of water and electrolytes. Their site of action is in the loop of Henle and proximal tubule.



- Increase in urine volume
- Increased urinary excretion of Na^+ , K^+ , Ca^{2+} , Mg^{2+} , Cl^- , HCO_3^- and PO_4^{3-}

Uses of Osmotic Diuretics

1. Mannitol is used to reduce the elevated intracranial tension (ICT) following head injury or tumour. It draws fluid from the brain into the circulation by osmotic effect, thus lowering ICT.
2. Mannitol 20% (i.v.), glycerol 50% (oral) and isosorbide (oral) are used to reduce the elevated IOP in acute congestive glaucoma. They draw fluid from the eye, by osmotic effect, into blood – IOP is decreased.
3. Mannitol is used to prevent acute renal shutdown in shock, cardiovascular surgery, haemolytic transfusion reactions, etc.
4. Mannitol is useful to maintain the osmolality of ECF after dialysis.

Adverse Effects

1. Too rapid and too much quantity of i.v. mannitol can cause marked expansion of ECF volume which can lead to pulmonary oedema.
2. Headache, nausea and vomiting may occur.
3. Glycerol can cause hyperglycaemia.

Contraindications. Mannitol is contraindicated in congestive cardiac failure (CCF) and pulmonary oedema because it expands ECF volume by increasing the osmolality of extracellular compartment and increases the load on heart, thus, aggravating the above condition. Other contraindications are chronic oedema, anuric renal disease, active intracranial bleeding and acute tubular necrosis.

Loop Diuretics (High-Ceiling Diuretics)

The important loop diuretics are furosemide, bumetanide and torsemide.

Mechanism of Action (Fig. 4.3). Site of action is the thick ascending limb of loop of Henle (site 2). Loop diuretics bind to luminal side of $\text{Na}^+-\text{K}^+-2\text{Cl}^-$ cotransporter and block its function. There is an increased excretion of Na^+ and Cl^- in urine. The tubular fluid reaching DCT contains large amount of Na^+ . Hence, more Na^+ exchanges with K^+ , leading to K^+ loss. Furosemide has weak carbonic anhydrase-inhibiting activity, hence, increases the excretion of HCO_3^- . Loop diuretics also increase the excretion of Ca^{2+} and Mg^{2+} .

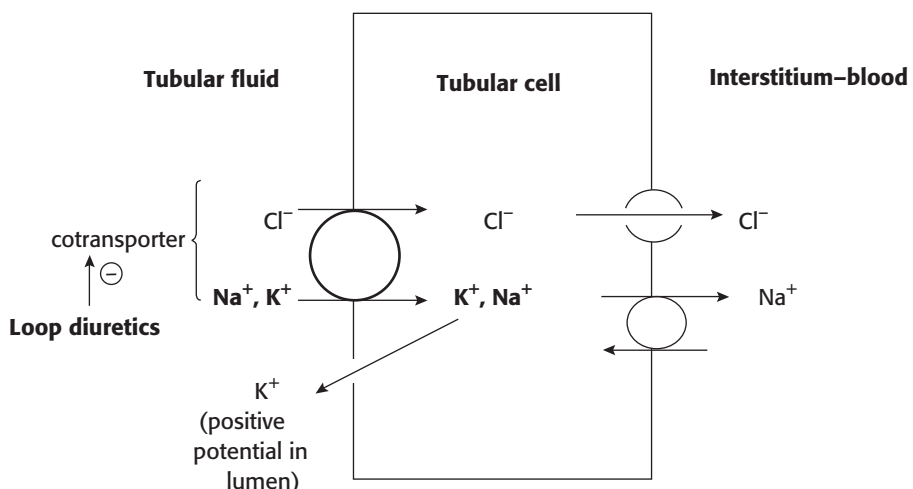


Fig. 4.3 $\text{Na}^+-\text{K}^+-2\text{Cl}^-$ cotransport system in thick ascending limb and the mechanism of action of loop diuretics.

Loop diuretics are called *high-ceiling diuretics* because they are highly efficacious – have maximal Na^+ excreting capacity when compared to thiazides and potassium-sparing diuretics.

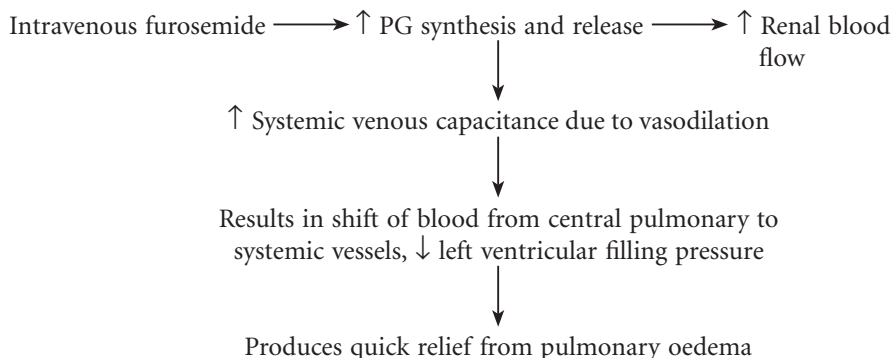
The loop diuretics are rapidly absorbed through the gastrointestinal tract. Furosemide and bumetanide are administered by oral, i.v. and i.m. routes. Torsemide is given orally and intramuscularly. Furosemide has a rapid onset of action within 2–5 minutes of i.v.; 10–20 minutes after i.m. and 30–40 minutes after oral administration. The duration of action of furosemide is short (2–4 hours).

Bumetanide and Torsemide

- Can be administered orally and parenterally.
- Are more potent than furosemide.
- Have better oral bioavailability than furosemide.
- Torsemide: Longer half-life than others.

Therapeutic Uses of Loop Diuretics

1. During the initial stages of renal and cardiac oedema, loop diuretics are preferred. They are also useful in hepatic oedema – vigorous diuresis should be avoided to prevent hepatic coma.
2. Intravenous furosemide, along with isotonic saline (to prevent volume depletion), is used in hypercalcaemia as it promotes the excretion of Ca^{2+} in urine.
3. Acute pulmonary oedema – loop diuretics act in the following way:



4. Loop diuretics may be used in cerebral oedema but i.v. mannitol is the preferred drug.
5. Hypertension: Loop diuretics can be used in hypertension associated with CCF/renal failure and in hypertensive emergencies. Furosemide is not preferred in uncomplicated primary hypertension because of its short duration of action.
6. To prevent volume overload, furosemide is administered during blood transfusion.

Adverse Effects of Loop Diuretics

1. **Electrolyte disturbances** are the common adverse effects seen with loop diuretics. They are as follows:
 - (a) **Hypokalaemia:** It is the most important adverse effect. It can cause fatigue, muscular weakness and cardiac arrhythmias. Hypokalaemia can be prevented by using a combination of loop diuretic with potassium-sparing diuretic. It can be treated by K^+ supplementation.
 - (b) **Hyponatraemia:** Loop diuretics can cause depletion of sodium from the body.

- (c) **Hypocalcaemia and hypomagnesaemia:** These are due to the increased urinary excretion of Ca^{2+} and Mg^{2+} , respectively. Hypomagnesaemia can predispose to cardiac arrhythmias.
- 2. The **metabolic disturbances** include:
 - (a) **Hyperglycaemia:** This can occur due to decreased insulin secretion.
 - (b) **Hyperuricaemia:** These drugs decrease the renal excretion of uric acid and may precipitate attack of gout.
 - (c) **Hyperlipidaemia:** They increase plasma triglycerides and LDL cholesterol levels.
- 3. **Ototoxicity** manifests as deafness, vertigo and tinnitus and is due to damage to hair cells in inner ear. The symptoms are usually reversible on stoppage of therapy. The risk of ototoxicity is increased in patients with renal impairment and in those receiving other ototoxic drugs like cyclosporine and aminoglycosides.
- 4. **Hypersensitivity:** Skin rashes, eosinophilia, photosensitivity, etc. may occur.

Drug Interactions

- 1. **Furosemide/thiazides × digoxin:** These diuretics cause hypokalaemia which increases the binding of digoxin to Na^+ - K^+ -ATPase leading to digoxin toxicity.
- 2. **Furosemide × aminoglycosides:** Both are ototoxic drugs and cause enhanced toxicity when used together.
- 3. **Furosemide × nonsteroidal anti-inflammatory drugs (NSAIDs):** NSAIDs inhibit PG synthesis and block prostaglandin-mediated haemodynamic changes of loop diuretics. Chronic use of NSAIDs leads to Na^+ and H_2O retention and diminish the antihypertensive effect of loop diuretics/thiazides.
- 4. **Furosemide/thiazides × lithium:** Diuretics cause hyponatraemia resulting in compensatory increase in reabsorption of sodium and lithium in the PCT leading to lithium toxicity.
- 5. **Furosemide/chlorthalidone × amiloride:** Furosemide/chlorthalidone causes hypokalaemia, whereas amiloride conserves potassium. The combination of these diuretics does not alter plasma potassium levels; also improves diuretic response – synergistic effect.

Thiazides (Benzothiadiazides) and Thiazide-Related Diuretics

Thiazides are medium-efficacy diuretics.

Mechanism of Action. Thiazides inhibit Na^+ - Cl^- symport in early distal tubule (site 3) and increase Na^+ and Cl^- excretion (Fig. 4.4). There is increased delivery of Na^+ to late distal tubule. Hence, there is increased exchange of Na^+ - K^+ which results in K^+ loss. Some of the thiazides also have weak carbonic anhydrase inhibitory action and increase HCO_3^- loss. Therefore, there is a net loss of Na^+ , K^+ , Cl^- , HCO_3^- in urine. Unlike loop diuretics, thiazides decrease Ca^{2+} excretion.

Pharmacokinetics. Thiazides are administered orally. They have long duration of action and are excreted in urine.

Uses

- 1. **Hypertension:** Thiazides are used in the treatment of essential hypertension (see p. 104).
- 2. **Oedema:** Thiazides are used in combination with loop diuretics in severe CHF. They are not very effective in hepatic oedema. Most thiazides, except metolazone, are not effective when glomerular filtration rate (GFR) is low.
- 3. **Hypercalciuria:** Thiazides are used in calcium nephrolithiasis as they reduce the urinary excretion of calcium.
- 4. **Diabetes insipidus (DI)** (see p. 163).

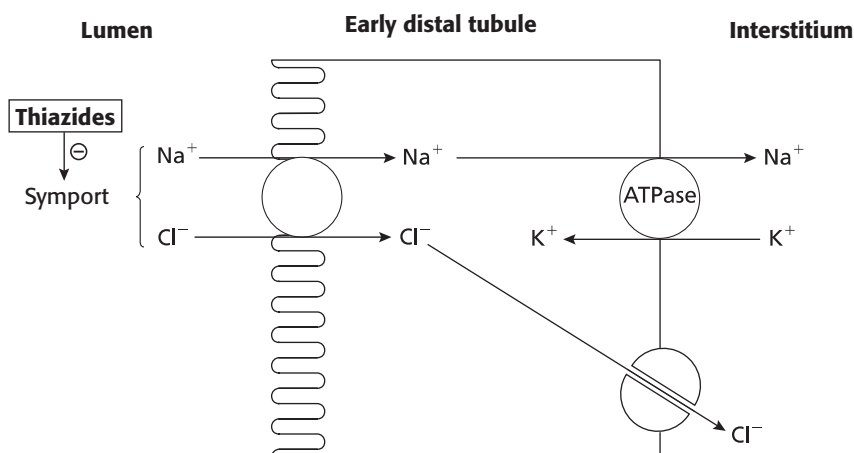


Fig. 4.4 NaCl reabsorption in early distal tubule and mechanism of action of thiazides. (Source: Adapted from Alfred Gilman Sr. and Louis S. Goodman: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 13th edition, McGraw Hill, 2018.)

Adverse Effects

1. Thiazides cause electrolyte disturbances which include hypokalaemia, hyponatraemia, hypomagnesaemia and hypercalcaemia.
 - (a) Hypokalaemia is more common with thiazides than loop diuretics because of their long duration of action.
 - (b) Hypercalcaemia is due to decreased urinary excretion of Ca^{2+} .
2. The metabolic disturbances are similar to that of loop diuretics – hyperglycaemia, hyperlipidaemia and hyperuricaemia.
3. They may cause impotence; hence, thiazides are not the preferred antihypertensives in young males.
4. Others: Skin rashes, photosensitivity, gastrointestinal disturbances like nausea, vomiting and diarrhoea can occur. Diuretics should be avoided in pregnancy as they reduce placental perfusion by decreasing blood volume which can cause fetal death.

Thiazide-Related Diuretics

Chlorthalidone is a frequently used thiazide-related diuretic in hypertension as it has a long duration of action. Indapamide and metolazone are longer acting than thiazides. They are used in hypertension. Metolazone and xipamide are also used for treatment of oedema. Metolazone can be used in severe renal failure.

Potassium-Sparing Diuretics

Aldosterone Antagonists

Spirolactone. Spirolactone is an aldosterone antagonist. It is a synthetic steroid and structurally related to aldosterone.

Aldosterone enters the cell and binds to specific mineralocorticoid receptor (MR) in the cytoplasm of late distal tubule and CD cells (site 4). The hormone receptor complex (MR–AL) enters the cell nucleus, where it induces synthesis of aldosterone-induced proteins (AIPs). The net effect of AIPs is to retain sodium and excrete potassium (Fig. 4.5).

Spirolactone competitively blocks the MR and prevents the formation of AIPs. Therefore, spirolactone promotes Na^+ excretion and K^+ retention. Spirolactone

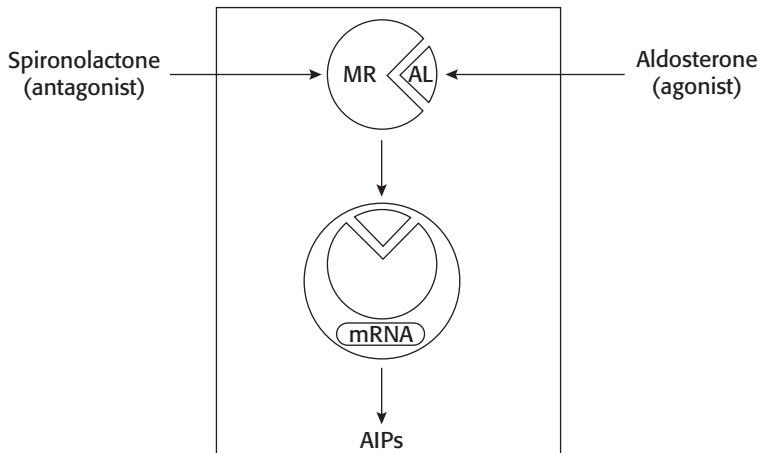


Fig. 4.5 The mechanism of action of spironolactone. MR, mineralocorticoid receptor; AL, aldosterone; AIPs, aldosterone-induced proteins.

is most effective when circulating aldosterone levels are high. It also increases Ca^{2+} excretion.

Pharmacokinetics. Spironolactone is administered orally, gets partly absorbed and is highly bound to plasma proteins; extensively metabolized in liver and forms active metabolite, canrenone, which has a long plasma half-life.

Uses

1. In oedematous conditions associated with secondary hyperaldosteronism (CCF, hepatic cirrhosis and nephrotic syndrome).
2. CCF: Spironolactone is often used in moderate-severe heart failure because it blocks the effects of aldosterone. It prevents hypokalaemia, ventricular remodeling and retards the progression of the disease.
3. Spironolactone is often used with thiazides/loop diuretics: Serum potassium level is maintained and antihypertensive efficacy is enhanced.
4. Resistant hypertension due to primary hyperaldosteronism (Conn's syndrome).

Adverse Effects. Hyperkalaemia is the major adverse effect of aldosterone antagonists. The risk is greater in patients with renal disease or in those receiving ACE inhibitors, ARBs, β -blockers, NSAIDs, etc.

The other adverse effects include nausea, vomiting, diarrhoea, peptic ulcer, drowsiness, mental confusion, menstrual disturbances, gynaecomastia and decreased libido (antiandrogenic effect).

Drug Interaction

- **ACE inhibitors $\times$ spironolactone:** Dangerous hyperkalaemia can occur.

Eplerenone, an **aldosterone antagonist**, is more selective for MR. Hence, it is less likely to cause gynaecomastia. Its therapeutic uses include hypertension and chronic heart failure.

Amiloride and Triamterene (Directly Acting Drugs). Both are directly acting potassium-sparing diuretics. They directly block Na^+ channels in the luminal membrane of the cells of late distal tubule and CD. The net effect of these drugs is to increase Na^+ excretion

and retain potassium; hence, these are called potassium-sparing diuretics. They are administered orally. Amiloride inhibits H^+ secretion in CD – acidosis can occur. Both are low-efficacy diuretics. Amiloride is more potent and longer acting than triamterene. Triamterene is extensively metabolized while amiloride is excreted unchanged in urine.

Uses

- 1. Potassium-sparing diuretics are used with thiazides/loop diuretics for the treatment of hypertension. The combination therapy increases diuretic and anti-hypertensive effects of thiazides or loop diuretics. They also correct hypokalaemia due to thiazides/loop diuretics.
- 2. Amiloride is used for the treatment of lithium-induced nephrogenic DI. It blocks lithium transport through Na^+ channels in the cells of the CD.
- 3. Amiloride (aerosol) improves mucociliary clearance in patients with cystic fibrosis.

Adverse Effects. These include hyperkalaemia, nausea, vomiting, diarrhoea, headache, dizziness, muscle cramps, etc.

Various diuretics with their site and mechanism of action are shown in [Table 4.1](#).

Diuretic Resistance

It is said to occur when the oedema does not respond to a diuretic. Decrease in diuretic response usually due to long-term therapy is common with thiazides; can also occur with loop diuretics. Prolonged use of diuretics causes some pathological changes in the renal tubules, which may lead to development of diuretic resistance.

Diuretic resistance is mainly seen in elderly patients due to age-related declined renal function.

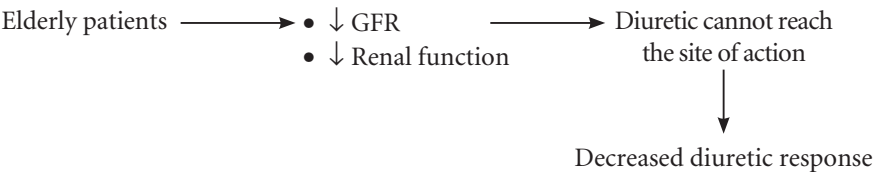


Table 4.1 ■ Diuretics with their site and mechanism of action

Diuretics	Site of action	Mechanism of action	Efficacy
Acetazolamide	PCT	Carbonic anhydrase inhibitor	Low
Loop diuretics	Thick ascending limb of loop of Henle	Inhibit $Na^+-K^+-2Cl^-$ cotransport	High
Thiazides	Early distal tubule	Inhibit Na^+-Cl^- symport	Medium
Potassium-sparing diuretics	DT and CD	• Aldosterone antagonists (spironolactone and eplerenone) • Directly acting (amiloride and triamterene)	Low
Mannitol	Loop of Henle and PCT	Osmotic effect	High

Other factors include chronic renal failure, liver diseases, heart failure and co-administration of diuretic with a NSAID. Resistance can be overcome to some extent by:

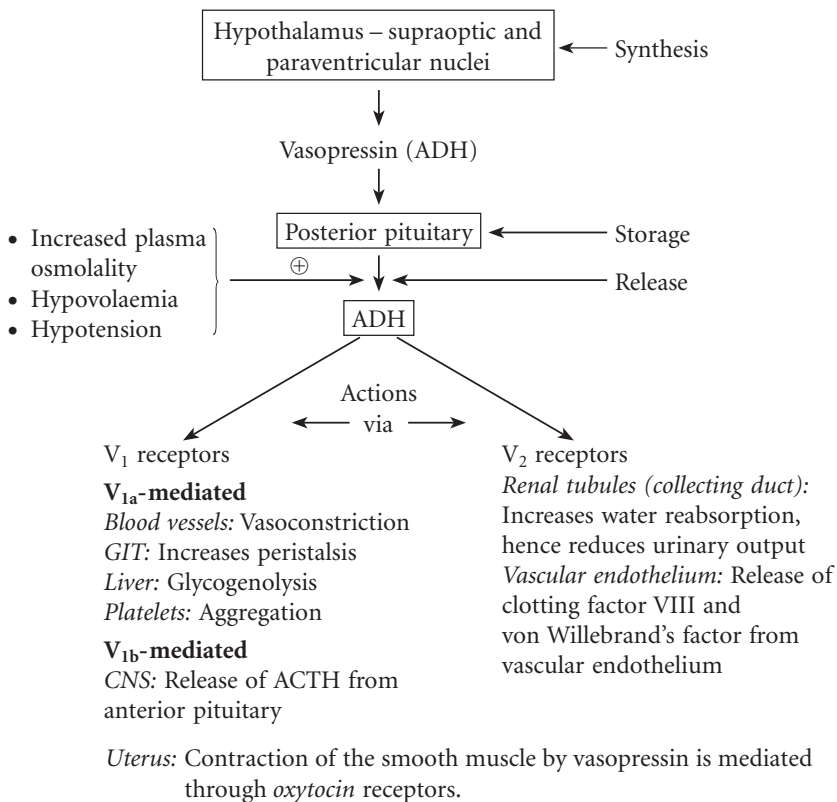
- i) Increasing the dose and frequency of a diuretic
- ii) Taking diuretic before meal
- iii) Salt-restricted diet
- iv) Proper bed rest
- v) Use of combination of diuretics

Antidiuretics

PH1.24

VASOPRESSIN

Vasopressin (AVP or arginine vasopressin; ADH) is a peptide hormone synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and stored in posterior pituitary.



Both V₁ and V₂ are G-protein-coupled receptors.

Synthetic AVP is a peptide, hence is not effective orally. It is administered by i.v., i.m., s.c. or intranasal routes and has a short duration of action (Table 4.2).

Vasopressin Analogues

Desmopressin: It is a selective V₂ receptor agonist and is more potent than vasopressin as an antidiuretic. It has negligible vasoconstrictor action. It is administered by oral, nasal and parenteral routes.

Table 4.2 ■ **Vasopressin and its analogues with their potency (relative to arginine vasopressin)**

Drug	Antidiuretic effect (V_2)	Vasopressor effect (V_1)	Preparations	Duration of action (hours)
Arginine vasopressin	1	1	i.m., i.v., s.c. and nasal	3–4
Desmopressin	12	0.004	s.c., i.v., nasal and oral	8–12
Lypressin	0.8	0.6	i.m., s.c. and i.v.	4–6
Terlipressin	-	+	i.v.	4–6

Lypressin: It acts on both V_1 and V_2 receptors. It is less potent but longer acting than vasopressin. It is administered parenterally.

Terlipressin: It is a prodrug of vasopressin with selective V_1 action. It is administered intravenously.

Uses of Vasopressin Analogues

1. For emergency control of bleeding oesophageal varices: Terlipressin is preferred to vasopressin because it is safer. It **acts on V_1 receptor** → constricts mesenteric blood vessels → decreases blood flow to portal vessels → reduces pressure in the varices → stops bleeding.
2. Vasopressin may be used before abdominal radiography to expel intestinal gas by **acting on V_1 receptor** in the intestine.
3. Central (neurogenic) DI – desmopressin (**V_2 -mediated action**) is the drug of choice (see Table 4.3). It is not effective in nephrogenic DI.
 - (a) Haemophilia and von Willebrand's disease – Desmopressin, administered intravenously, controls bleeding by promoting release of factor VIII and von Willebrand's factor (by **acting on V_2 receptors**).
 - (b) Primary nocturnal enuresis – Administration of desmopressin at bedtime reduces nocturnal urine volume (**V_2 -mediated action**).

DI is a condition characterized by excretion of large volume of dilute urine either due to decreased secretion of ADH from the neurohypophysis (neurogenic DI) or due to an inadequate renal tubular response to ADH (nephrogenic DI).

Adverse Effects of Vasopressin Analogues

1. Nausea, vomiting, diarrhoea, belching and abdominal cramps.
2. Backache is due to uterine contraction.
3. Vasopressin can precipitate an attack of angina by constricting coronary blood vessels. Hence, it is contraindicated in patients with hypertension and coronary artery disease.
4. Intranasal administration of desmopressin may cause local irritation and ulceration.
5. Fluid retention and hyponatraemia can occur (V_2 -mediated). It should not be given to patients with acute renal failure.

Syndrome of Inappropriate Antidiuretic Hormone (SIADH) Secretion

In SIADH, there is impaired water excretion along with hyponatraemia and low plasma osmolality due to inappropriate ADH secretion. The conditions that may be associated

Table 4.3 ■ Types of diabetes insipidus with their treatment

Central DI (neurogenic or pituitary)	Nephrogenic DI (renal DI)
- There is decreased ADH secretion. - Drug of choice: Desmopressin (since it has more selective action on V_2 receptors). Route: Intranasal, oral, s.c., i.v. Duration of therapy: Usually lifelong. <i>Desmopressin</i> has more selective action on V_2 receptors, hence preferred in central DI. Its action on V_2 receptors in the cells of collecting duct results in a decrease in urine volume. - Other drugs, if patient does not tolerate desmopressin. <i>Chlorpropamide</i> (oral antidiabetic agent): Increases antidiuretic effect of ADH on kidney. <i>Carbamazepine</i> (antiepileptic drug): Decreases urine volume in high doses. <i>Thiazides</i> are also useful in central DI as they decrease urine volume; they act paradoxically in these patients.	- ADH levels are normal, but renal tubules (CD) fail to respond to ADH. - Drugs: <i>Thiazides</i>: Exact mechanism of action of thiazides in DI is not clear. Thiazides probably act by depleting sodium and ECF volume which results in a compensatory increase in proximal tubular reabsorption of Na^+ and water leading to a decrease in urine volume. Moreover, action of thiazides in the early distal tubule results in the formation of less dilute urine. <i>Amiloride</i> is the preferred drug for lithium-induced nephrogenic DI as it blocks lithium and sodium entry into the renal epithelial cells. <i>Indomethacin</i> reduces urine volume in nephrogenic DI by inhibiting renal prostaglandin synthesis.

with syndrome of inappropriate secretion of antidiuretic hormone (SIADH) are head injury, meningitis, brain tumour, pulmonary diseases, etc. The signs and symptoms of SIADH may include anorexia, nausea, vomiting, muscle cramps, lethargy, coma, convulsions and death.

Treatment

1. Restricted water intake
2. Drugs

Demeclocycline is useful in the treatment of SIADH. It inhibits the action of ADH in the CD.

Vasopressin receptor antagonists like conivaptan (V_{1a}/V_2) and tolvaptan (V_2 selective) are useful in the treatment of SIADH. They are nonpeptides which are administered intravenously and orally, respectively.

Drugs Acting on Central Nervous System

Neurotransmitters and Central Nervous System

PH1.19

NEUROTRANSMITTERS IN CNS

Neurotransmitters in the central nervous system (CNS) could be inhibitory, excitatory or both (Fig. 5.1).

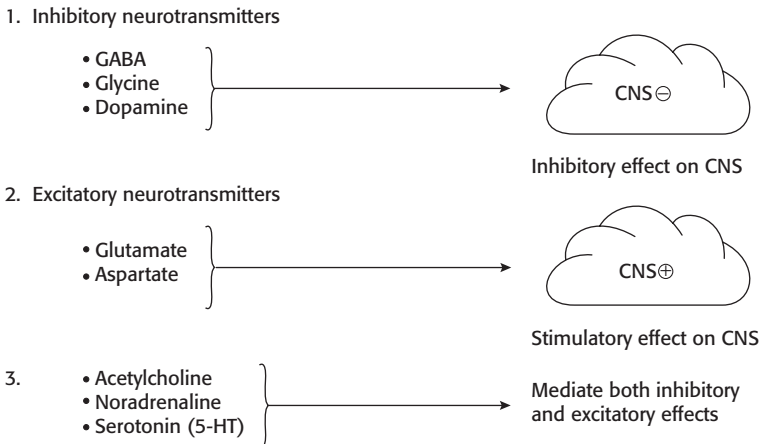


Fig. 5.1 Neurotransmitters in CNS. GABA, γ -Aminobutyric acid; 5-HT, 5-hydroxytryptamine; $\ominus$, inhibition; $\oplus$, stimulation.

Inhibitory Postsynaptic Potential (IPSP)

When an inhibitory transmitter binds and interacts with specific receptors on postjunctional membrane, the membrane permeability to K^+ or Cl^- increases (Fig. 5.2).

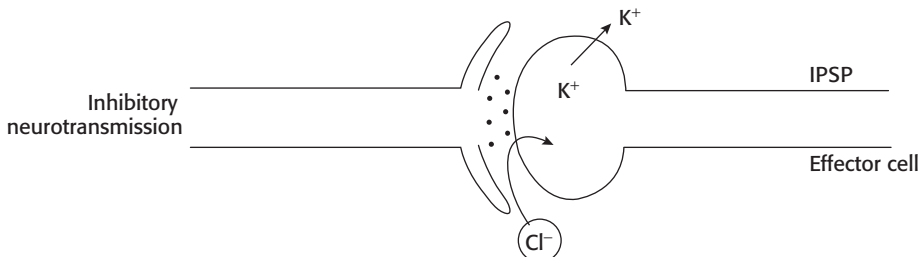


Fig. 5.2 K^+ ions move out and Cl^- ions move in, resulting in hyperpolarization (IPSP). (Source: Alfred Gilman Sr. and Louis S. Goodman: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th edition, p. 183, Fig. 8.3, McGraw Hill, 2018.)

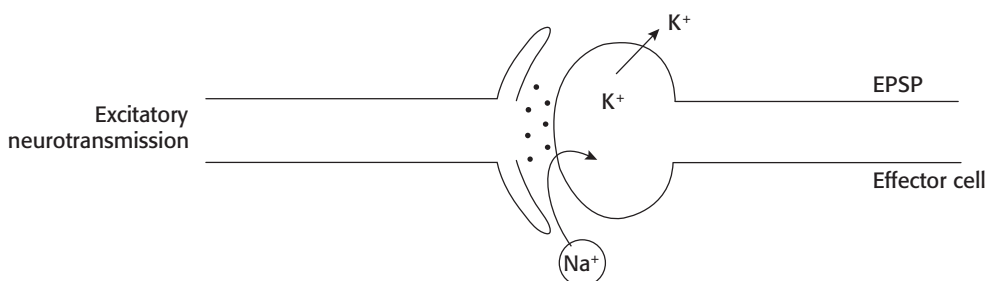


Fig. 5.3 Na⁺ ions move in (Na⁺ influx), resulting in depolarization followed by K⁺ efflux (EPSP). (Source: Alfred Gilman Sr. and Louis S. Goodman: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th edition, p. 183, Fig. 8.3, McGraw Hill, 2018.)

Excitatory Postsynaptic Potential (EPSP)

When an excitatory neurotransmitter binds and interacts with specific receptors on postjunctional membrane, the membrane permeability to cations increases (Fig. 5.3).

Manifestations of CNS Depression and Stimulation

CNS depression	CNS stimulation
Drowsiness	Excitement
Sedation	Euphoria
Hypnosis	Insomnia
Disorientation	Tremors
Confusion	Twitching
Unconsciousness	Convulsions
Coma	Coma
Death	Death

Sedatives and Hypnotics

PH1.19

Sedative is a drug that reduces excitement and calms the person. Hypnotic is a drug that produces sleep-resembling normal sleep.

SLEEP

The phases of sleep include nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep is divided into the following stages: 0, 1, 2, 3 and 4. Normally, about 50% of sleep time is spent in stage 2. Slow wave sleep includes stages 3 and 4. REM sleep constitutes about 30% of the sleep time and lasts for 5–30 minutes in each cycle of sleep.

Types of sleep disorders and their treatment are given in Table 5.1.

CLASSIFICATION OF SEDATIVES AND HYPNOTICS

- 1. Benzodiazepines (BZDs)*:** Diazepam, lorazepam, clonazepam, clobazam, chlordi-azepoxide, oxazepam, temazepam, midazolam, alprazolam, triazolam, flurazepam, nitrazepam.

*Mnemonic to recollect BZDs: Sleep aids – De Lux C₃OT, MAT, FaN.

Table 5.1 ■ Types of sleep disorder and their treatment

Sleep disorder	Treatment
Lack of sleep (insomnia) • Transient insomnia (<3 days) • Short-term insomnia (3 days–3 weeks) • Long-term insomnia (>3 weeks)	Sedatives and hypnotics
Hypersomnia (narcolepsy)	Amphetamine, modafinil, amitriptyline
Nocturnal enuresis (bed wetting)	Tricyclic antidepressants

2. Barbiturates:

Long acting: Phenobarbitone

Short acting: Pentobarbitone

Ultrashort acting: Thiopentone, methohexitone

3. Nonbenzodiazepine hypnotics: Zolpidem, zopiclone, zaleplon, eszopiclone

4. Others: Melatonin, ramelteon suvorexant

Benzodiazepines

PH1.19

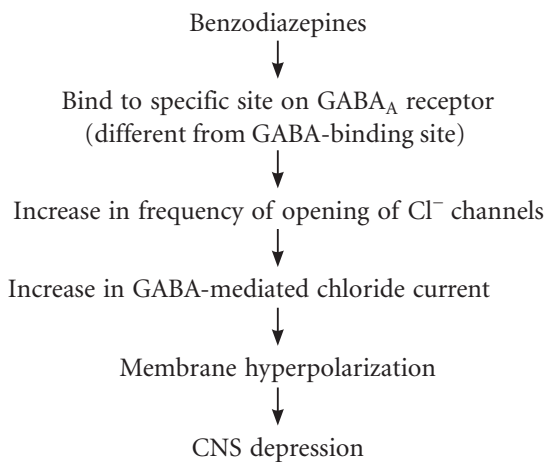
All BZDs have a benzene ring fused to a seven-membered diazepine ring.

Sites of Action

Midbrain (ascending reticular formation), limbic system, brain stem, etc.

Mechanism of Action

BZDs facilitate action of GABA – they potentiate inhibitory effects of GABA.



BZDs have no GABA-mimetic action.

Pharmacological Actions and Therapeutic Uses

1. **Sedation and hypnosis:** BZDs decrease time required to fall asleep (sleep latency). The total sleep time is increased. They shorten all stages of NREM sleep except stage 2, which is prolonged. The duration of REM sleep is usually decreased. BZDs reduce night awakenings and produce refreshing sleep.

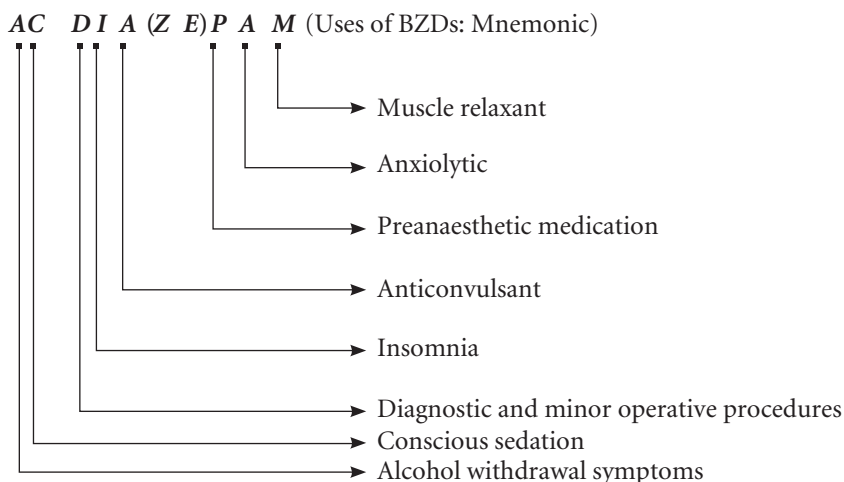
At present, BZDs are preferred to barbiturates for treatment of short-term insomnia because:

- They have a wide therapeutic index.
- They cause near-normal sleep; less rebound phenomena on withdrawal.
- They produce minimal hangover effects (headache and residual drowsiness on waking).
- They cause minimal respiratory depression.
- They are less likely to cause tolerance and dependence when used for short period.
- They have no enzyme-inducing property; hence, drug interactions are less.
- They have a specific BZD-receptor antagonist, flumazenil, for the treatment of overdosage.

Long-term use of BZDs for insomnia is not recommended because of development of tolerance, dependence and hangover effects; but these drugs are ideal for occasional use by air travellers, shift workers, etc.

2. **Anticonvulsant:** Diazepam, lorazepam, clonazepam, clobazam, etc. have anticonvulsant effect. Intravenous (i.v.) diazepam/lorazepam is used to control life-threatening seizures in status epilepticus, tetanus, drug-induced convulsions, febrile convulsions, etc. Clonazepam is used in the treatment of absence seizures.
3. **Diagnostic (endoscopies) and minor operative procedures:** i.v. BZDs are used because of their sedative–amnesic–analgesic and muscle relaxant properties.
4. **Preanaesthetic medication and general anaesthesia (GA):** These drugs are used as preanaesthetic medication because of their sedative–amnesic and anxiolytic effects. Hence, the patient cannot recall the perioperative events later. i.v. diazepam, lorazepam, midazolam, etc. are combined with other CNS depressants to produce GA.
5. **Antianxiety (anxiolytic) effect:** Some of the BZDs (diazepam, oxazepam, alprazolam, lorazepam, chlordiazepoxide, etc.) have selective antianxiety action at low doses. The anxiolytic effect is due to their action on limbic system. Tolerance to antianxiety action of BZDs develops only on prolonged use.
6. **Muscle relaxant (centrally acting):** They reduce skeletal muscle tone by inhibiting polysynaptic reflexes in the spinal cord. The relaxant effect of BZDs is useful in spinal injuries, tetanus, cerebral palsy and to reduce spasm due to joint injury or sprain.
7. **To treat alcohol-withdrawal symptoms:** Long-acting BZDs, such as chlordiazepoxide and diazepam are used.
8. **Conscious sedation:** See p. 181.

The above-mentioned uses/actions can be summarized as follows:



Pharmacokinetics

BZDs are usually given orally or intravenously and occasionally by rectal route (diazepam) in children. The rate of absorption following oral administration is variable; absorption is erratic from intramuscular (i.m.) site of administration; hence rarely used. They have a large volume of distribution. They have a short duration of action on occasional use because of rapid redistribution, hence, are free of residual (hangover) effects, even though elimination half-life is long. BZDs are metabolized in liver. Some undergo enterohepatic recycling. Some of them produce active metabolites which have long half-life; hence, cumulative effects may be seen. Oxazepam is not significantly metabolized in liver. The metabolites are excreted in urine. BZDs cross placental barrier.

Adverse Effects

BZDs have a wide margin of safety. They are generally well tolerated. The common side effects are drowsiness, confusion, blurred vision, amnesia, disorientation, tolerance and drug dependence. Withdrawal after chronic use causes symptoms like tremor, insomnia, restlessness, nervousness and loss of appetite. Use of BZDs during labour may cause respiratory depression and hypotonia in newborn (Floppy baby syndrome). In some patients, these drugs may produce paradoxical effects, i.e. convulsions and anxiety.

Important features of BZDs are given in [Table 5.2](#).

Inverse Agonist (β -Carboline). Its interaction with BZD receptors will produce anxiety and convulsions.

Benzodiazepine Antagonist (Flumazenil). Flumazenil competitively reverses the effects of both BZD agonists (CNS depression) and BZD inverse agonists (CNS stimulation, [Fig. 5.4](#)). Flumazenil is not used orally because of its high first-pass metabolism. It is given by i.v. route and has a rapid onset of action. Flumazenil is used in the treatment of BZD overdosage and to reverse the sedative effect of BZDs during GA. It can also be used to reverse the hypnotic effect of zolpidem, zaleplon and eszopiclone. Adverse

Table 5.2 ■ Important features of benzodiazepines

Drug	Formulations with oral dose	Important points
Diazepam (prototype drug)	Oral, i.v., i.m., rectal, 5–10 mg	• Rapidly absorbed from GI tract • Produces active metabolites • No residual effects on occasional use due to redistribution • It is used to control convulsions but not for long-term therapy of epilepsy because of rapid development of tolerance to anticonvulsant effect • It can be used rectally to control convulsions • Other points: See p. 168
Flurazepam	Oral, 15 mg	• Useful in insomnia • Causes hangover effects – because of active metabolite with long half-life
Nitrazepam	Oral, 5–10 mg	• Useful in insomnia • Residual effects are less on occasional use
Oxazepam	Oral, 15 mg	• Slowly absorbed • No active metabolite • Preferred in elderly and in patients with liver disease • Mainly used as antianxiety agent
Lorazepam	Oral, i.m., i.v., 0.5–2 mg	• Rate of GI absorption is slow • No active metabolite • Anticonvulsant effect lasts longer than with diazepam because it is less lipid soluble and redistribution is slow • Mainly used as anticonvulsant, antianxiety and preanaesthetic medication • Less irritant, hence thrombophlebitis is rare on i.v. administration
Alprazolam	Oral, 0.5–2 mg	• Useful in insomnia • Produces active metabolite • Has antianxiety and antidepressant effects
Temazepam	Oral, 7.5–30 mg	• No active metabolite • Mainly used for insomnia
Triazolam	Oral, 0.125–0.25 mg	• Has rapid onset of action; short acting • Mainly used for insomnia – reduces sleep latency
Midazolam	i.v., i.m., 1–2.5 mg (i.v.)	• Has rapid onset of action; short acting • Used as preanaesthetic medication, i.v. general anaesthesia when combined with other CNS depressant, in status epilepticus when not responding to other drugs
Chlordiazepoxide	Oral, i.m., i.v., 50–100 mg	• Slow oral absorption • Produces active metabolite; long acting • Used in alcohol withdrawal and anxiety

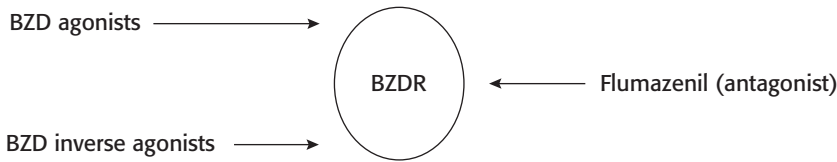


Fig. 5.4 Competitive antagonism. BZDR, Benzodiazepine receptor.

effects include confusion, dizziness and nausea. It may precipitate withdrawal symptoms (anxiety and convulsions) in dependent subjects.

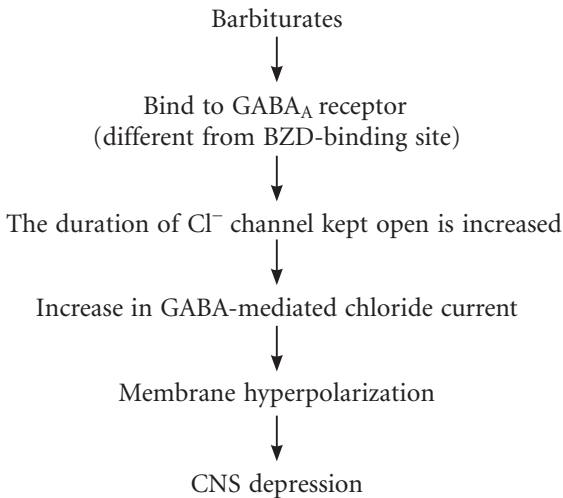
Barbiturates

PH1.19

All barbiturates are derivatives of barbituric acid. They are nonselective CNS depressants and act at many sites, ascending reticular activating system (ARAS) being the main site.

Mechanism of Action

Barbiturates have GABA facilitatory action – they potentiate inhibitory effects of GABA.



At high concentrations, barbiturates have **GABA-mimetic effect** (i.e. barbiturates can directly increase Cl^- conductance into the neuron).

Pharmacological Actions and Uses

- 1. Sedation and hypnosis:** Barbiturates were used in the treatment of insomnia. They decrease sleep latency, duration of REM sleep, stage 3 and 4 of NREM sleep. They cause marked alteration of sleep architecture. At present, barbiturates are not recommended because:
 - They have a low therapeutic index.
 - They cause rebound increase in REM sleep on stoppage of therapy.

- They cause marked respiratory depression.
 - They produce marked hangover effects (headache and drowsiness next day morning).
 - They cause high degree of tolerance and drug dependence.
 - They are potent enzyme inducers and cause many drug interactions.
 - They have no specific antidote.
2. **General anaesthesia (GA):** Ultrashort-acting barbiturates (thiopentone and methohexitone) may be used for induction of GA.
 3. **Anticonvulsant:** Phenobarbitone has anticonvulsant effect and is used in the treatment of status epilepticus and generalized tonic–clonic seizures (GTCS, grand mal epilepsy).
 4. **Neonatal jaundice of nonhaemolytic type:** Phenobarbitone may be used to reduce serum bilirubin levels. It induces glucuronyl transferase enzyme and hastens the metabolism of bilirubin.

Adverse Effects

1. The common side effects are drowsiness, confusion, headache, ataxia, hypotension and respiratory depression.
2. Hypersensitivity reactions like skin rashes, itching and swelling of face may occur.
3. Tolerance develops to their sedative and hypnotic actions on repeated use.
4. Physical and psychological dependence develops on repeated use.
5. Prolonged use of phenobarbitone may cause megaloblastic anaemia by interfering with absorption of folic acid from gut.
6. They may precipitate attacks of acute intermittent porphyria by inducing ALA synthase that catalyses the production of porphyrins; hence, barbiturates are contraindicated in porphyria.
7. Acute barbiturate poisoning: The signs and symptoms are drowsiness, restlessness, hallucinations, hypotension, respiratory depression, convulsions, coma and death.

Treatment of acute barbiturate poisoning

- Maintain airway, breathing and circulation.
- Maintain electrolyte balance.
- Gastric lavage – after stomach wash, administer activated charcoal that may enhance the elimination of phenobarbitone. Endotracheal intubation is performed before gastric lavage to protect the airway in unconscious patients.
- Alkaline diuresis – there is no specific antidote for barbiturates; main treatment is alkaline diuresis. i.v. NaHCO_3 alkalinizes urine. Barbiturates are weakly acidic drugs. In alkaline urine, barbiturates exist in ionized form, so they are not reabsorbed while passing through renal tubules and are rapidly excreted in urine.
- Haemodialysis is employed in severe cases.

Drug Interactions

Barbiturates are potent inducers of hepatic microsomal enzymes and reduce the effectiveness of co-administered drugs (e.g. oral contraceptives [OCs], oral anticoagulants and oral hypoglycaemics).

Nonbenzodiazepine Hypnotics

PH1.19

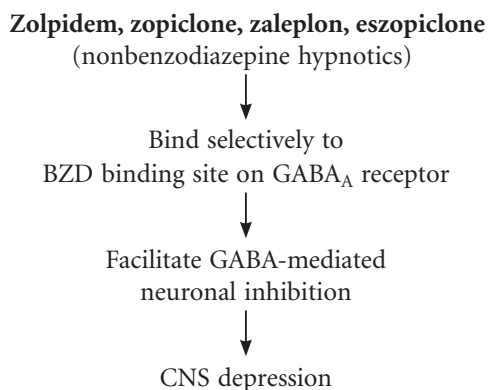
They include zolpidem, zopiclone, zaleplon, eszopiclone and etizolam. They have less potential for abuse than BZDs.

They have less antianxiety, anticonvulsant and muscle relaxant effects than BZDs. Effect on REM sleep is less as compared to BZDs.

ZOLPIDEM

Zolpidem mainly produces hypnotic effect – decreases sleep latency and increases duration of sleep time in insomnia. It produces near-normal sleep like BZDs with minimal alteration in REM sleep; causes minimal hangover effects and rebound insomnia; less likely to produce tolerance and drug dependence; lacks anticonvulsant, antianxiety and muscle relaxant effects. It is given orally, well absorbed, metabolized in liver and excreted in urine. It has a short duration of action and is used for short-term treatment of insomnia. The actions of zolpidem are antagonized by flumazenil. The common side effects are headache, confusion, nausea and vomiting.

Mechanism of Action



ZOPICLONE

It is orally effective and is used for short-term treatment of insomnia. It produces near-normal sleep like BZDs. The side effects are headache, drowsiness, GI disturbances and metallic taste.

ZALEPLON

It is useful in sleep onset insomnia. It is the shortest acting non-BZD hypnotic.

ESZOPICLONE

It is used orally for short- and long-term treatment of insomnia.

ETIZOLAM

It is a BZD analogue with hypnotic, anticonvulsant, muscle relaxant and antianxiety effects. It is useful for short-term treatment of insomnia.

MELATONIN

It is the hormone secreted by the pineal gland; involved in the maintenance of sleep–wake cycle and circadian rhythm.

RAMELTEON

It is a melatonin-receptor (MT_1 and MT_2) agonist, can be used orally for the treatment of sleep onset insomnia. It reduces sleep latency and prolongs total duration of sleep. There is no rebound insomnia on withdrawal; does not cause tolerance on chronic use. The important adverse effects are fatigue and dizziness.

TASIMELTEON

It is another melatonin-receptor agonist used for the treatment of circadian rhythm disorder in blind patients.

SUVOREXANT

It prevents orexin from maintaining wakefulness by blocking orexin receptors. It is useful in chronic insomnia.

General Anaesthetics

PH1.18

GA refers to drug-induced reversible loss of consciousness and all sensations. The features of GA are as follows:

1. Reversible loss of consciousness.
2. Reversible loss of sensation.
3. Analgesia and amnesia.
4. Muscle relaxation and abolition of reflexes.

There is no single anaesthetic agent that can produce all the above effects. Hence, anaesthetic protocol includes:

1. Premedication.
2. Induction of anaesthesia (e.g. propofol).
3. Maintenance of anaesthesia (e.g. N_2O + isoflurane).
4. Skeletal muscle relaxation.
5. Analgesia – as premedication, during and after the operation.
6. Use of other drugs:
 - To reverse neuromuscular blockade.
 - To reverse the residual effects of opioids (naloxone) and BZDs (flumazenil).

Minimal alveolar concentration (MAC) is the minimum concentration of an anaesthetic in alveoli required to produce immobility in response to a painful stimulus in 50% patients. It indicates the potency of inhalational general anaesthetics (N_2O > 100%, halothane 0.75%).

MECHANISM OF ACTION OF GENERAL ANAESTHETICS

The main site of action of anaesthetics is reticular formation, which normally maintains a state of consciousness. Most anaesthetics decrease transmission in reticular formation by enhancing the activity of inhibitory transmitters like GABA (e.g. BZDs, barbiturates

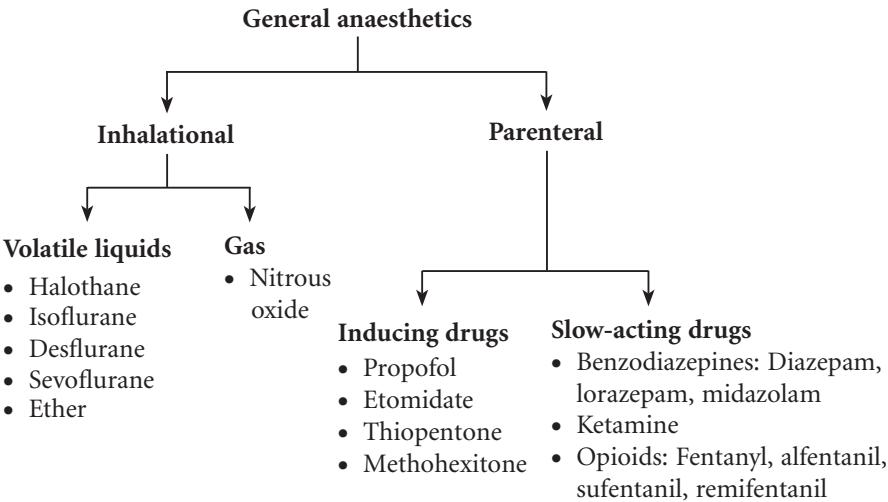
Table 5.3 ■ Stages of anaesthesia

I. Stage of analgesia	II. Stage of excitement	III. Stage of surgical anaesthesia	IV. Stage of medullary paralysis
The patient is conscious but drowsy	• Patient loses consciousness • Sympathetic activity is increased • ↑ Heart rate (HR), ↑ blood pressure (BP), pupils are dilated; muscle tone is increased; breathing is irregular	• Respiration becomes regular • Muscles relax • Reflexes are gradually lost • Intercostal muscles are paralysed • Pupils dilated and eyeballs are fixed	Respiration and vaso-motor centre are depressed; death occurs within a few minutes

and propofol) and blocking the activity of excitatory transmitters (e.g. blockade of N-methyl-D-aspartate [NMDA] glutamate receptors by ketamine and nitrous oxide).

Stages of GA (Table 5.3): Stages I–IV are seen mainly with ether because of its slow action. Stage II is the most dangerous period. Surgical procedures are performed in stage III. The aim of induction is to reach stage III as early as possible followed by maintenance anaesthesia and muscle relaxation.

CLASSIFICATION



INHALATIONAL ANAESTHETICS

These are discussed under the following headings (Tables 5.4 and 5.5).

1. Gas/volatile liquid
2. Nonflammable/inflammable

Table 5.4 ■ Comparative features of ether, halothane and nitrous oxide

Ether	Halothane	Nitrous oxide
Volatile liquid	Volatile liquid	Gaseous general anaesthetic
Induction and recovery are slow because of its high solubility in blood	Induction and recovery are faster than ether	Induction and recovery are rapid because of low blood solubility
Irritant, inflammable and highly explosive	Nonirritant, noninflammable, not pungent, well tolerated – preferred for induction and maintenance in children	Nonirritant and non-inflammable
Has wide margin of safety	Margin of safety is not wide	Very wide margin of safety
Potent anaesthetic, MAC: 1.9%	Potent anaesthetic, MAC: 0.75%	Poor anaesthetic, MAC: >100%
Excellent analgesia	Poor analgesia	Excellent analgesia
Has curarimimetic effect on skeletal muscles, so the dose of d-tubocurarine (d-TC) required is less	Muscular relaxation is inadequate but potentiates the action of d-TC	Poor skeletal muscle relaxant
Does not sensitize the heart to catecholamines	Sensitizes the myocardium to catecholamines and may precipitate arrhythmias	Has little effect on heart, respiration and BP
Cheap	Expensive	Cheap
Irritant anaesthetic, increases salivary, respiratory secretions – may induce cough and laryngeal spasm; therefore, preanaesthetic atropine is used to overcome these effects	Causes bronchodilatation – preferred in asthmatics	–
Postoperative nausea and vomiting are common	Nausea and vomiting rare	–
No hepatotoxicity	Hepatotoxicity: especially if used repeatedly (halothane hepatitis)	–
<i>Other points:</i> - On exposure to light, it forms ether peroxide which is an irritant; to avoid this, ether is supplied in amber-coloured bottles covered with black paper - Ether is inflammable and highly explosive; hence, electric cautery cannot be used	<i>Adverse effects: (Note ‘H’s)</i> Hypotension: It has direct depressant effect on the myocardium and causes hypotension - Respiratory depression - Both Hepatotoxicity and malignant Hyperthermia are rare Hearth: Halothane sensitizes the myocardium to adrenaline and can cause arrhythmias	- Second gas effect and diffusion hypoxia occur with N₂O only - May increase intracranial tension

Table 5.5 ■ Comparative features of halogenated anaesthetics (fluorinated anaesthetics)

Halothane	Isoflurane	Desflurane	Sevoflurane
Volatile liquid	Volatile liquid	Volatile liquid	Volatile liquid
Noninflammable and nonexplosive	Noninflammable and non-explosive	Noninflammable and non-explosive	Noninflammable and non-explosive
Induction and recovery are slow MAC: 0.75%	Induction and recovery are rapid than halothane MAC: 1.4%	Induction and recovery are rapid MAC: 6%	Induction and recovery are rapid MAC: 2%
Hypotension +	Hypotension +	Hypotension +	Hypotension +
Sensitizes the heart to catecholamines and may cause cardiac arrhythmias	–	–	–
Respiratory depression +	Respiratory depression +	Respiratory depression +	Respiratory depression +
Poor muscle relaxant	Skeletal muscle relaxation +	Skeletal muscle relaxation +	Skeletal muscle relaxation +
Nonirritant to respiratory passages, causes bronchodilatation and is preferred in asthmatics	Causes bronchodilatation; irritates air passages	Causes bronchodilatation; irritates air passages	Does not irritate airways and is a potent bronchodilator
Hepatotoxicity on repeated use	No hepatotoxicity	No hepatotoxicity	No hepatotoxicity
Not pungent, well tolerated – preferred for induction and maintenance in children	- Commonly used for maintenance of anaesthesia - Pungent odour – hence not commonly used for induction - Does not cause seizures - Can be used for neurosurgical procedures - No renal toxicity	- Irritates airways – not used for induction - Does not cause seizures - No renal toxicity - Can be used in outpatients because of rapid onset of action and rapid recovery	- Nonirritant to airways, not pungent – can be used for induction - Suitable for induction and maintenance of anaesthesia in children - Can be used even in outpatients because of rapid recovery - Interacts with soda lime – should not be used in closed circuit system

Note: Halogenated anaesthetics: The newer agents like isoflurane, desflurane and sevoflurane are expensive.

+, Present; –, absent.

3. Margin of safety
4. Induction and recovery
5. Skeletal muscle relaxation
6. Analgesia
7. Sensitization of myocardium
8. Hepatotoxicity
9. Irritation of respiratory passages
10. Postoperative nausea and vomiting
11. Other points

- Use of ether is obsolete.
- Halothane sensitizes the myocardium to the arrhythmogenic effect of catecholamines.
- Speed of induction and recovery depends on solubility of anaesthetic agent in blood and fat.
- Anaesthetics with low blood solubility produce rapid induction and recovery (e.g. N₂O and desflurane).
- Anaesthetics with high solubility in blood produce slow induction and recovery (e.g. ether).
- Desflurane, isoflurane and ether irritate respiratory passages and can induce cough.
- The basis for combining halothane/isoflurane and nitrous oxide:
 - (a) The concentration (MAC) of halothane/isoflurane required to produce anaesthesia is reduced when given with N₂O because of second gas effect. As the concentration of halothane/isoflurane required is reduced, the side effects of halothane/isoflurane (hypotension and respiratory depression) are reduced.
Second gas effect: N₂O rapidly diffuses, whereas halothane/isoflurane diffuses poorly into the blood (alveoli ↔ blood ↔ brain). When these (halothane/isoflurane and N₂O) anaesthetics are administered simultaneously, halothane/isoflurane also enters the blood rapidly along with rapidly diffusible gas (N₂O). This is known as ‘second gas effect’.
 - (b) Because of reduction in the dosage, recovery will be faster.
 - (c) Halothane/isoflurane is a potent anaesthetic and poor analgesic, whereas N₂O is a good analgesic and poor anaesthetic; hence, the combined effect of these two drugs results in potent anaesthesia and good analgesia.

Diffusion Hypoxia. Nitrous oxide has low blood solubility – when the administration of N₂O is discontinued, it rapidly diffuses from the blood into alveoli and causes marked reduction of PaO₂ in the alveoli resulting in hypoxia which is known as diffusion hypoxia. It can be avoided by giving 100% O₂ for a few minutes immediately after N₂O is discontinued.

Comparative features of halogenated anaesthetics are given in [Table 5.5](#).

PARENTERAL GENERAL ANAESTHETICS

Inducing Drugs

Propofol. It is available as 1% emulsion for i.v. administration. Propofol is a commonly used, popular, rapidly acting anaesthetic.

Propofol acts on GABA receptors to increase chloride conductance and hyperpolarization of neurons, thus produces CNS depression. It has a rapid onset and short duration of action; for long procedures – it can be given in repeated doses or as continuous

i.v. infusion. It is highly bound to plasma protein; crosses placental barrier and can be used in pregnant woman. It is metabolized in liver and excreted rapidly in urine.

1. Induction of anaesthesia and recovery are rapid. Residual symptoms are less.
2. Most suitable for outpatient surgical procedures.
3. No irritation of air passages; suitable for use in asthmatics.
4. Has antiemetic effect; hence, postoperative nausea and vomiting are rare.
5. Can be used for both induction and maintenance of anaesthesia.
6. Frequently used to sedate patients in ICU (intensive care unit) who are intubated.
7. It is used in status epilepticus when not controlled by other drugs.
8. Causes respiratory depression and fall in BP.
9. Pain on injection occurs – can be reduced with lignocaine.
10. In high doses, can cause acidosis and rise in blood lipid levels.

Note: Propofol – Popular, Rapid acting, preferred for **OP** surgical procedures, causes **FOL** (fall) in BP.

Thiopentone Sodium (Fig. 5.5). It is an ultra short-acting barbiturate. It is a commonly used i.v. anaesthetic for induction of anaesthesia. It is **highly** lipid soluble, hence has a rapid onset and short duration (5–8 minutes) of action. It is **highly** alkaline (pH 10.5–11), hence **highly** irritant. It should be prepared as a fresh solution before injection. It is injected as 2.5% solution.

After a single i.v. dose, it rapidly enters **highly** perfused organs like brain, liver and heart, and produces anaesthesia. As blood level of the drug falls rapidly, it diffuses out of the central nervous system into the blood and then to less perfused organs like skeletal muscle and adipose tissue. This redistribution results in termination of drug action. Repeated doses will result in accumulation and delayed recovery.

Uses

1. Thiopentone sodium is used for induction of anaesthesia.
2. It is occasionally used as anticonvulsant in cases not controlled by other drugs.
3. In subanaesthetic doses, thiopentone can be used for narcoanalysis in psychiatry.

Advantages of Thiopentone

1. Rapid induction of anaesthesia and rapid recovery.
2. Does not sensitize the myocardium to circulating catecholamines.

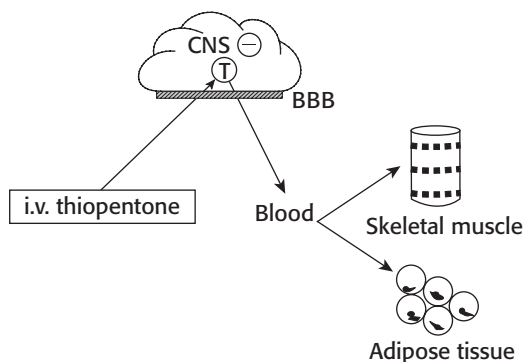


Fig. 5.5 Redistribution of thiopentone. CNS, Central nervous system; BBB, blood-brain barrier; T, thiopentone; ⊖, inhibition.

Disadvantages/Adverse Effects of Thiopentone

1. Depresses the respiratory centre.
2. Depresses the vasomotor centre and myocardium.
3. Poor analgesic.
4. Poor muscle relaxant.
5. Causes laryngospasm.
6. Accidental intra-arterial injection causes vasospasm and gangrene of the arm.
7. It can precipitate acute intermittent porphyria by inducing the synthesis of ALA synthase, hence contraindicated in susceptible individuals (absolute contraindication).

Etomidate. It is an i.v. anaesthetic used for induction – has a rapid onset and short duration of action. It causes minimal cardiovascular and respiratory depression.

Disadvantages/Adverse Effects

1. Has poor analgesic effect.
2. High incidence of pain on injection, postoperative nausea and vomiting.
3. Restlessness and rigidity are common.

Slow-Acting Drugs

Ketamine. It produces ‘dissociative anaesthesia’, which is characterized by sedation, amnesia, marked analgesia, unresponsiveness to commands and dissociation from the surroundings. It acts by blocking NMDA type of glutamate receptors. It is commonly given by i.v. route; other routes are i.m., oral and rectal. Ketamine has good **analgesic effect**. It causes **bronchodilatation**, suitable for use in asthmatics. Ketamine causes **sympathetic stimulation** – heart rate, BP, cardiac output and skeletal muscle tone are usually increased. It is used in patients with **hypovolaemia**. It is well tolerated by **children**.

Site of action: cortex and subcortical areas.

Ketamine is highly lipid soluble, rapidly enters highly perfused organs like brain, liver and heart; later, it redistributes to less perfused organs. It is metabolized in liver; excreted in urine and bile.

Uses

1. For operations on the head, neck and face.
2. For dressing burn wounds.
3. Well suited for children/asthmatics undergoing short procedures.

Adverse Effects and Contraindications

1. Increases BP and heart rate, hence is contraindicated in patients with hypertension and ischaemic heart disease.
2. Increases intracranial pressure.
3. Causes emergence delirium and hallucinations.

Benzodiazepines. BZDs are slow-acting parenteral anaesthetics. They include diazepam, lorazepam and midazolam. Use of large doses delays recovery and prolongs amnesia. They have poor analgesic effect. They do not cause postoperative nausea and vomiting. The effects of BZDs can be reversed by flumazenil. They are useful for angiography, endoscopies, fracture reduction, etc.

Opioid Analgesics. They include fentanyl, alfentanil, sufentanil and remifentanil. They are potent analgesics and can be used along with anaesthetics – to decrease the

requirement of anaesthetic. Alfentanil, sufentanil and remifentanil are shorter acting than fentanyl.

Dexmedetomidine

- Central α_2 -agonist → Sedation and analgesia.
- Causes minimal respiratory depression.
- Used intravenously to sedate critically ill patients.
- Common adverse effects are hypotension and bradycardia due to decreased central sympathetic outflow.

COMPLICATIONS OF GENERAL ANAESTHESIA

CVS: Hypotension, cardiac arrhythmias, cardiac arrest

Respiratory depression, aspiration pneumonia, apnoea

CNS: Convulsions, persistent sedation

GIT: Nausea, vomiting, hepatotoxicity

Nephrotoxicity

Malignant hyperthermia

PREANAESTHETIC MEDICATION

PH1.18

It is the use of drugs before administration of anaesthetics to make anaesthesia more pleasant and safe.

Objectives/Aims of Premedication

1. **To reduce anxiety and apprehension:** BZDs like diazepam, lorazepam or midazolam are preferred because of their sedative, amnesic, calming, anxiolytic effects and wide margin of safety. They reduce anxiety by acting on limbic system.
2. **To prevent vagal bradycardia and to reduce salivary secretion caused by anaesthetics:** Antimuscarinic agents such as atropine or glycopyrrolate are used to prevent vagal bradycardia and hypotension. They also prevent laryngospasm by reducing respiratory secretion. Glycopyrrolate is preferred because it is potent, does not produce CNS effects and causes less tachycardia.
3. **To relieve pre- and postoperative pain:** Opioid analgesics such as morphine, pethidine or fentanyl may be used to relieve pain. The limitations with opioids are respiratory depression, hypotension, nausea, vomiting, constipation, biliary spasm and bronchospasm in asthmatics. NSAIDs like diclofenac can also be used.
4. **For antiemetic effect:** Metoclopramide, domperidone or ondansetron may be used to control vomiting. Acute dystonias and extrapyramidal symptoms (EPS) are the main side effects of metoclopramide; domperidone rarely produces EPS. 5-HT₃ antagonist like ondansetron is the preferred antiemetic as it rarely causes adverse effects and is well tolerated.
5. **To prevent acid secretion and stress ulcer:** H₂-blocker such as ranitidine or proton-pump inhibitor like omeprazole may be used to reduce gastric acid secretion and aspiration pneumonia especially before prolonged surgery.
6. **To hasten gastric emptying before emergency surgery:** Metoclopramide or domperidone may be used. They are prokinetic drugs – increase the tone of lower oesophageal sphincter and accelerate gastric emptying, thus prevent aspiration pneumonia.

CONSCIOUS SEDATION

It is a level of CNS depression where a patient does not lose consciousness but is able to communicate and cooperate during the procedure/treatment. It is used in:

1. Uncooperative patients.
2. Anxious patients.
3. Emotionally compromised patients.

It should be avoided in chronic obstructive pulmonary disease (COPD), pregnancy, prolonged surgery, psychoses, etc. The drugs used are BZDs such as diazepam (oral, i.v.), midazolam (i.v.) and temazepam (oral); nitrous oxide + oxygen (inhalation); propofol (i.v. infusion) and fentanyl (i.v.).

Local Anaesthetics

PH1.17

Local anaesthetics (LAs) are drugs which, when applied topically or injected locally, block nerve conduction and cause reversible loss of all sensation in the part supplied by the nerve. The order of blockade of nerve function proceeds in the following manner – pain, temperature, touch, pressure and finally skeletal muscle power.

CHEMISTRY (Fig. 5.6)

LAs are weak bases. They consist of three parts: (i) hydrophilic amino group; (ii) lipophilic aromatic group; and (iii) intermediate ester or amide linkage.

CLASSIFICATION OF LOCAL ANAESTHETICS

1. According to clinical use

- Surface anaesthetics*: Cocaine, lignocaine, tetracaine, benzocaine, oxethazaine, proparacaine, butylaminobenzoate.
- Injectable anaesthetics*
 - Short acting with low potency*: Procaine, chlorprocaine.
 - Intermediate acting with intermediate potency*: Lignocaine, mepivacaine, prilocaine, articaine.
 - Long acting with high potency*: Tetracaine, bupivacaine, dibucaine, ropivacaine.

2. According to structure

- Esters***: Cocaine, procaine, chlorprocaine, benzocaine, tetracaine.
- Amides***: Lignocaine, mepivacaine, bupivacaine, prilocaine, articaine, ropivacaine.

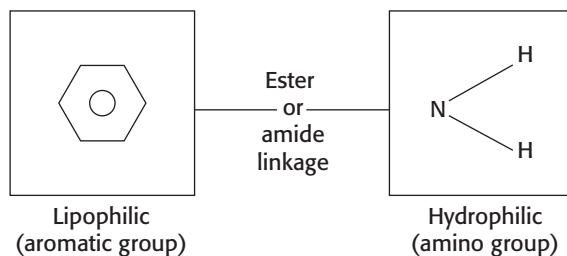


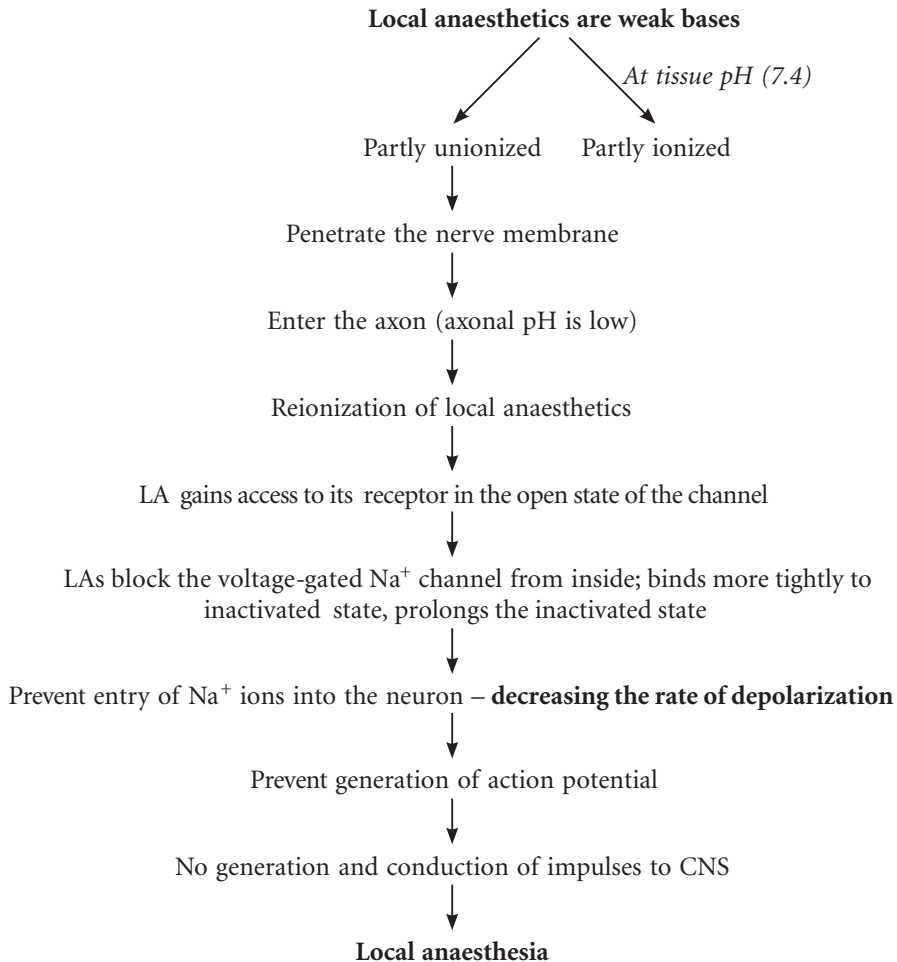
Fig. 5.6 Basic structure of local anaesthetics.

*Note: Esters have one 'i'; amides have two 'i' (i, i).

MECHANISM OF ACTION

LAs act on voltage-sensitive Na^+ channels. Sodium channels exist in resting, open and inactivated states (resting $\rightarrow$ open $\rightarrow$ inactivated state). The channels have to recover from the inactivated state to resting state before they can be opened in response to an impulse.

The LAs in 'unionized' form easily penetrate nerve sheath and axon membrane. Within the axoplasm, the molecules become 'ionized' and block the voltage-gated Na^+ channels.



- Blockade is frequency dependent.
- Action of LA is pH dependent and the penetrability of LA is increased at alkaline pH (i.e. when the unionized form is more). Penetrability is very poor at acidic pH of tissues. In infected tissues, there is a low pH, which causes ionization of the drug. This reduces penetration of LA through the cell membrane, thus decreases the effectiveness of LAs. Therefore, LAs are **less effective in inflamed and infected areas**.
- Diameter of nerve fibres: LAs block small fibres first followed by larger fibres.
- Myelinated fibres are blocked earlier than nonmyelinated nerves of the same diameter.
- Sensory fibres are blocked earlier than motor fibres because of their high firing rate and longer duration of action potential.

- Fibres in the centre are blocked later than the ones located in the circumference of the nerve bundle.

FACTORS AFFECTING LOCAL ANAESTHETIC ACTION

1. **pK_a :** Higher the pK_a , more is the ionized fraction of the drug at physiological pH. Hence, onset of action is slow and vice versa, e.g. the pK_a of procaine is 9.1. So, it has slow onset of action; whereas pK_a of lignocaine is 7.7 – it has rapid onset of action. Although pK_a of chlorprocaine is 9.1, it has a rapid onset of action.
2. **Degree of plasma protein binding:** Higher the plasma protein binding, longer the duration of action of the drug, e.g. procaine is poorly bound to plasma proteins, hence has a short duration of action, whereas bupivacaine is highly plasma protein bound and has longer duration of action.
3. **Rate of diffusion from the site of administration:** It depends on the initial concentration gradient of the drug. Higher the concentration, rapid is the onset of action.
4. **Lipid solubility:** Higher the lipid solubility, more is the potency of the drug, e.g. lignocaine is more potent than procaine as it is more lipid soluble.
5. **Presence of vasoconstrictor:** Prolongs the duration of action of LAs. The commonly used vasoconstrictor with LAs is adrenaline.

COMBINATION OF VASOCONSTRICTOR WITH LOCAL ANAESTHETIC

Addition of a vasoconstrictor (e.g. adrenaline) to the LA has the following advantages:

1. Slow absorption from the local site which results in prolonged duration of action of LAs.
2. Decreased bleeding in the surgical field.
3. Slow absorption of LA reduces its systemic toxicity.

Disadvantages and contraindications of combining vasoconstrictor with LA:

1. Intense vasospasm and ischaemia in tissues with end arteries may cause gangrene of the part (e.g. fingers, toes, penis, ear lobule and tip of the nose). Hence, use of vasoconstrictors is contraindicated in these sites.
2. Absorption of adrenaline can cause systemic toxicity – tachycardia, palpitation, rise of BP and precipitation of angina or cardiac arrhythmias. Hence, combined preparation (LA with adrenaline) should be avoided in patients with hypertension, congestive cardiac failure (CCF), arrhythmias, ischaemic heart disease and uncontrolled hyperthyroidism.
3. May delay wound healing by reducing the blood flow to the affected area.

PHARMACOLOGICAL ACTIONS

1. Nervous system

- (a) *Peripheral nerves:* Autonomic fibres are blocked earlier than somatic fibres. Sensation of pain disappears first followed by temperature, touch, pressure and motor functions.
- (b) *CNS:* Most of the LAs cross the blood–brain barrier (BBB) – initially they cause CNS stimulation and then depression in higher doses. They cause excitement, tremor, twitching, restlessness and convulsions. Large doses can cause respiratory depression, coma and death.

2. Cardiovascular system

- (a) *Heart*: LAs, by blocking Na^+ channels, decrease abnormal pacemaker activity, contractility, conductivity, excitability, heart rate, cardiac output and increase effective refractory period.
 - (i) At higher concentrations, i.v. administration of LAs may precipitate cardiac arrhythmias.
 - (ii) Bupivacaine is more cardiotoxic than other LAs – may cause cardiovascular collapse and death.
 - (iii) Lignocaine decreases automaticity and is useful in ventricular arrhythmias.
- (b) *Blood vessels*: LAs produce hypotension due to vasodilatation and myocardial depression.

PHARMACOKINETICS

Most of the ester-linked LAs are rapidly metabolized by plasma cholinesterase, whereas amide-linked drugs are metabolized mainly in liver. LAs (procaine, lignocaine, etc.) are not effective orally because of high first-pass metabolism. In liver diseases, the metabolism of lignocaine may be impaired; hence, dose must be reduced accordingly.

Comparative features of esters and amides are shown in [Table 5.6](#).

ADVERSE EFFECTS

1. **CNS**: LAs initially cause CNS stimulation followed by depression. They are restlessness, tremor, headache, drowsiness, confusion, convulsions followed by respiratory depression, coma and death.
 2. **CVS**: Bradycardia, hypotension, cardiac arrhythmias and rarely cardiovascular collapse and death. Bupivacaine is highly cardiotoxic.
 3. **Allergic reactions**: These are skin rashes, itching, erythema, urticaria, wheezing, bronchospasm and rarely anaphylactic reaction. The incidence of allergic reactions is more with ester-linked LAs than with amide-linked LAs.
 4. Mucosal irritation (cocaine) and methaemoglobinaemia (prilocaine) may be seen.
 5. Methylparaben, preservative in LA preparation, may cause allergic reaction.
- Important properties of LAs are given in [Table 5.7](#).
6. **Adverse effects due to the use of vasoconstrictor** (see p. 183)

Table 5.6 ■ Comparative features of procaine and lignocaine

Procaine	Lignocaine
Ester type of LA	Amide type of LA
Short acting	Intermediate acting
Has poor tissue penetrability, hence no surface anaesthetic effect	Has good tissue penetrability
Has slow onset of action	Has rapid onset of action
Is metabolized by plasma cholinesterase	Is metabolized by hepatic microsomal enzymes
Allergic reactions are common with esters	Allergic reactions are rare
Useful for infiltration and nerve block anaesthesia; at present, it is rarely used	Widely used for all types of anaesthesia – spinal, epidural, i.v. regional block, nerve block, infiltration and surface anaesthesia

Table 5.7 ■ Properties of local anaesthetics

Drug	Group	Duration of action (minutes)	Potency	Onset	Tissue penetrability	Other points
Procaine	Ester	15–30 (short)	Low	Slow	Poor	No surface anaesthesia
Chloroprocaine	Ester	15–30 (short)	Low	Rapid	–	–
Tetracaine	Ester	120–240 (long)	High	Very slow	Moderate	- Widely used in spinal and corneal anaesthesia - High systemic toxicity because of slow metabolism
Cocaine	Ester	–	–	Intermediate	Good	- Inhibits the reuptake of NA in both central and peripheral nerves - Causes tachycardia, rise in BP, mydriasis and euphoria - Rarely used
Lignocaine	Amide	30–60 (intermediate)	Intermediate	Rapid	Good	Most widely used local anaesthetic; also used in ventricular arrhythmias
Mepivacaine	Amide	45–90 (intermediate)	Intermediate	Intermediate	–	No surface anaesthesia
Bupivacaine	Amide	120–240 (long)	High	Intermediate	Moderate	Highly cardiotoxic, widely used for spinal, epidural, infiltration and nerve block – because of long duration of action; low concentration used for epidural analgesia during labour
Ropivacaine	Amide	120–360 (long)	Intermediate	Intermediate	Moderate	Similar to bupivacaine, less cardiotoxic
Prilocaine	Amide	Intermediate	–	Intermediate	Moderate	Widely used; can cause methaemoglobinaemia
Dibucaine	Amide	180–600 (long)	High	Slow	Good	Useful as topical anaesthetic for anal mucous membrane
Articaine	Amide	60	–	Rapid	–	Used for infiltration and nerve block anaesthesia; can cause methaemoglobinaemia, paraesthesia and neuropathy

Note: NA, noradrenaline.

Procaine (see Table 5.6). It is a prototype drug for esters. It is rarely used now because of availability of better agents.

Cocaine. It is an alkaloid; excellent surface anaesthetic but rarely used because of its addiction liability.

Chloroprocaine has a pK_a of 9.1, but has rapid onset of action.

Tetracaine. An ester type of LA, it has long duration but slow onset of action. It is useful for spinal anaesthesia because of its long duration of action. It is mainly used as a surface anaesthetic for eye, nose and upper respiratory tract.

Lignocaine. It is a prototype agent for amides. It is a very popular anaesthetic used widely for topical application, infiltration, spinal and conduction block anaesthesia. It is also available as a patch – can be used to control severe pain of postherpetic neuralgias.

Bupivacaine. It is a widely used LA. It is potent and has a long duration of action. It produces more sensory than motor blockade, hence very popular for obstetric analgesia. It is highly cardiotoxic and may precipitate ventricular arrhythmias.

Levobupivacaine: It is similar to bupivacaine; but less cardiotoxic and less likely to cause seizures.

Ropivacaine. It is less potent and less cardiotoxic than bupivacaine. Its duration of action is similar to bupivacaine. It is used for both epidural and regional anaesthesia. It is more selective for sensory fibres than motor fibres, hence used in obstetric analgesia.

Prilocaine. It is an amide type of LA. It has intermediate onset and duration of action. It has poor vasodilatory effect, hence can be used without a vasoconstrictor. Prilocaine is not suitable for labour pain because of the risk of neonatal methaemoglobinaemia. It is mainly used for infiltration and i.v. regional anaesthesia.

Eutectic Mixture (EMLA – Eutectic Mixture of Local Anaesthetics – Lignocaine [2.5%] and Prilocaine [2.5%]). The melting point of the mixture is less than that of either compound alone. It can anaesthetize intact skin. EMLA has to be applied 1 hour before the procedure and is used for dermal anaesthesia during venesection and skin graft procedures. It should not be used on mucous membranes or abraded skin. It is contraindicated in patients with methaemoglobinaemia and infants.

Dibucaine. It is a very potent, highly toxic and the longest acting LA. It is rarely used for spinal anaesthesia, and is also available for topical application on mucous membrane and skin.

Benoxinate. It is a surface anaesthetic; useful for corneal anaesthesia.

Benzocaine and Butylaminobenzoate. Surface anaesthetics; cause minimal systemic toxicity; available as ointment and lozenges; used for haemorrhoids, anal fissure and sore throat.

Oxethazaine. It is a topical anaesthetic and is used to **anaesthetize gastric mucosa**. It produces symptomatic relief in gastritis. It is available in combination with antacids.

TECHNIQUES OF LOCAL ANAESTHESIA (Table 5.8)**Surface Anaesthesia (Topical Anaesthesia)**

LA is applied on the abraded skin and mucous membrane of the nose, mouth, eyes, throat, upper respiratory tract, oesophagus, urethra, ulcers, burns, fissures, etc. Motor function is intact. Tetracaine 2%, lignocaine 2%–10%, benzocaine 1%–2%, etc. are used for topical application. Surface anaesthetics are available as solution, ointment, gel, jelly, cream, spray, lozenges, etc.

Addition of adrenaline does not prolong the duration of surface anaesthesia because of poor penetration. Topical anaesthetics are useful in many diagnostic procedures like tonometry in eye and during endoscopies.

EMLA is used to anaesthetize the intact skin and structures in the superficial subcutaneous tissues.

Infiltration Anaesthesia

LA is injected directly into tissues to be operated; it blocks sensory nerve endings. The most frequently used LAs for infiltration are lignocaine (0.5%–1%), procaine (0.5%–1%) and bupivacaine (0.125%–0.25%). Addition of adrenaline to LA (1:50,000–250,000) prolongs the duration of anaesthesia.

Infiltration anaesthesia is suitable only for small areas. The main disadvantage of infiltration anaesthesia is the requirement of large amounts of the drug to anaesthetize relatively small area. It can be used for drainage of an abscess, excision of small swelling,

Table 5.8 ■ Methods of administration and uses of local anaesthetics

LA technique	Drugs	Therapeutic application (uses)
Surface anaesthesia (topical)	• Lignocaine (2%–10%) • Tetracaine (2%) • Benzocaine	Anaesthetize mucous membrane of the eyes, nose, mouth, cornea, urinary and upper respiratory tracts, fissures, ulcers, etc.
Infiltration anaesthesia	Most of the anaesthetics • Lignocaine (0.5%–1%) • Procaine (0.5%–1%) • Bupivacaine (0.125%–0.25%) • Ropivacaine	• Abscess drainage • Excision of small swellings (e.g. lipoma) • Suturing of cut wounds, episiotomy, etc.
Nerve block anaesthesia	Most of the anaesthetics	Used for surgery and neuralgias
Spinal anaesthesia	• Lignocaine (1.5%–5%) • Tetracaine (0.25%–0.5%) • Bupivacaine (0.5%–0.75%)	Surgery on lower limbs, lower abdomen, perineum, etc., caesarean section
Epidural anaesthesia	• Lignocaine (2%) • Bupivacaine (0.5%–0.75%) • Ropivacaine	Obstetric analgesia
i.v. regional anaesthesia (Bier's block)	• Lignocaine (0.5%) • Prilocaine (0.5%)	For upper and lower limb surgeries
To anaesthetize gastric mucosa	• Oxethazaine	Peptic ulcer

suturing of cut wounds, episiotomy, etc. Infiltration anaesthesia is contraindicated, if there is local infection and clotting disorders.

Conduction Block

(i) *Field Block Anaesthesia*. It is achieved by injecting an LA subcutaneously, which anaesthetizes the area distal to the injection. This principle is used in case of minor procedures of scalp, anterior abdominal wall, upper and lower extremities in which a smaller dose produces larger area of anaesthesia.

(ii) *Nerve Block Anaesthesia*. LA is injected very close to or around the peripheral nerve or nerve plexuses. It produces larger areas of anaesthesia than field block.

1. Brachial plexus block for procedures on upper limb.
2. Cervical plexus block for surgery of the neck.
3. Intercostal nerve block for anterior abdominal wall surgery.
4. Sciatic and femoral nerve block for surgery distal to the knee.

In this procedure, the requirement of LA is less than that of field block and infiltration anaesthesia.

Spinal Anaesthesia

It is one of the most popular forms of anaesthesia. LA is injected into the subarachnoid space to anaesthetize spinal roots.

Site of Injection. The anaesthetic is injected into the space between L2 and L3 or L3 and L4 below the lower end of the spinal cord. The level of anaesthesia is influenced by (i) site of injection, (ii) amount of fluid injected, (iii) force of injection, (iv) specific gravity of the drug solution (hyperbaric [in 10% glucose], hypobaric [in distilled water] or isobaric) and (v) position of the patient – lying prone/lateral or tilted with head-down position.

LAs Used for Spinal Anaesthesia. They are lignocaine, tetracaine, bupivacaine, etc. Addition of adrenaline to spinal anaesthetic increases the duration or intensity of block.

Uses. Spinal anaesthesia can be used for surgical procedures below the level of umbilicus, i.e. lower limb surgery, caesarean section, obstetric procedures, prostatectomy, surgery on perineum, appendicectomy, etc.

Advantages of Spinal Anaesthesia. No loss of consciousness, good muscle relaxation and good analgesia. Patients with cardiac, pulmonary and renal disease tolerate spinal anaesthesia better than GA.

Complications

1. Headache is due to leakage of CSF and can be reduced by using very fine needle.
2. Hypotension is due to blockade of sympathetic vasoconstrictor fibres to blood vessels. Venous return to the heart is reduced due to paralysis of skeletal muscles in the legs. Hypotension is treated by raising foot end and administration of sympathomimetics such as ephedrine, mephentermine and phenylephrine.
3. Respiratory paralysis: It is due to paralysis of intercostal muscles. Respiratory failure may occur due to respiratory centre ischaemia as a result of hypotension.
4. Septic meningitis and nerve injury are extremely rare at present, because of good anaesthetic practice.
5. Postoperative urinary retention may occur.

Contraindications. Spinal anaesthesia should not be used in young children, vertebral abnormalities, sepsis in the region of lumbar puncture site, hypotension and shock.

Epidural Anaesthesia

LA is injected into epidural space (thoracic or lumbar region or sacral canal) where it acts on spinal nerve roots. Lignocaine and bupivacaine are commonly used. It is safer, but the technique is more difficult than spinal anaesthesia. Epidural anaesthesia is slower in onset than spinal anaesthesia. It requires a much larger amount of the drug. Epidural analgesia is being used in obstetrics during labour. Low concentration of bupivacaine or ropivacaine is used to block pain sensation without significant motor block. Ropivacaine is less cardiotoxic and motor blockade is less than bupivacaine.

Intravenous Regional Anaesthesia (Bier's Block)

It is mainly used in anaesthetizing the upper limb. Lignocaine and prilocaine are commonly used. LA is injected into vein of the limb in which the blood flow is occluded by a tourniquet.

Drug Interactions

1. **Lignocaine × propranolol:** Propranolol by reducing hepatic blood flow, impairs the clearance of lignocaine, which may result in toxicity.
2. **Procaine × sulphonamides:** Procaine is hydrolysed to PABA – reduces the effect of sulphonamides.

Alcohols (Ethanol and Methanol)

PH1.20

The actions of alcohol are depicted in Fig. 5.7.

- Ethyl alcohol follows zero-order kinetics of elimination.
- In chronic alcoholics, increased amount of toxic metabolite of paracetamol is formed as a result of induction of its metabolizing enzyme, CYP2E1.
- As alcohol is present in exhaled air, it can be detected by breath analyser.

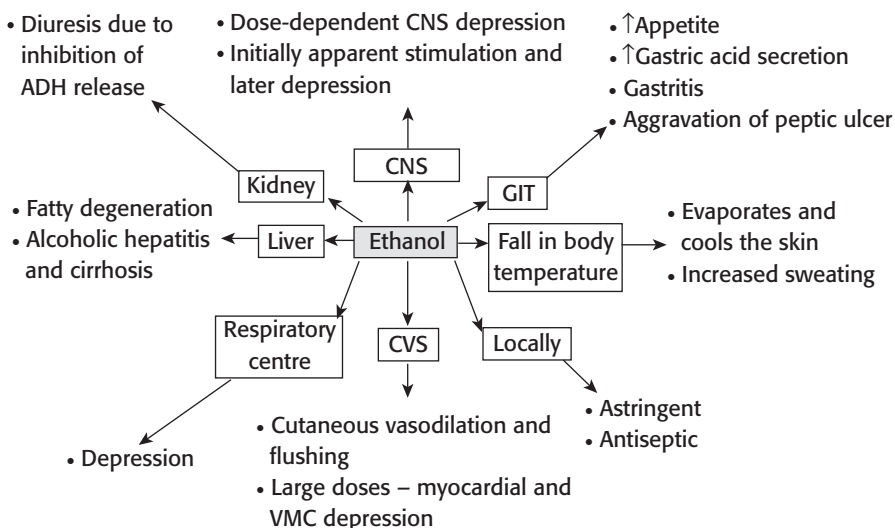


Fig. 5.7 Actions of alcohol. CNS, Central nervous system; ADH, antidiuretic hormone; VMC, vasomotor centre (medulla); CVS, cardiovascular system; GIT, gastrointestinal tract.

THERAPEUTIC USES OF ALCOHOL

1. **Antiseptic:** 70% ethyl alcohol is used as an antiseptic on skin before giving injection and surgical procedure. Its antiseptic efficacy decreases above 90%. It should not be used on open wounds, mucosa, ulcers and on scrotum as it is highly irritant. It is not useful for disinfecting instruments as it promotes rusting.
2. **Trigeminal and other neuralgias:** Injection of alcohol directly into nerve trunk relieves pain by destroying them.
3. **Prevent bedsores:** Alcohol is used locally to prevent bedsores in bedridden patients.
4. **Methanol poisoning:** Ethanol competes with methanol for metabolic enzymes and saturates them. Hence, it prevents the formation of toxic metabolites of methanol (formaldehyde and formic acid).
5. **Fever:** Alcoholic sponges are useful to reduce body temperature.

Acute Ethanol Overdosage (Acute Alcohol Intoxication). The signs and symptoms of acute alcohol intoxication are drowsiness, nausea, vomiting, ataxia, hypotension, respiratory depression, hypoglycaemia, etc.

Treatment (Note A–G). It is a medical emergency. The main aim of therapy is to prevent severe respiratory depression and aspiration of vomitus.

1. Maintain Airway, Breathing, Circulation, Fluid and Electrolyte balance, and Gastric lavage if necessary.
2. Intravenous glucose to correct hypoglycaemia.
3. Thiamine is administered as i.v. infusion in glucose solution.
4. HaemoDialysis helps to hasten the recovery.

Withdrawal Syndrome. Sudden reduction/stoppage of alcohol in chronic alcoholics results in alcohol withdrawal syndrome. It manifests as restlessness, tremors, insomnia, nausea, vomiting, hallucinations, delirium, convulsions and collapse.

Treatment of Alcohol Withdrawal Syndrome

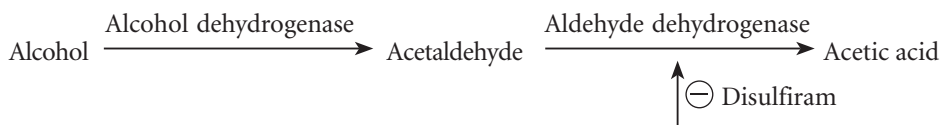
- BZDs (diazepam, chlordiazepoxide, etc.) are used to control anxiety, tremor, palpitation, sleep disturbances, confusion and convulsions associated with alcohol withdrawal.
- Psychological support.

Treatment of Chronic Alcoholism

PH1.23

- Psychotherapy, occupational therapy and rehabilitation
- Drug treatment of chronic alcoholism

(a) Disulfiram (alcohol aversion therapy): It causes aversion to alcohol.



Disulfiram inhibits aldehyde dehydrogenase and causes accumulation of acetaldehyde in blood and tissues (acetaldehyde syndrome). The signs and symptoms include nausea, vomiting, flushing, headache, sweating, tachycardia, palpitation, breathlessness, chest pain, hypotension, hypoglycaemia, confusion, shock and even death. This reaction is unpleasant; hence, person on disulfiram develops aversion to alcohol.

Drugs like metronidazole, griseofulvin and cefoperazone also have disulfiram-like action and produce similar reaction with alcohol. Doctors should warn the patient not to take alcohol and alcohol-containing products when they are on above-mentioned drugs.

- (b) *Naltrexone* (opioid antagonist): It reduces alcohol craving and helps to maintain abstinence.
- (c) *Acamprosate*: It activates GABA_A receptors and reduces relapse.
- (d) *Ondansetron* (5-HT₃ antagonist): It reduces alcohol consumption.
- (e) *Topiramate*: It decreases craving for alcohol.

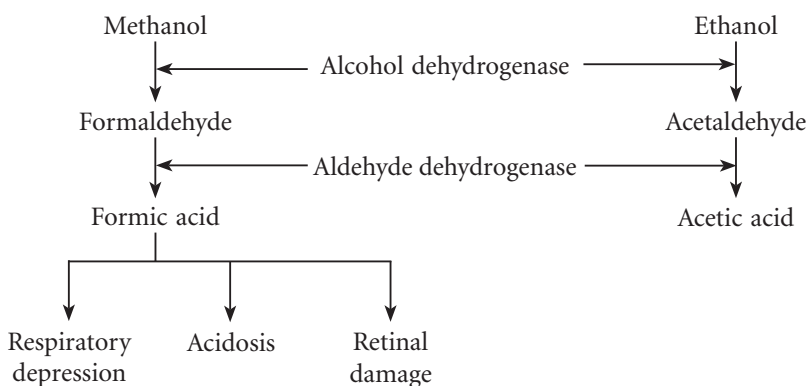
METHANOL POISONING (METHYL ALCOHOL POISONING)

PH1.21

This occurs when methylated spirit is consumed or when liquor is adulterated with methyl alcohol. Methanol is a mild CNS depressant. It is metabolized to formaldehyde and formic acid which, in turn, cause metabolic acidosis and injury to retina. The signs and symptoms of methanol poisoning are nausea, vomiting, abdominal pain, headache, vertigo, confusion, hypotension, convulsions and coma. Metabolic acidosis is due to formic acid which also causes dimness of vision, retinal damage and blindness.

Treatment

1. Patient is kept in a dark room to protect the eyes from light.
2. Maintain airway, breathing and circulation.
3. Gastric lavage is done after endotracheal intubation.
4. Intravenous sodium bicarbonate is given to correct acidosis and to prevent retinal damage.
5. Ethanol (10%) is administered via nasogastric tube. Ethanol competes with methanol for metabolic enzymes and saturates them, thus prevents formation of toxic metabolites (formaldehyde and formic acid). Methanol is excreted unchanged in urine and breath.

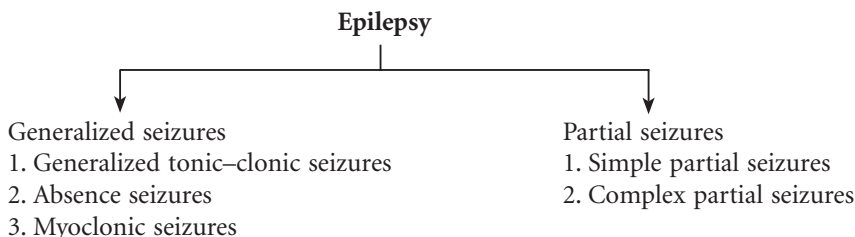


6. Fomepizole, an alcohol dehydrogenase inhibitor, is the preferred agent for the treatment of methanol poisoning. CNS depression is rare with fomepizole as compared to ethanol. It can also be used in ethylene glycol poisoning.
7. Calcium leucovorin is administered intravenously (folate adjuvant therapy) to enhance metabolism of formate, thereby decreasing its levels.
8. Haemodialysis is done to promote excretion of methanol and its toxic metabolites.

Antiepileptic Drugs

PH1.19

Epilepsy is a Greek word that means convulsions. Epilepsy is a disorder of brain function characterized by paroxysmal cerebral dysrhythmia. Major types of epilepsy are shown below.



GENERALIZED SEIZURES

1. **Generalized tonic-clonic seizures (GTCS, grand mal epilepsy):** It is characterized by the following sequence of symptoms: Aura–epileptic cry–loss of consciousness–fall to the ground–tonic phase–clonic phase–period of relaxation–postepileptic automatism with confusional states.
2. **Absence seizures (petit mal epilepsy):** It is characterized by sudden onset of staring, unresponsiveness with momentary loss of consciousness.
3. **Myoclonic seizures:** It consists of single or multiple sudden, brief, shock-like contractions.

PARTIAL SEIZURES

1. **Simple partial seizures (SPS):** The manifestations depend on the region of cortex involved. There may be convulsions (focal motor symptoms) or paraesthesia (sensory symptoms) without loss of consciousness.
2. **Complex partial seizures (CPS, temporal lobe epilepsy, psychomotor epilepsy):** It is characterized by aura–amnesia–abnormal behaviour and automatism with impaired consciousness.

CHEMICAL CLASSIFICATION OF ANTIEPILEPTIC DRUGS

1. **Hydantoins:** Phenytoin, fosphenytoin.
2. **Barbiturate:** Phenobarbitone.
3. **Iminostilbenes:** Carbamazepine, oxcarbazepine.
4. **Carboxylic acid derivatives:** Sodium valproate, divalproex.
5. **Succinimide:** Ethosuximide.
6. **BZDs:** Lorazepam, diazepam, clonazepam, clobazam.
7. **Others:** Lamotrigine, topiramate, gabapentin, pregabalin, tiagabine, vigabatrin, zonisamide, levetiracetam, lacosamide.

CLINICAL CLASSIFICATION OF ANTIEPILEPTIC DRUGS

The classification of antiepileptic drugs is presented in [Table 5.9](#).

Table 5.9 ■ Antiepileptic drugs: clinical classification

Seizure type	Preferred drug	Alternative/adjunct drugs
Generalized tonic-clonic seizures (grand mal epilepsy)	• Sodium valproate • Lamotrigine • Carbamazepine	• Oxcarbazepine • Levetiracetam • Phenytoin • Clobazam • Topiramate • Phenobarbitone
Simple/complex partial seizures (SPS)	• Carbamazepine • Lamotrigine • Sodium valproate	• Levetiracetam • Gabapentin, phenytoin • Topiramate • Tiagabine • Zonisamide
Absence seizures (petit mal epilepsy)	• Sodium valproate • Ethosuximide	• Clonazepam • Lamotrigine • Clobazam • Levetiracetam • Topiramate
Myoclonic seizures	• Sodium valproate	• Clonazepam • Clobazam • Levetiracetam • Topiramate
Status epilepticus	• Lorazepam • Diazepam • Fosphenytoin • Phenytoin • Phenobarbitone	General anaesthetics • Midazolam • Propofol

MECHANISM OF ACTION OF ANTIEPILEPTIC DRUGS (Fig. 5.8A and B)

Phenytoin (Diphenylhydantoin)

Phenytoin is one of the most commonly used antiepileptic drugs. It has a selective anti-epileptic effect and does not produce significant drowsiness.

Mechanism of Action. Phenytoin acts by stabilizing neuronal membrane (Fig. 5.9) and prevents spread of seizure discharges. The sodium channels exist in three forms: resting, activated and inactivated states. Phenytoin delays recovery of Na^+ channels from inactivated state, thereby reduces neuronal excitability (Fig. 5.9) and inhibits high-frequency firing.

At high concentrations, phenytoin inhibits Ca^{2+} influx into neuron, reduces glutamate levels and increases responses to GABA.

Pharmacokinetics. Phenytoin is absorbed slowly through the GI tract, widely distributed and highly (about 90%) bound to plasma proteins. It is almost completely metabolized in liver by hydroxylation and glucuronide conjugation. Repeated administration of phenytoin causes enzyme induction and increases the rate of metabolism of co-administered drugs. Phenytoin exhibits dose-dependent elimination, i.e. at low concentration (<10 mcg/mL), elimination occurs by first-order kinetics and plasma half-life is

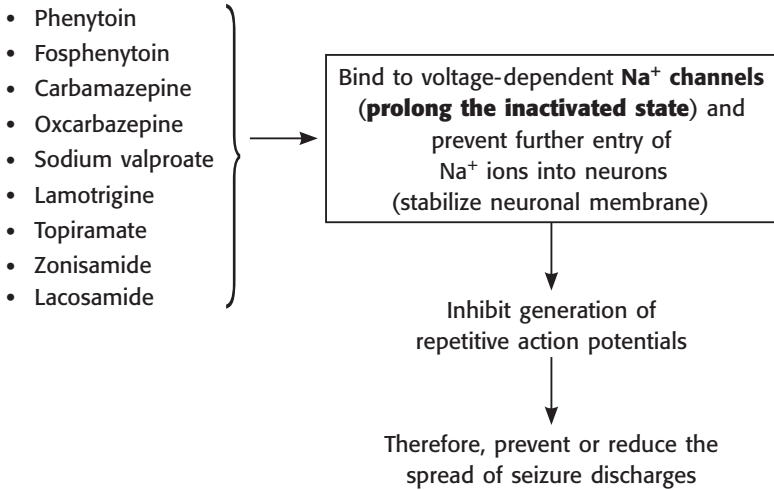


Fig. 5.8 (A) Mechanism of action of antiepileptic drugs: effect on sodium channels.

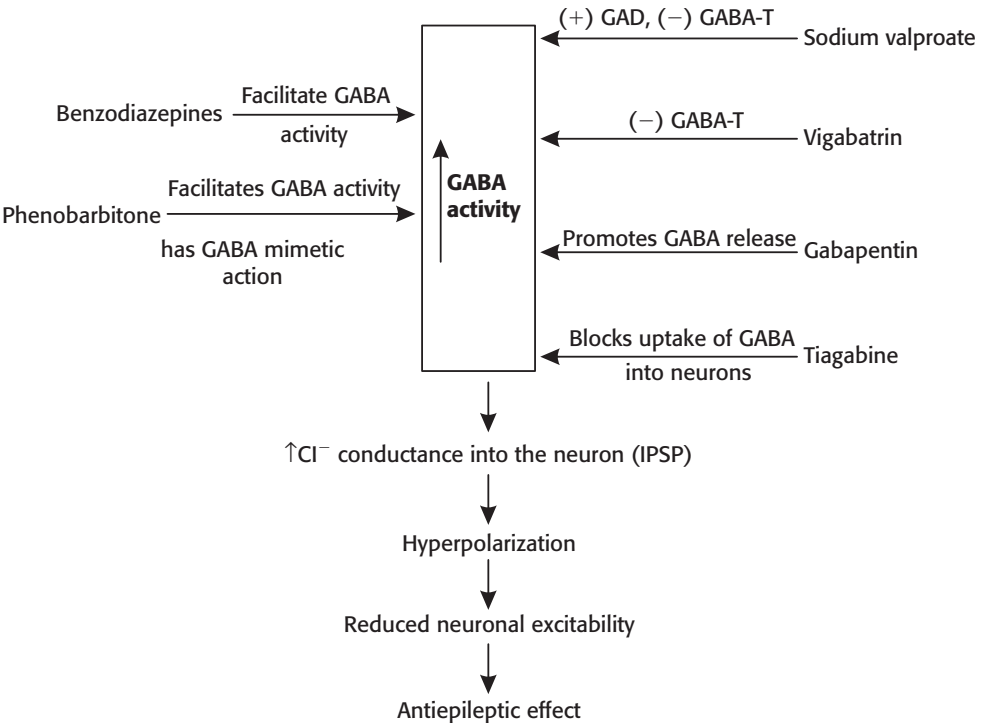


Fig. 5.8 (B) Mechanism of action of antiepileptics: effect on GABA. GAD, Glutamic acid de-carboxylase; GABA-T, GABA transaminase; IPSP, inhibitory postsynaptic potential.

10–24 hours; as the rate of administration increases, the metabolizing enzymes get saturated, kinetics changes to zero order, and plasma half-life increases to 60 hours; the plasma concentration increases markedly with slight increase in dose resulting in toxicity. Hence, therapeutic monitoring of phenytoin is essential for adjustment of dosage.

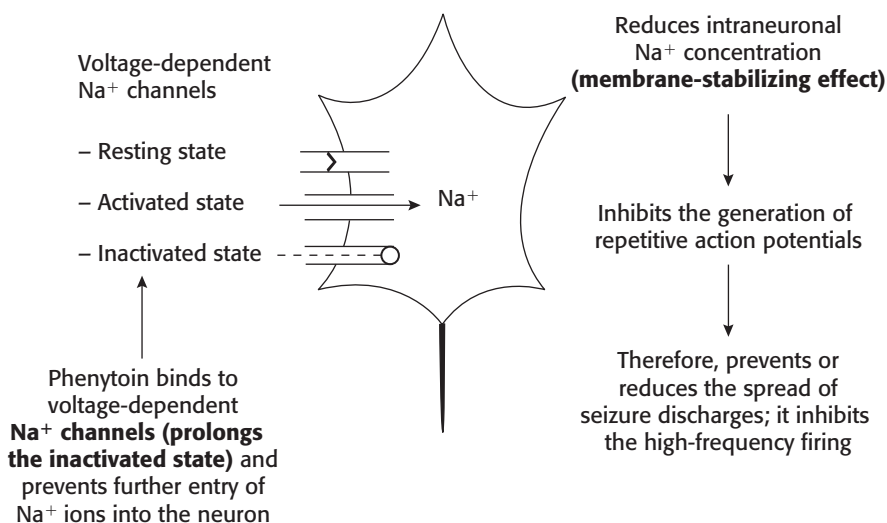


Fig. 5.9 Mechanism of action of phenytoin.

Uses. Phenytoin is used for the treatment of:

1. Generalized tonic-clonic seizures (grand mal epilepsy).
2. Partial seizures.
3. Trigeminal and other neuralgias.
4. Status epilepticus: Phenytoin is administered intravenously in normal saline (it precipitates in glucose solution).

Adverse Effects (Note the 'H's). Phenytoin has dose-dependent toxicity. The adverse effects are as follows:

1. **Hypertrophy** and **Hyperplasia** of gums (due to defect in collagen catabolism) – seen on chronic therapy and can be minimized by proper oral hygiene.
2. **Hypersensitivity** reactions include skin rashes, neutropenia and rarely **Hepatic** necrosis.
3. **Hirsutism** – due to increased androgen secretion.
4. **Hyperglycaemia** – due to decreased insulin release.
5. Megaloblastic anaemia – due to folate deficiency.
6. Osteomalacia – due to increased metabolism of vitamin D.
7. **Hypocalcaemia** – due to decreased absorption of Ca^{2+} from the gut.
8. Fetal **Hydantoin** syndrome – cleft lip, cleft palate, digital **Hypoplasia**, etc. due to use of phenytoin during pregnancy.

At high concentration, phenytoin may cause the following side effects:

1. **CNS:** Vestibulocerebellar syndrome – vertigo, ataxia, tremor, headache, nystagmus, psychological disturbances, etc. occur on chronic therapy.
2. **CVS:** Hypotension and cardiac arrhythmias may occur on i.v. administration; extravasation of the drug causes local tissue necrosis.
3. **GIT:** Nausea, vomiting and dyspepsia can be minimized by giving phenytoin after food.

Fosphenytoin

It is a prodrug of phenytoin, which is converted to phenytoin by phosphatases. Dose of fosphenytoin is expressed as phenytoin equivalents (PE). It is available for i.m. and i.v.

administration. Fosphenytoin can be administered in normal saline or glucose. It has significantly *less* irritant effect on the veins than phenytoin. It is preferred to phenytoin in status epilepticus because of above advantages. The rate of i.v. infusion should not exceed 150 mg PE/minute. Hypotension and cardiac arrhythmias may occur with rapid administration.

Carbamazepine (Iminostilbene)

Carbamazepine is chemically related to tricyclic antidepressants (TCAs).

Mechanism of Action. Like phenytoin, carbamazepine slows the rate of recovery of Na⁺ channels from inactivation, thereby reduces neuronal excitability.

Pharmacokinetics. Carbamazepine is absorbed slowly and erratically from GI tract, binds to plasma proteins, is well distributed in the body including the cerebrospinal fluid (CSF) and metabolized in liver. One of its metabolites retains anticonvulsant activity. Repeated use causes enzyme induction and reduces the effectiveness of the drug itself (autoinduction) as well as that of valproate, phenytoin, lamotrigine, topiramate, OC pills, etc.

Adverse Effects. The common adverse effects of carbamazepine include sedation, drowsiness, vertigo, ataxia, diplopia, blurred vision, nausea, vomiting and confusion. Hypersensitivity reactions are skin rashes, eosinophilia, lymphadenopathy and hepatitis. Rarely, it causes bone marrow depression with neutropenia, aplastic anaemia and agranulocytosis. On chronic therapy, it may cause water retention due to the release of antidiuretic hormone (ADH).

Uses

1. Carbamazepine is one of the most commonly used antiepileptic drugs. It is the drug of choice in GTCS and partial (SPS and CPS) seizures.
2. Carbamazepine is the drug of choice in the treatment of trigeminal neuralgias. It inhibits high-frequency discharges. The other drugs useful are phenytoin, gabapentin, TCAs (amitriptyline), etc. Other treatment options are surgical division, cryosurgery, injection of alcohol or phenol in close proximity to nerve or ganglia. It is not effective for diabetic neuropathy.
3. It is used in the treatment of acute mania and bipolar disorder.

Oxcarbazepine (Iminostilbene)

Oxcarbazepine is an analogue of carbamazepine. Mechanism of action and therapeutic uses are similar to carbamazepine. It is a prodrug and is converted to active form after administration. Its enzyme-inducing property is much *less*; hence, drug interactions are few. It is *less* potent and *less* hepatotoxic than carbamazepine.

Eslicarbazepine

It is similar in structure to carbamazepine. It is useful for treatment of partial seizures.

Phenobarbitone (Barbiturate)

Phenobarbitone is a barbiturate and was widely used as an antiepileptic drug. Its use has declined because of availability of safer drugs. It acts by potentiating GABA activity. Phenobarbitone is absorbed slowly but completely after oral administration; about 50% is bound to plasma proteins. Repeated administration causes enzyme induction and reduces the effectiveness of co-administered drugs.

Adverse Effects. The most common side effect of phenobarbitone is sedation, but tolerance develops gradually with continued administration. The other side effects are

nystagmus, ataxia, confusion, megaloblastic anaemia and skin rashes. On chronic therapy, it may cause behavioural disturbances with impairment of memory in children (see Pharmacological actions of barbiturates on pp. 170–171).

Uses. Phenobarbitone is effective in GTCS and partial seizures. It is the cheapest antiepileptic drug. It is also useful in the prophylactic treatment of febrile convulsions. In status epilepticus, phenobarbitone is injected intravenously when convulsions are not controlled with diazepam and phenytoin.

Ethosuximide (Succinimide)

It is effective for the treatment of absence seizures. It acts by inhibiting T-type Ca^{2+} current in thalamic neurons. It is completely absorbed after oral administration. The common side effects are GI disturbances like nausea, vomiting and anorexia. The other side effects are headache, hiccough, eosinophilia, neutropenia, thrombocytopenia with bone marrow depression and rarely skin rashes.

Valproic Acid (Sodium Valproate): Carboxylic Acid Derivative

Sodium valproate is a broad-spectrum antiepileptic drug.

Mechanism of Action

1. Like phenytoin and carbamazepine, valproate delays the recovery of Na^+ channels from inactivation.
2. Like ethosuximide, it blocks T-type Ca^{2+} current in thalamic neurons.
3. Increases the activity of GABA in the brain by:
 - (a) Increased synthesis of GABA by stimulating GAD (glutamic acid decarboxylase) enzyme.
 - (b) Decreased degradation of GABA by inhibiting GABA-T (GABA-transaminase) enzyme.

Pharmacokinetics. Valproate is rapidly and almost completely absorbed from the GI tract, highly (about 90%) bound to plasma proteins, metabolized in liver and excreted in urine.

Adverse Effects (Note the Mnemonic VALPROATE)

1. The common side effects related to GI tract are nausea, Vomiting, Anorexia and abdominal discomfort.
2. CNS side effects include sedation, ataxia and tremor.
3. A rare but serious complication is fulminant hepatitis (Liver), hence avoided in children younger than 3 years. Monitoring of hepatic function is essential during valproate therapy; Elevation of liver enzymes occurs.
4. Teratogenicity: Orofacial and digital abnormalities; neural tube defects with increased incidence of spina bifida, so it should not be given during pregnancy.
5. The other adverse effects include skin Rashes, Alopecia and curling of hair; acute Pancreatitis may occur rarely.

Uses. Sodium valproate is highly effective in absence, myoclonic, partial (SPS and CPS) and generalized tonic–clonic seizures. Other uses of valproate are mania, bipolar disorder and migraine prophylaxis.

Divalproex: It contains valproic acid and sodium valproate in 1:1 ratio. It is administered orally. It causes less GI side effects than valproic acid.

Diazepam, Lorazepam, Clonazepam (Benzodiazepines)

Diazepam and lorazepam are effective in controlling status epilepticus. Intravenous diazepam is used in the emergency treatment of status epilepticus, tetanus, eclamptic convulsions, febrile convulsions, drug-induced convulsions, etc. Diazepam has a rapid onset but short duration of action; hence, repeated doses are required. Diazepam can be administered rectally in children during emergency. Lorazepam is preferred in status epilepticus because:

- 1. It has a rapid onset and long duration of action.
- 2. It has less damaging effect on injected vein.

Clonazepam, a long-acting BZD, is used in absence and myoclonic seizures.

Mechanism of Action (See p. 166)

Adverse Effects. Intravenous diazepam and lorazepam may cause hypotension and respiratory depression. The main side effects of clonazepam are sedation and lethargy, but tolerance develops on chronic therapy. Other side effects are hypotonia, dysarthria, dizziness and behavioural disturbances like irritability, hyperactivity and lack of concentration.

Newer Antiepileptics

These are lamotrigine, topiramate, zonisamide, lacosamide, gabapentin, pregabalin, tiagabine, vigabatrin and levetiracetam. They are administered orally. Important features are given in [Table 5.10](#).

Table 5.10 ■ Newer antiepileptics

Drugs	Mechanism of action	Uses	Adverse effects and other important points
Lamotrigine	Delays the recovery of Na ⁺ channels from inactivation	As monotherapy or add-on therapy in GTCS, absence, myoclonic and partial (SPS and CPS) seizures	• Sedation, ataxia, headache, nausea, vomiting and skin rashes • Enzyme inhibitors – like sodium valproate increases its plasma concentration • Enzyme inducers – carbamazepine, phenytoin, etc. decrease its plasma concentration
Topiramate	• Delays the recovery of Na⁺ channels from inactivation • Increases GABA, decreases glutamate activity	• Can be used as monotherapy in GTCS, myoclonic and partial (SPS and CPS) seizures • Migraine prophylaxis • Chronic alcoholism	• Sedation, ataxia, weight loss, nervousness and confusion • Reduces the effectiveness of oral contraceptives

Table 5.10 ■ Newer antiepileptics—cont'd

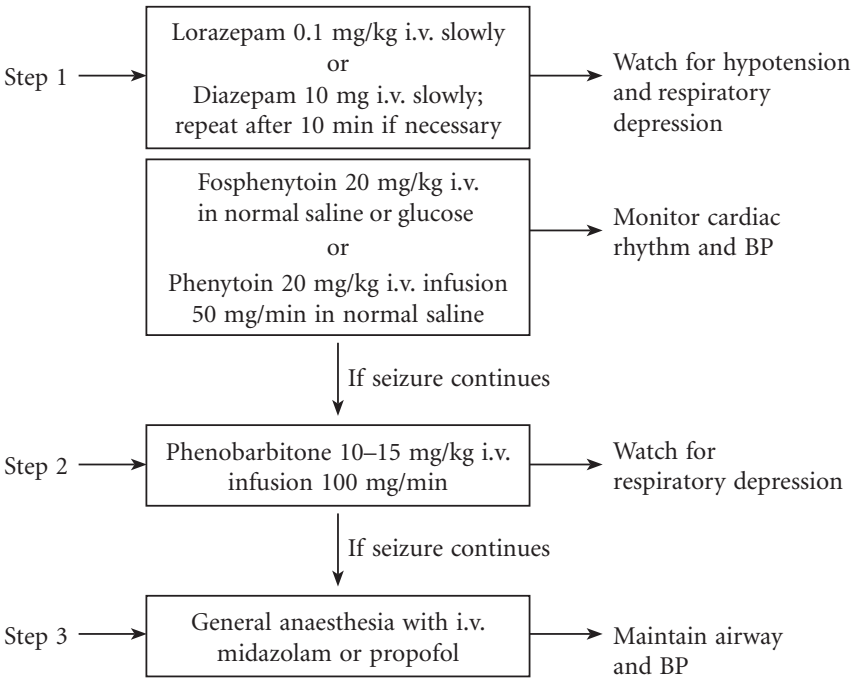
Drugs	Mechanism of action	Uses	Adverse effects and other important points
Zonisamide	Delays the recovery of Na ⁺ channels from inactivation	As add-on drug in simple partial and complex partial seizures	- Ataxia, headache, sedation and nervousness - Structurally related to sulphonamides
Lacosamide	Delays the recovery of Na ⁺ channels from inactivation	As add-on drug in refractory partial seizures	Dizziness, diplopia, ataxia and cardiac arrhythmias
Gabapentin	Acts by releasing GABA	- Used as adjunct in partial (SPS and CPS) seizures - Diabetic neuropathy - Bipolar disorders - Postherpetic neuralgias - Prophylaxis of migraine	- Sedation, fatigue, headache - Drug interactions are rare
Pregabalin	Acts by releasing GABA	Useful in partial seizures and neuralgias	Skin rashes and sedation
Tiagabine	Inhibits the uptake of GABA into the neurons, thus, increases GABA activity	Used as add-on drug in partial seizures	Sedation, dizziness
Vigabatrin	Increases GABA activity in brain by inhibiting GABA transaminase	As an adjunct in partial seizures	Visual disturbances, sedation, confusion and psychosis
Levetiracetam	Not exactly known; binds to synaptic vesicle protein and modulates release of neurotransmitters like GABA	As an adjunct in GTCS, partial and myoclonic seizures	Sedation, dizziness and fatigue

STATUS EPILEPTICUS

It is a medical emergency and should be treated immediately. It is characterized by recurrent attacks of tonic–clonic seizures without the recovery of consciousness in between or a single episode lasts longer than 30 minutes.

Treatment

- 1. Hospitalize the patient.
- 2. Maintain airway and establish a proper i.v. line.
- 3. Administer oxygen.
- 4. Collect blood for estimation of glucose, calcium, electrolytes and urea.
- 5. Maintain fluid and electrolyte balance.



Dose and drug interactions of antiepileptics are summarized in [Table 5.11](#).

Table 5.11 ■ Total daily dose and drug interactions of antiepileptics

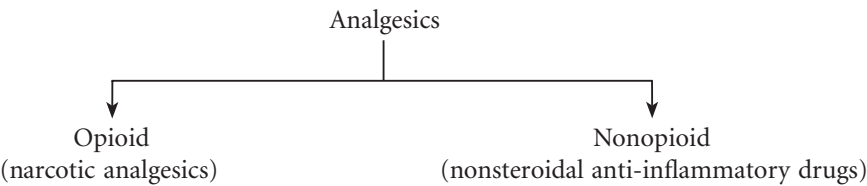
Drug	Dose	Interactions
Phenytoin	200–400 mg	1. <i>Phenytoin</i> × <i>OC pills, steroids, vitamin D, theophylline, etc.</i> Phenytoin induces microsomal enzymes and enhances the breakdown of OC pills, vitamin D, steroids, etc. reduces the effectiveness of co-administered drug 2. <i>Phenytoin</i> × <i>carbamazepine</i> Mutual induction of metabolism and reduced plasma concentration of both the drugs 3. <i>Chloramphenicol</i> <i>NH</i> <i>Warfarin</i> } × <i>Phenytoin</i> These drugs inhibit the metabolism of phenytoin → plasma concentration of phenytoin increases → phenytoin toxicity may occur

Table 5.11 ■ Total daily dose and drug interactions of antiepileptics—cont'd

Drug	Dose	Interactions
Carbamazepine	600–1200 mg	<i>Carbamazepine</i> × <i>phenytoin</i> , <i>phenobarbitone</i> , <i>sodium valproate</i> , <i>OC pills</i> 1. <i>Carbamazepine</i> induces the metabolism of these drugs and reduces their effects 2. <i>INH</i> <i>Erythromycin</i> } × <i>Carbamazepine</i> These drugs inhibit carbamazepine metabolism; carbamazepine toxicity may occur
Phenobarbitone	100–200 mg	<i>Phenobarbitone</i> × <i>OC pills</i> , <i>warfarin</i> , <i>griseofulvin</i> , <i>theophylline</i> Phenobarbitone induces the metabolism of these drugs and reduces their effects
Ethosuximide	500–1500 mg	<i>Ethosuximide</i> × <i>valproate</i> Valproate inhibits the metabolism and increases plasma concentration of ethosuximide
Sodium valproate	1500–2000 mg	<i>Sodium valproate</i> × <i>phenytoin</i> : Phenytoin toxicity can occur due to displacement interaction <i>Sodium valproate</i> × <i>phenobarbitone</i> : Valproate inhibits the degradation of phenobarbitone and increases its plasma concentration <i>Sodium valproate</i> × <i>carbamazepine</i> : Increased incidence of teratogenicity when administered simultaneously

Analgesics

Analgesics are drugs that relieve pain without significantly altering consciousness. They relieve pain without affecting its cause.



Opioid Analgesics

PH1.19

Morphine is the most important alkaloid of opium – the dried juice obtained from the capsules of *Papaver somniferum*. Opium contains many other alkaloids, e.g. codeine, thebaine, papaverine, etc. The term ‘opiates’ refers to drugs derived from opium poppy, whereas ‘opioid analgesic’ applies to any substance (endogenous peptides or drugs), which produces morphine-like analgesia.

CLASSIFICATION OF OPIOIDS

1. Opioid agonists
 - (a) *Natural opium alkaloids*: Morphine, codeine, thebaine,* papaverine,* noscapine.*
 - (b) *Semisynthetic opiates*: Heroin, pholcodine,* hydromorphone, oxymorphone.
 - (c) *Synthetic opioids*: Pethidine, tramadol, tapentadol, methadone, dextropropoxyphene, fentanyl, alfentanil, sufentanil, remifentanil.
2. Opioid agonist–antagonists: Pentazocine, butorphanol, nalorphine, nalbuphine.
3. Partial μ -receptor agonist and κ -receptor antagonist: Buprenorphine.

Note: *Have no analgesic activity.

OPIOID RECEPTORS

The three main types of opioid receptors are μ (mu), κ (kappa) and δ (delta). These receptor-mediated effects are given below.

- μ : Analgesia (spinal + supraspinal level), respiratory depression, dependence, sedation, euphoria, miosis, decrease in GI motility.
- κ : Analgesia (spinal + supraspinal level), respiratory depression, dependence, dysphoria, psychotomimetic effect.
- δ : Analgesia (spinal + supraspinal level), respiratory depression, proconvulsant action.

OPIOID AGONISTS

Mechanism of Action

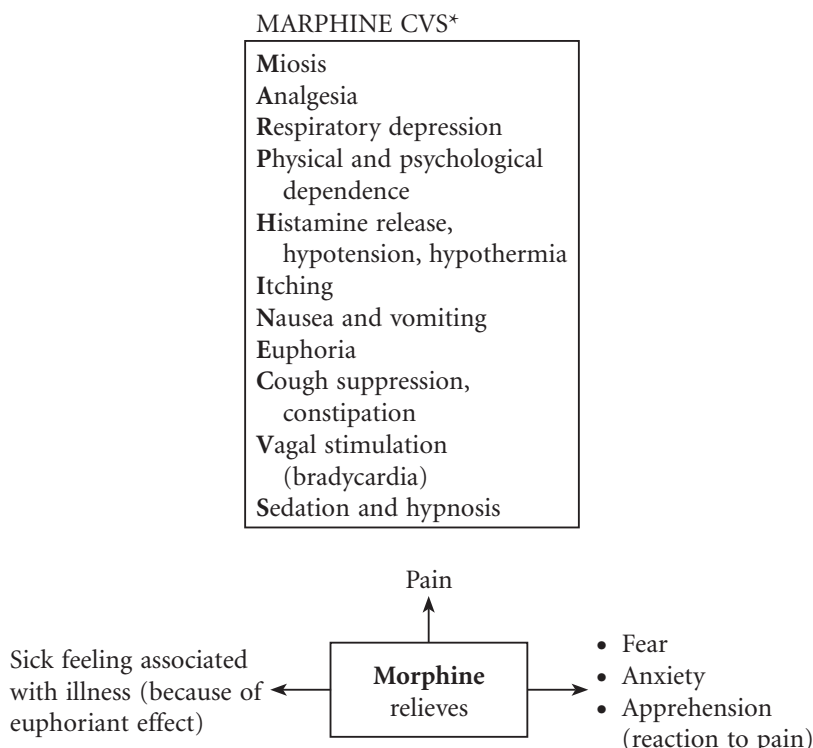
Morphine and other opioids produce their actions by interacting with various opioid receptors – mu (μ), delta (δ) and kappa (κ). They are located at spinal, supraspinal (medulla, midbrain, limbic system and cortical areas) and peripheral nerves. Morphine is the prototype drug.

Pharmacological Actions of Morphine. Morphine has mainly CNS-depressant effects but also has stimulant effects at certain sites in the CNS.

1. CNS

(a) The depressant effects:

- (i) **Analgesic effect:** Mediated mainly through μ -receptors at spinal and supraspinal sites (central action), it is the most important action of morphine. At the spinal level, it decreases release of excitatory neurotransmitters from primary pain afferents in substantia gelatinosa of dorsal horn. The excitability of neurons in dorsal horn is decreased. In the supraspinal level, it alters transmission of pain impulses. It is a very potent and efficacious analgesic. It causes sedation, drowsiness, euphoria, makes the person calm and raises the pain threshold. Perception of pain and reaction to it (fear, anxiety and apprehension) are altered by these drugs. Moderate doses of morphine relieve dull and continuous pain, whereas sharp, severe intermittent pain such as traumatic or visceral pain requires larger doses of morphine. Opioids also act peripherally to alter the sensitivity of small nerve endings in the skin to painful stimuli associated with tissue injury/inflammation.



Therefore, morphine relieves 'total pain'.

- (ii) Euphoria (feeling of well-being): It is an important component of analgesic effect. Anxiety, fear, apprehension associated with painful illness or injury are reduced by opioids.
 - (iii) Sedation: Morphine, in therapeutic doses, causes drowsiness and decreases physical activity.
 - (iv) Respiratory depression: It depresses respiration by a direct effect on the respiratory centre in the medulla; both rate and depth are reduced because it reduces sensitivity of respiratory centre to CO_2 . Respiratory depression is the commonest cause of death in acute opioid poisoning.
 - (v) Cough suppression: It has a direct action on cough centre in the medulla.
 - (vi) Hypothermia: In high doses, morphine depresses temperature-regulating centre and produces hypothermia.
- (b) **The stimulant effects:**
- (i) Miosis: Morphine produces constriction of pupils due to stimulation of III cranial nerve nucleus. Some tolerance develops to this action. Pin-point pupils are an important feature in acute morphine poisoning. Miosis is not seen on topical application of morphine to the eye.
 - (ii) Nausea and vomiting: It is due to direct stimulation of the CTZ in medulla. 5-HT_3 antagonists are the drugs of choice to control opioid-induced nausea and vomiting. H_1 -blockers, such as cyclizine or prochlorperazine may also be used.

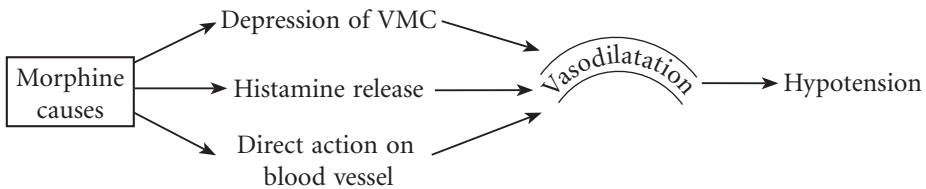
*Mnemonic for actions of morphine: 'MORPHINE CVS'.

(iii) Vagal centre: It stimulates vagal centre in the medulla and can cause bradycardia.

(c) **Other effects:**

Physical and psychological dependence: Repeated use of opioids causes physical and psychological dependence.

2. **CVS:** Morphine produces vasodilatation and fall of BP.



It mainly causes vasodilatation of peripheral vessels, which results in shift of blood from pulmonary to systemic vessels leading to relief of pulmonary oedema associated with acute left ventricular failure.

3. **GIT:** It causes constipation by direct action on GI tract and CNS – decreases GI motility and increases tone of the sphincters.
4. **Urinary bladder:** It may cause urinary retention by increasing tone of urethral sphincter.
5. **Biliary tract:** It increases intrabiliary pressure by increasing tone of sphincter of Oddi.
6. **Histamine release:** Morphine is a histamine liberator and causes itching, skin rashes, urticaria, vasodilatation, bronchoconstriction, etc.

Pharmacokinetics. On oral administration, morphine is absorbed slowly and erratically. It also undergoes extensive first-pass metabolism; hence, oral bioavailability of morphine is poor. Morphine is commonly administered by i.v., i.m. or s.c. routes. It can also be administered by oral, epidural or intrathecal routes. It is widely distributed in the body, crosses placental barrier and is metabolized in liver by glucuronide conjugation. Morphine-6-glucuronide has more potent analgesic action than morphine and is excreted in urine.

Adverse Effects

PH1.19

1. Nausea, vomiting and constipation.
2. Respiratory depression.
3. Hypotension due to vasodilatation.
4. Drowsiness, confusion and mental clouding.
5. Itching (due to histamine release) and skin rashes.
6. Difficulty in micturition.
7. Respiratory depression in newborn due to administration of morphine to the mother during labour.
8. Drug tolerance develops to most of the effects of morphine (some tolerance develops to miotic effect). There is cross-tolerance among the opioids.
9. Seizure threshold is lowered.
10. Drug dependence (physical and psychological dependence) is the main drawback of opioid therapy. Psychological dependence is associated with intense craving for the drug. Physical dependence is associated with the development of withdrawal symptoms (abstinence syndrome) when administration of an opioid is stopped abruptly. The symptoms and signs are irritability, body shakes,

yawning, lacrimation, sweating, fever, diarrhoea, palpitation, insomnia, rise in BP, loss of weight, etc. (the symptoms are just opposite to morphine actions). Dependence is mediated through μ -receptors.

Treatment of morphine dependence:

- (a) Hospitalization of the patient.
- (b) Gradual withdrawal of morphine.
- (c) Substitution therapy with methadone. Opioid agonist like methadone is preferred because:
 - (i) It is orally effective.
 - (ii) It has longer duration of action.
 - (iii) Withdrawal symptoms are mild.
- 1 mg of methadone will substitute 4 mg of morphine. Later, methadone is gradually reduced and completely stopped within 10 days. Buprenorphine can also be used for the treatment of opioid dependence.
- (d) Pure opioid antagonist like naltrexone is used after detoxification to produce opioid blockade to prevent relapse in patients who have a sincere desire to leave the habit. It is the preferred antagonist because it is orally effective and has a long duration of action.
- (e) Psychotherapy, occupational therapy, community treatment and rehabilitation.

PH1.23

11. Acute morphine poisoning: The characteristic triad of symptoms are respiratory depression, pinpoint pupils and coma. The other signs and symptoms are cyanosis, hypotension, shock and convulsions. Death is usually due to respiratory depression.

Treatment of acute morphine poisoning:

1. Hospitalization.
2. Maintain airway, breathing and circulation.
3. Ventilatory support (positive pressure respiration).
4. Gastric lavage with potassium permanganate.
5. Specific antidote: Naloxone 0.4–0.8 mg intravenously; dose is repeated till respiration becomes normal. Naloxone is a pure antagonist, competitively blocks opioid receptors and rapidly reverses the respiratory depression (Fig. 5.10). The duration of action of naloxone is short; hence, repeated administration is needed.

Note: Administration of naloxone to morphine addicts should be done with caution because it may precipitate severe withdrawal symptoms.

Contraindications

1. Head injury: Morphine is contraindicated in cases with head injury because:
 - (a) Vomiting, miosis and mental clouding produced by morphine interfere with assessment of progress in head injury patients.
 - (b) Morphine $\rightarrow$ Respiratory depression $\rightarrow$ CO_2 retention $\rightarrow$ Cerebral vasodilation $\rightarrow$ $\uparrow\uparrow$ Intracranial tension.
2. Bronchial asthma: Morphine may cause severe bronchospasm due to histamine release.

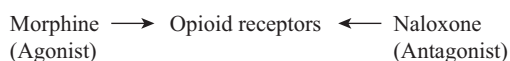


Fig. 5.10 Competitive antagonism.

3. COPD: It should be avoided in patients with low respiratory reserve – emphysema, chronic bronchitis, cor pulmonale, etc.
4. Hypotensive states: It should be used cautiously in shock or when there is reduced blood volume.
5. Hypothyroidism and hypopituitarism: There is a prolonged and exaggerated response to morphine.
6. Infants and elderly: They are more prone to respiratory depressant effect of morphine. In elderly male, there is an increased chance of urinary retention.
7. Undiagnosed acute abdominal pain: Morphine, if given before diagnosis interferes with diagnosis by masking the pain. Its spasmogenic effect may aggravate the pain (biliary colic).

Codeine: Natural Opium Alkaloid

1. Codeine has analgesic and cough-suppressant effects; it is administered orally.
2. Compared to morphine:
 - (a) It is less potent and less efficacious as an analgesic.
 - (b) It has less respiratory depressant effect.
 - (c) It is less constipating.
 - (d) It has low addiction liability.
3. It has selective cough suppressant effect (antitussive), hence used to suppress dry cough.
4. It potentiates analgesic effect of aspirin and paracetamol.

Codeine is used for relief of moderate pain. The main side effects are constipation and sedation.

Pholcodine: see p. 255

Pethidine (Meperidine) (Table 5.12). Pethidine is a synthetic opioid; it has some anticholinergic actions. Dry mouth and tachycardia can occur.

It can be administered by oral, i.v., s.c. and i.m. routes. It is well absorbed from the GI tract, but bioavailability is about 50% because of first-pass effect; widely distributed in the body, crosses placental barrier and is metabolized in liver. The metabolites are excreted in urine.

Adverse Effects. The adverse effects of pethidine are similar to those of morphine. It can cause tremors, hallucinations, muscle twitches and rarely convulsions due to its metabolite, norpethidine. Tolerance, physical and psychological dependence can also develop with pethidine.

Diphenoxylate. It is a pethidine congener and is useful in the treatment of diarrhoea. It is available in combination with atropine. It is rarely used at present because of its side effect (paralytic ileus).

Loperamide. Loperamide is a pethidine congener. It reduces GI motility and secretions but increases the tone of anal sphincter. It is used in the symptomatic treatment of diarrhoea. Common side effects are constipation and abdominal cramps.

Therapeutic Uses of Opioids

1. **As analgesic** (Fig. 5.11): Morphine and other opioids are potent and efficacious analgesics, hence used for moderate to severe painful conditions, such as acute myocardial infarction (MI), burns, pulmonary embolism, fracture mandible and

Table 5.12 ■ Comparative features of morphine and pethidine

Morphine	Pethidine (Meperidine)
Natural opium alkaloid	Synthetic opioid
Analgesic dose: 10 mg i.m., i.v. (morphine is 10 times more potent)	Analgesic dose: 100 mg i.m., i.v. (1/10 as potent as morphine)
It produces sedation, euphoria, respiratory depression and drug addiction	In equianalgesic doses, pethidine also produces same amount of sedation, euphoria, respiratory depression and drug addiction as morphine At times, pethidine can cause CNS stimulation with tremor, twitches and convulsions due to its metabolite, norpethidine
Effects on smooth muscles: 1. Constipation + 2. Biliary spasm + 3. Urinary retention + 4. Miosis +	Effects on smooth muscles: 1. Spasmodic effects – constipation, biliary spasm, urinary retention, etc. are less prominent 2. Miosis is less prominent
Has antitussive effect	Has no significant antitussive effect
Releases histamine	It causes less histamine release
It has a rapid onset and longer duration of action (6–8 hours)	It has a rapid onset but shorter duration of action (3–4 hours)
Morphine causes severe respiratory depression in the newborn, when it is given to mother during labour	Pethidine causes less respiratory depression in newborn

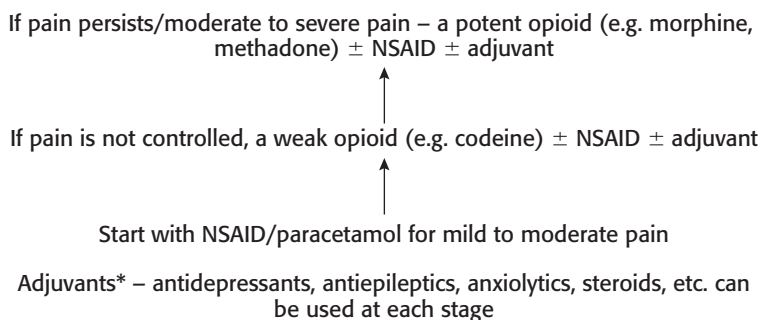


Fig. 5.11 World Health Organization analgesic ladder. (*Adjuvants, e.g. carbamazepine, amitriptyline, diazepam, prednisolone.) (Source: <https://www.who.int/cancer/palliative/painladder/en/>)

long bones, bullet wound, etc. Opioids are also used to control severe pain in terminal stages of cancer. In renal and biliary colic, atropine is used with morphine to counteract spasmogenic effect of morphine. Opioids are the preferred analgesics in severe painful conditions (WHO analgesic ladder) (Fig. 5.11).

Patient controlled analgesia: This allows the patient to control the delivery of s.c., epidural or i.v. analgesic in a safe and effective way through a pump. The patient should inform nurse when he or she takes a dose so that it can be replaced.

- 2. **Preanaesthetic medication:** Opioids like morphine and pethidine are used about half an hour before anaesthesia because of their sedative, analgesic and euphoric effects; the dose of anaesthetic required is reduced.
- 3. **Acute pulmonary oedema (cardiac asthma):** i.v. morphine relieves breathlessness associated with acute left ventricular failure due to pulmonary oedema by:
 - (a) Reducing preload on heart by peripheral vasodilatation.
 - (b) Shifting blood from pulmonary to systemic circulation.
 - (c) Reducing anxiety, fear and apprehension associated with illness.
- 4. Postanaesthetic shivering – pethidine is effective.
- 5. Cough: Codeine and dextromethorphan are used for suppression of dry cough.
- 6. Diarrhoea: Synthetic opioids such as loperamide and diphenoxylate are used for symptomatic treatment of diarrhoea.

Other Opioids

The route of administration, uses and important features are represented in [Table 5.13](#).

Table 5.13 ■ Important points and uses of other opioids

Opioid	Actions and uses	Important adverse effects
• Codeine (p.o.) metabolized to morphine	• Analgesia – less potent than morphine • Cough suppressant – more selective for cough centre	• Constipation • Low addiction liability
Pethidine (i.m., i.v., s.c.) • Synthetic opioid • Rapid but short acting • No significant antitussive effect	Analgesic – less potent than morphine Action on smooth muscle Histamine release } Less than morphine	• Similar to morphine (urinary retention, constipation less common) • Anticholinergic effects – dry mouth, tachycardia • Seizures, tremors (due to norpethidine) • With SSRI → serotonin syndrome
Methadone (p.o., i.m.) • μ-Receptor agonist • Oral route: well absorbed • Long duration of action • Repeated dosing: persistent action • Substitution therapy in opioid dependence	• Actions similar to morphine • Tolerance, dependence more slowly than morphine • Withdrawal symptoms – mild • 1 mg methadone substituted for 4 mg of morphine • Uses – substitution therapy in opioid dependent subjects; for chronic pain	Similar to morphine
Tramadol (p.o., i.m., i.v.) • μ-Agonist • (–) reuptake of 5-HT, NA into neurons	• Similar to morphine but less marked • Haemodynamic effects minimal • Uses – mild to moderate pain due to trauma and surgery; cancer pain	• Similar to morphine • Seizures • With SSRI → serotonin syndrome

Table 5.13 ■ Important points and uses of other opioids—cont'd

Opioid	Actions and uses	Important adverse effects
Fentanyl (i.v., transdermal, epidural) • Highly lipid soluble • i.v.: peak analgesia in 5 minutes, short duration	• Similar to morphine but less marked and short acting; except analgesia, respiratory depression (80–100 times more potent than morphine) • Few cardiovascular effects • Use – as analgesic to supplement anaesthetics; cancer pain; postoperative pain	Similar to morphine
Buprenorphine (i.m., i.v., sublingual) • Thebaine congener • Slow onset • Longer acting	Similar to morphine • Analgesia: more potent than morphine • Less tolerance, dependence • Withdrawal symptoms: milder, longer • Uses – postoperative pain, cancer pain, MI, preanaesthetic medication; substitution therapy in opioid dependent subjects	• Similar to morphine • Constipation less marked • Postural hypotension prominent • Actions of buprenorphine not completely reversed by naloxone
Pentazocine (oral, i.m., s.c.)	Similar to morphine but less • Uses – traumatic and postoperative pain	• Sympathetic stimulation ↑ HR, BP • High dose – psychotomimetic effect • Precipitates withdrawal in morphine dependent subjects
• Butorphanol (i.v., i.m.) • Nalbuphine	• Similar to morphine but less marked • Analgesia – more than pentazocine • Psychotomimetic effect – less • Use – postoperative pain	• Cardiac stimulation (butorphanol) • Sedation

Note Special 'S' for each opioid.**Codeine:** Selective cough suppressant**Pethidine:** Effect on **S**mooth muscles (**S**pasmodic action) is less than morphine

Seizures may occur due to its metabolite, norpethidine; used in the treatment of Postanaesthetic Shivering

Methadone: Used for **S**ubstitution therapy in opioid dependent subjects**Tramadol:** Seizures can occur. Potential to cause **S**erotonin syndrome**Tapentadol:** Potential to cause **S**erotonin syndrome**Buprenorphine:** Sublingual route can be used; used for **S**ubstitution therapy in opioid-dependent subjects**Pentazocine:** Sympathetic stimulation**Fentanyl and congeners:** Short acting**Butorphanol:** Sedation – its prominent side effect**Heroin:** Causes **S**evere addiction liability

Tramadol. It is a synthetic codeine derivative with weak agonistic activity at μ -receptors. It also inhibits the reuptake of NA and 5-HT. It decreases seizure threshold.

Tapentadol. It is a μ -agonist. It also predominantly inhibits reuptake of NE than 5-HT into the neurons. It is useful in mild to moderate pain. Adverse effects are similar to tramadol but vomiting is less.

Fentanyl. It is a synthetic opioid with a potent μ -agonistic effect (100 times more potent than morphine as an analgesic).

Pharmacological actions are similar to morphine. Alfentanil, sufentanil and remifentanyl are short-acting fentanyl analogues. They are useful for short procedures where intense analgesia is required.

Methadone. It is a synthetic opioid with agonistic effect at μ -receptors and has a long duration of action. Pharmacological actions are similar to morphine.

Dextropropoxyphene. It is structurally similar to methadone. The side effects are nausea, constipation, sedation, abdominal pain, etc. It may cause cardiotoxicity and pulmonary oedema.

Opioid Agonist–Antagonists and Partial Agonists

Pentazocine. Pentazocine is an opioid agonist–antagonist. It has agonistic action at κ - and weak antagonistic action at μ -receptors. In low doses, its pharmacological actions are almost similar to that of morphine. In higher doses, it causes sympathetic stimulation.

Buprenorphine. It is a partial μ -receptor agonist and κ -receptor antagonist; it is about 25 times more potent than morphine as analgesic. The pharmacological actions are qualitatively similar to morphine but it has a delayed onset and prolonged duration of action. It can be administered by parenteral and sublingual routes.

Opioid Antagonists: Naloxone, Naltrexone and Nalmefene (Fig. 5.10)

They are pure opioid antagonists. These drugs have no agonistic activity.

Naloxone, naltrexone and nalmefene competitively reverse the effects of both natural and synthetic opioids, but do not completely reverse buprenorphine-induced respiratory depression. Naloxone also blocks analgesic effect of placebo and acupuncture, and effects of endogenous opioid peptides. It is orally not effective because of high first-pass metabolism. It is short acting. On i.v. administration, it immediately antagonizes all the actions, especially respiratory depression, of morphine and other opioids. i.v. naloxone precipitates withdrawal symptoms in morphine and heroin addicts.

Uses of Naloxone

1. The main therapeutic use of naloxone is for the treatment of morphine and other opioid poisoning (see p. 205).
2. In the treatment of opioid overdosage, i.v. naloxone rapidly reverses respiratory depression induced by opioids (except buprenorphine where it causes partial reversal of respiratory depression).
3. To treat neonatal asphyxia due to use of opioids in the mother during labour.

Uses of Naltrexone. Naltrexone is orally more potent and has longer duration of action than naloxone.

1. Naltrexone is used for opioid blockade therapy to prevent relapse in opioid-dependent individuals.
 2. It is also used for the treatment of alcoholism, as it reduces the urge to drink.
- Methylnaltrexone**, a derivative of naltrexone, has only peripheral actions. It can be used for treatment of constipation due to opioids.

Nalmefene

- It is administered intravenously.
- It is longer acting than naloxone.
- It is useful in the treatment of opioid overdosage.

Endogenous Opioid Peptides

Endorphins, enkephalins and dynorphins are naturally occurring substances present in the brain and other body tissues. They are called endogenous opioid peptides because their effects are similar to opium alkaloids (e.g. morphine) in their actions. These peptides appear to be involved in placebo and acupuncture-induced analgesia.

Antiparkinsonian Drugs

PH1.19

Parkinson disease (PD) was first described by Sir James Parkinson. It is characterized by tremor, rigidity, bradykinesia (slowness of movements) and the loss of postural reflexes.

In idiopathic parkinsonism, there is degeneration of the dopamine-containing neurons in the substantia nigra, resulting in dopamine deficiency. Hence, the balance between inhibitory dopaminergic neurons and excitatory cholinergic neurons is disturbed resulting in relative cholinergic overactivity (Fig. 5.12).

CLASSIFICATION

1. Drugs influencing brain dopaminergic system:
 - (a) Dopamine precursor: Levodopa (L-Dopa).
 - (b) Dopamine agonists: Bromocriptine, pramipexole, ropinirole.
 - (c) NMDA-receptor antagonist: Amantadine.
 - (d) Monoamine oxidase (MAO)-B inhibitors: Selegiline (deprenyl), rasagiline.
 - (e) Catechol-O-methyltransferase (COMT) inhibitors: Tolcapone, entacapone.
2. Drugs influencing brain cholinergic system
 - (a) Centrally acting anticholinergic drugs: Benztropine, benzhexol (trihexyphenidyl), procyclidine, biperiden.
 - (b) Antihistaminics (H_1 -blockers) with anticholinergic activity: Promethazine, diphenhydramine, orphenadrine.

The main aim of drug therapy in parkinsonism is to either enhance dopamine activity or reduce cholinergic activity in the striatum.

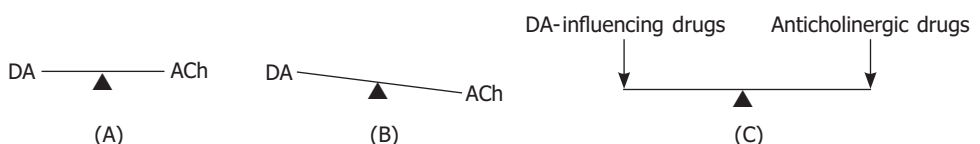


Fig. 5.12 (A) Normally, there is a balance between DA and ACh in the striatum; (B) parkinsonism – deficiency of DA leads to a relative increase in ACh activity; (C) balance between DA and ACh is restored with the use of antiparkinsonian drugs.

Dopamine Precursor: Levodopa

L-Dopa is the main drug for the treatment of idiopathic parkinsonism. Dopamine does not cross BBB; hence, its immediate precursor L-Dopa (prodrug) is used. It is converted to dopamine by decarboxylase enzyme in the dopaminergic neurons of the striatum. Dopamine produced then interacts with D_2 -receptors in the basal ganglia to produce antiparkinsonian effect. In early stages of the disease, improvement is almost complete. All the clinical symptoms (rigidity, bradykinesia and tremor) of parkinsonism improve, but the progression of the disease is not stopped. A large amount of the drug is converted to dopamine in the peripheral tissues by peripheral decarboxylase enzyme. Only a small amount (2%–3%) of L-Dopa enters the brain. Therefore, L-Dopa is used in combination with carbidopa/benserazide (peripheral decarboxylase inhibitor) which does not cross the BBB; the peripheral metabolism of L-Dopa is reduced, thus increasing its bioavailability in the basal ganglia (Fig. 5.13).

Pharmacokinetics. On oral administration, L-Dopa is rapidly absorbed from the small intestine by an active transport system. Amino acids present in food may interfere with the absorption of L-Dopa; hence, it should be given 30–60 minutes before meal. Active transport of L-Dopa into the brain may be inhibited by competition from dietary amino acids. The main metabolic products of L-Dopa are homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) (Fig. 5.14). The metabolites are excreted in urine.

Adverse Effects

1. GIT: Nausea, vomiting and anorexia are common during initial treatment with L-Dopa. Tolerance to emetic effect develops slowly.
2. CVS: The commonest cardiovascular side effect is postural hypotension, which is usually asymptomatic. It can also cause tachycardia, palpitation and rarely cardiac arrhythmias.
3. Dyskinesias (abnormal involuntary movements): Tics, tremors and choreoathetoid movements may occur. Tolerance does not develop to abnormal movements.
4. Alteration in taste sensation.
5. Mental changes like insomnia, confusion, delusions, euphoria, depression, anxiety, hallucinations and nightmares.

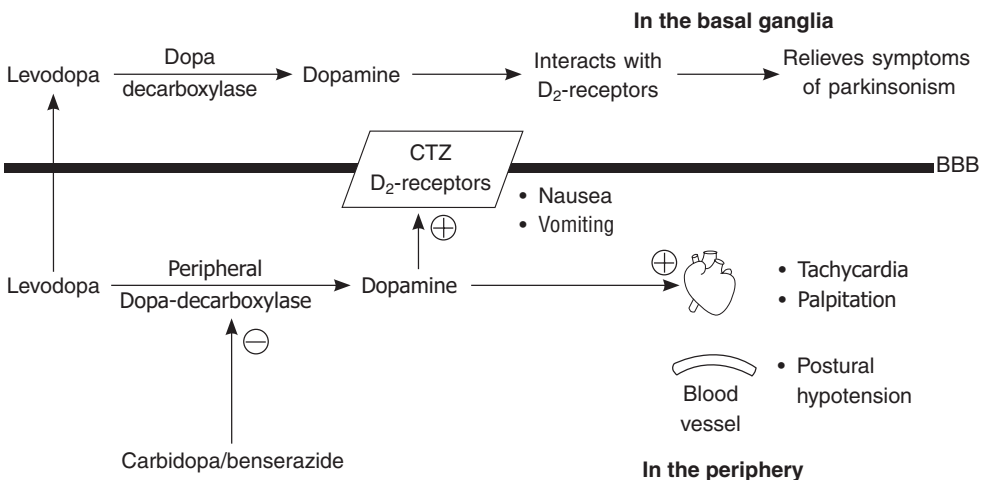


Fig. 5.13 L-Dopa–carbidopa in parkinsonism. BBB, Blood–brain barrier; CTZ, chemoreceptor trigger zone. (Source: Adapted from Katzung BG, editor: Basic & Clinical Pharmacology, 11th ed. McGraw-Hill, 2009: Fig. 28-5.)

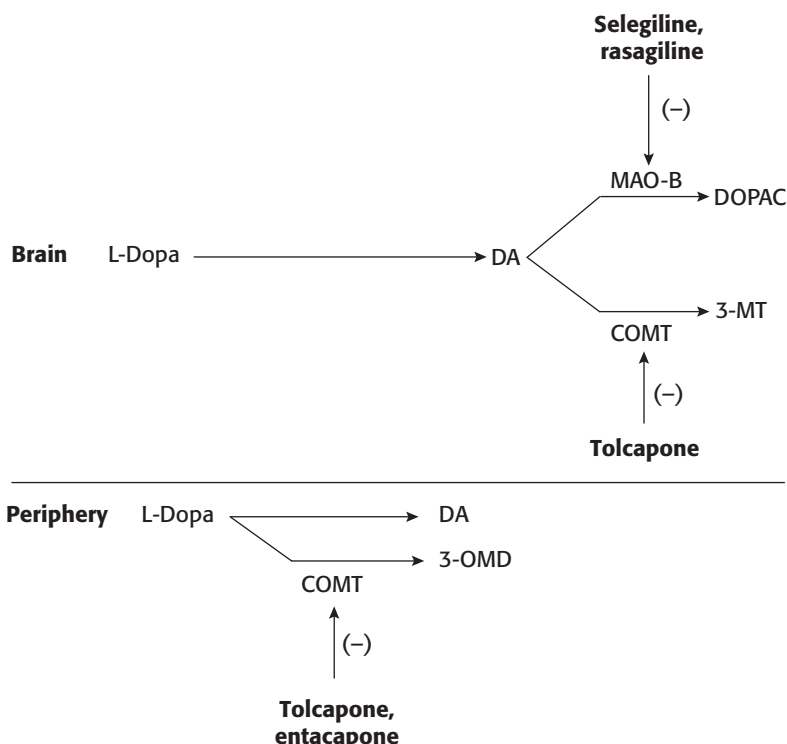


Fig. 5.14 Mechanism of action of MAO and COMT inhibitors in parkinsonism. DA, Dopamine; MAO, monoamine oxidase; COMT, catechol-O-methyltransferase; 3-MT, 3-methoxytyramine; DOPAC, 3,4-dihydroxyphenylacetic acid; 3-OMD, 3-O-methyldopa L-Dopa, levodopa. (Source: Adapted from Alfred Gilman Sr. and Louis S. Goodman: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th edition, p. 615, Fig. 22.5, McGraw Hill, 2018.)

6. Fluctuations in response: After 3–5 years of therapy, with progressing disease, control becomes poor and fluctuations in symptoms occur frequently. Wearing off (end-of-dose) is due to decrease in plasma concentration of L-Dopa towards the end-of-a-dose interval. Patient may show fluctuation in response – being ‘off’ (loss of beneficial effect of the drug) and being ‘on’ (relief of most of the symptoms but with disabling dyskinesias) called the on/off phenomenon. Sustained release formulation of L-Dopa –carbidopa produces more stable plasma L-Dopa levels and helps to reduce fluctuation in response (on/off phenomena). End-of-dose deterioration can also be improved by administering L-Dopa in smaller and more frequent doses.

Peripheral Decarboxylase Inhibitors: Carbidopa and Benserazide

Carbidopa and benserazide are peripheral decarboxylase inhibitors. These drugs do not cross BBB. L-Dopa is always given in combination with carbidopa/benserazide. The currently used combinations are as follows:

- L-Dopa + carbidopa (4:1 or 10:1 ratio).
- L-Dopa + benserazide (4:1 ratio).

The advantages of these fixed-dose combinations are as follows:

1. Increased bioavailability of dopamine in the basal ganglia (Fig. 5.13). Hence, the dose of L-Dopa can be reduced by 75%.
2. Prolongation of plasma half-life of L-Dopa.
3. Reduction in the incidence of GI side effects like nausea and vomiting.

4. Cardiovascular side effects like tachycardia, hypotension and cardiac arrhythmias are minimized.
5. Better patient compliance.
6. Sustained release preparation of L-Dopa –carbidopa helps to reduce on/off phenomenon.

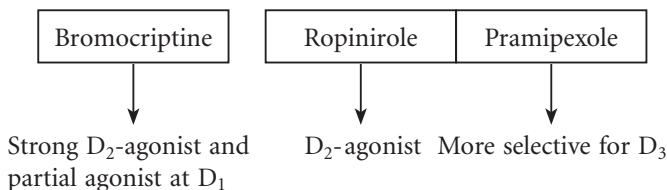
Dopamine-Receptor Agonists: Bromocriptine, Ropinirole and Pramipexole

These drugs have direct action on dopamine receptors. Like L-Dopa, they can relieve signs and symptoms of parkinsonism. They are administered orally. The duration of action of these drugs is longer than that of L-Dopa and these are used particularly in patients who have frequent fluctuation of symptoms (on/off phenomena).

Bromocriptine. Bromocriptine is an ergot derivative; it has agonistic action at D₂- and partial agonist at D₁-receptors.

Adverse Effects. Adverse effects include anorexia, nausea, vomiting, constipation, postural hypotension, cardiac arrhythmias, digital vasospasm, dyskinesias, headache, confusion, hallucinations and nasal congestion. It is contraindicated in patients with history of mental illness, recent MI, peptic ulcer and peripheral vascular diseases.

Ropinirole and Pramipexole. These are nonergoline derivatives; hence, ergot-related side effects are not seen. These drugs are often used in the initial treatment of parkinsonism. They can be used as monotherapy in mild parkinsonism or in combination with L-Dopa –carbidopa. They also exert neuroprotective effect. Dyskinesias and fluctuation in response are less with these drugs than L-Dopa. The other indication of these nonergolines is in 'restless leg syndrome'.



Adverse Effects. Nausea, vomiting, confusion, fatigue, somnolence, hallucinations, postural hypotension, dyskinesia and rarely, sudden attacks of irresistible sleep during day time. GIT side effects are lower as compared to bromocriptine.

COMT Inhibitors: Tolcapone, Entacapone

Tolcapone and entacapone are reversible COMT inhibitors. By inhibiting the peripheral metabolism of L-Dopa to 3-O-methyldopa, they increase the half-life of L-Dopa and also enhance its bioavailability in the CNS. The 'on' time is prolonged and the dose of L-Dopa can be reduced. Tolcapone has both peripheral and central actions with relatively longer duration of action, whereas entacapone inhibits COMT only in the periphery (Fig. 5.14). These drugs are used as adjunct to L-Dopa –carbidopa for advanced cases of PD. Combined preparation of L-Dopa + carbidopa + entacapone is available.

Adverse Effects. These include dyskinesia, nausea, diarrhoea, confusion, hypotension and hallucinations. Tolcapone may rarely cause fulminant hepatitis; hence, it should be avoided in patients with liver disease. Entacapone does not cause hepatotoxicity.

MAO-B Inhibitors: Selegiline (Deprenyl) and Rasagiline

They selectively and irreversibly inhibit MAO-B enzyme in the brain (Fig. 5.14). They are administered orally. They do not inhibit MAO in the periphery. They retard the metabolism of DA in the brain and prevent the formation of toxic metabolites. Thus, they

produce neuroprotective effect in idiopathic PD and retard the progression of disease. They are used as an adjunct with L-Dopa. They enhance as well as prolong the effect of L-Dopa, thus reducing the dose of L-Dopa required. They also reduce 'on-off' and 'wearing off' phenomena. Rasagiline is more potent and longer acting than selegiline; hence, single daily dose is adequate. The metabolites of selegiline are amphetamine and methamphetamine which cause side effects like insomnia, anxiety, nausea and vomiting.

NMDA-Receptor Antagonist: Amantadine

Amantadine is an antiviral drug used for the treatment and prophylaxis of influenza A. It is also used in parkinsonism. It facilitates the synthesis and release of dopamine from dopaminergic neurons in the brain. It also has NMDA-receptor antagonist action – decreases glutamate neurotransmission in the basal ganglia which could contribute to its beneficial effect in parkinsonism. It is less effective than L-Dopa and hence used for the initial treatment of mild parkinsonism. Its therapeutic activity may be increased by combining with L-Dopa. It is given by oral route and is well tolerated.

Adverse Effects. They include headache, heart failure, hypotension, hallucinations, nausea, vomiting, constipation, dry mouth, insomnia and livedo reticularis (discoloured patches on the skin).

Central Anticholinergics

Centrally acting anticholinergics like benzhexol (trihexyphenidyl) and benztropine are the treatment of choice in drug-induced parkinsonism and are also effective in idiopathic parkinsonism. They have mainly central anticholinergic action with minimal peripheral action. They act by reducing the increased cholinergic activity in the striatum. They are less effective than L-Dopa, but are cheap and better tolerated. They are mainly effective in relieving tremor and rigidity of parkinsonism with little effect on hypokinesia. Adverse effects are dry mouth, confusion, constipation, blurring of vision, drowsiness, hallucinations and urinary retention.

Antihistaminics with anticholinergic action like promethazine, diphenhydramine and orphenadrine are also effective in decreasing cholinergic overactivity in basal ganglia.

L-Dopa is not effective in drug-induced parkinsonism, because:

- (a) Dopamine receptors are blocked.
- (b) There is no deficiency of dopamine.

Drug Interactions

1. **L-Dopa × MAO inhibitors (nonselective):** Inhibition of MAO retards the metabolism of dopamine → plasma concentration of dopamine increases → may precipitate hypertensive crisis.
2. **L-Dopa × pyridoxine:** Pyridoxine promotes the peripheral conversion of L-Dopa to dopamine and reduces the therapeutic effect of L-Dopa.
3. **L-Dopa × antihypertensive agents:** Worsening of postural hypotension.
4. **L-Dopa × metoclopramide:** Metoclopramide crosses the BBB, blocks the D₂-receptors in the basal ganglia and causes drug-induced parkinsonism (i.e. interferes with antiparkinsonian effect of L-Dopa); domperidone poorly crosses BBB; hence, there is no interference with therapeutic effect of L-Dopa.

Drugs for Alzheimer's Disease

It is a degenerative disease of the cerebral cortex with decreased cholinergic transmission. Drugs used are donepezil, galantamine and rivastigmine. They are cerebroselective

anticholinesterases. They increase cerebral levels of acetylcholine and have shown to produce some benefit in these patients. Other drugs used are memantine (NMDA-receptor antagonist), *Ginkgo biloba*, etc.

Cognitive Enhancers (Nootropics)

PH1.19

Cognition enhancers are drugs which help to reduce the impairment of cognitive functions associated with age, head injury, stroke and neurodegenerative disorders. They improve memory (Table 5.14).

Table 5.14 ■ Cognitive enhancers

Drug	Route of administration	Mechanism of action	Uses	Adverse effects
• Rivastigmine • Donepezil • Galantamine (cerebroselective anticholinesterases)	Oral	Anticholinesterases → inhibit both true and pseudo ChEs → ↑cholinergic transmission in the brain → improvement of cognitive function	Mild to moderate Alzheimer's disease produce small improvement in cognition Donepezil – can be used in severe cases; it is administered once daily	Gastrointestinal side effects
Memantine (NMDA-receptor antagonist)	Oral	Inhibits glutamate transmission	Moderate to severe Alzheimer's disease; it can also be used in combination with anticholinesterases	Dizziness
Piracetam	Oral, i.m.	Decreases viscosity and improves microcirculation; has neuroprotective effect	Dementia	Insomnia, headache
Citicoline	Oral, i.m., i.v.	Increases oxygen and blood flow to the brain	Vascular dementia, parkinsonism, stroke	Headache
Piribedil	Oral	Dopamine agonist	Dementia of parkinsonism	Nausea, vomiting
<i>Ginkgo biloba</i>	Oral	Neuroprotective	Evidence for clinical benefit in dementia is not convincing	Avoided in patients on anticoagulants-increased risk of bleeding

Table 5.15 ■ CNS stimulants

Drug	Route of administration	Action	Uses	Adverse effects
Doxapram	Intravenous infusion	Respiratory stimulant (analeptic) Stimulates peripheral carotid chemoreceptors + direct stimulation of respiratory centre	Respiratory depression following general anaesthesia	Nausea, vomiting, arrhythmias
Modafinil	Oral	Psychostimulant – enhances wakefulness and vigilance	Narcolepsy	Headache
Amphetamine Dextroamphetamine	Oral	Increase NE, DA levels in the synaptic cleft in the brain CNS stimulant	ADHD, narcolepsy	Insomnia, tachycardia, palpitation
Methylphenidate	Oral	Increase NE, DA levels in the synaptic cleft in the brain	ADHD	Suppression of appetite, weight loss

Note: NE, Norepinephrine; DA, dopamine; ADHD, attention deficit hyperactivity disorder.

CNS Stimulants

PH1.19, PH1.22

Some of the CNS stimulants are given in [Table 5.15](#).

ATOMOXETINE

- Norepinephrine reuptake inhibitor (not a CNS stimulant).
- Route of administration – oral; used in the treatment of attention deficit hyperactivity disorder (ADHD) – increases ability to pay attention and decreases hyperactivity.
- Adverse effects include insomnia, gastrointestinal side effects; rarely, suicidal ideas.

Psychopharmacology

PH1.19

The major types of psychiatric illnesses are psychoses and neuroses ([Table 5.16](#)).

Antipsychotic Drugs

PH1.19

Antipsychotic drugs are also known as neuroleptic drugs or antischizophrenic drugs. Neuroleptic drugs are mainly used in schizophrenia, acute mania and other acute psychotic states.

Table 5.16 ■ Differences between psychoses and neuroses

Psychoses	Neuroses
Major mental illness	Minor mental illness
Insight into the illness is lost	Insight is present
Judgement is lost (capacity to discriminate between right and wrong, good and bad)	Judgement is not lost
Disturbance of mental function (thinking, emotion, etc.)	Rare
Disturbance of thought: present, e.g. schizophrenia	Disturbance of thought: rare, e.g. anxiety neurosis, phobic states (abnormal fear), obsessive compulsive disorder, hysterical attacks and reactive depression

CLASSIFICATION

- 1. **Phenothiazines:** Chlorpromazine, triflupromazine, trifluoperazine, thioridazine, fluphenazine
- 2. **Thioxanthenes:** Flupenthixol
- 3. **Butyrophenones:** Haloperidol, trifluperidol
- 4. **Atypical antipsychotics:** Risperidone, clozapine, olanzapine, quetiapine, zotepine, aripiprazole, amisulpride, ziprasidone
- 5. **Others:** Loxapine, pimozide

MECHANISM OF ACTION OF ANTIPSYCHOTICS

- Conventional antipsychotics → Mainly block dopamine (D₂)-receptors in the limbic system and mesocortical areas.
- Atypical antipsychotics → Block 5-HT₂ receptors in mesolimbic system.

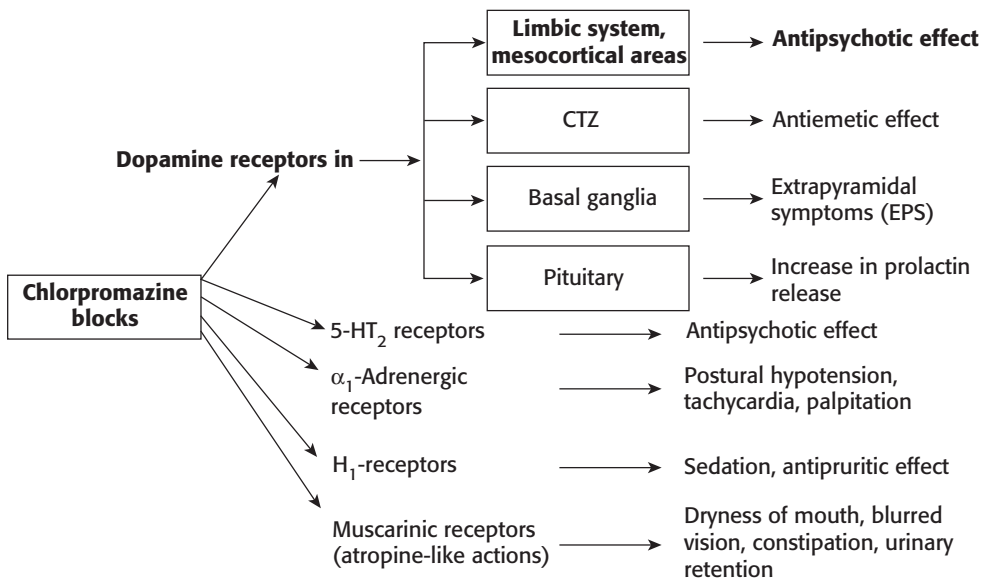
Chlorpromazine (Phenothiazines)

Chlorpromazine is the prototype drug.

Pharmacological Actions of Chlorpromazine (Fig. 5.15)

- Central nervous system: In patients with schizophrenia, chlorpromazine:
 - (a) Reduces agitation and aggressiveness.
 - (b) Reduces spontaneous movements.
 - (c) Suppresses hallucinations and delusions.
 - (d) Relieves anxiety.
 - (e) Corrects disturbed thought and behaviour.
 - (f) Does not affect intelligence but impairs vigilance.
- Endocrine: Prolactin secretion is under the control of prolactin-releasing factor (PRF) and prolactin-inhibitory factor (PIF). PIF itself is dopamine; hence, the blockade of DA-receptors in pituitary may cause increased production of prolactin leading to galactorrhoea, amenorrhoea and infertility in females; gynaecomastia in males.
- Other actions (Fig. 5.15).
- Tolerance to sedative and hypotensive actions develops within a few weeks.

Pharmacokinetics. Phenothiazines are effective orally and parenterally. Chlorpromazine is highly bound to plasma proteins – reaches high concentration in the brain. It is metabolized in liver and excreted in urine.



Phenothiazines decrease seizure threshold and may precipitate convulsions.

Fig. 5.15 Mechanism of action, pharmacological actions and adverse effects of chlorpromazine. CTZ, Chemoreceptor trigger zone.

ADVERSE EFFECTS OF ANTIPSYCHOTICS

Important side effects of these drugs are dose-dependent EPS.

1. Parkinsonism: They are tremors, rigidity, hypokinesia, etc. Centrally acting anticholinergics (benzhexol, benztropine and antihistamines like promethazine, diphenhydramine, etc.) are effective in controlling these symptoms.
2. Acute dystonias: Sudden onset of muscle spasms resulting in uncontrolled muscular movements involving the face, tongue, neck, etc. It responds to centrally acting anticholinergics, e.g. benzhexol.
3. Akathisia: Feeling of restlessness – the person cannot sit at a place and has a desire to move about. It is treated with a BZD (e.g. clonazepam) or β -blocker (e.g. propranolol) or centrally acting anticholinergic.
4. Neuroleptic malignant syndrome: It is a rare but serious complication, characterized by muscular rigidity, hyperpyrexia, mental confusion and coma. It is treated with i.v. dantrolene.
5. Tardive dyskinesia (*Tardive* – late occurring): It is characterized by involuntary movements of the mouth, tongue and the upper limbs. It develops in about 20% of patients after months or years of antipsychotic treatment. Treatment is usually unsuccessful.
6. Muscarinic, α_1 -adrenergic and H_1 -receptor–blocking side effects (Fig. 5.15).
7. Weight gain is common with clozapine and olanzapine.
8. Endocrine side effects are due to increased prolactin level resulting in amenorrhoea, galactorrhoea and infertility in females; gynaecomastia in males. Hyperglycaemia and precipitation of diabetes can occur with chlorpromazine.
9. Hypersensitivity reactions can occur – skin rashes, itching, dermatitis, leucopenia and rarely obstructive jaundice. Agranulocytosis is a serious adverse effect with clozapine.

Haloperidol (Butyrophenone)

1. Widely used antipsychotic drug; pharmacological actions are similar to chlorpromazine
2. Causes severe EPS.

3. Has less seizure potential.
4. Does not cause weight gain.
5. Does not cause hyperglycaemia and dyslipidaemia.
6. Rarely causes jaundice.
7. Preferred agent for acute schizophrenia, acute mania, senile psychoses, Huntington disease, etc.

Atypical Antipsychotics (Table 5.17)

These drugs exert antipsychotic effect mainly by 5-HT₂ blockade. They have weak D₂-blocking effects – low risk of EPS.

Table 5.17 ■ Features of antipsychotic drugs

Drug	Receptor	Actions
Chlorpromazine	Potent D ₂ -blockade M, H ₁ and α-blockade	• Low potency • Significant sedation and hypotension • Other actions (p. 219)
Haloperidol, fluphenazine	Potent D ₂ -blockade M, H ₁ and α-blockade	• Potent antipsychotics • Less sedation and hypotension • Weak anticholinergic • Marked EPS • Hyperprolactinaemia • Jaundice rare
Clozapine	Potent 5-HT ₂ blockade D ₂ - (weak), M, H ₁ and α-blockade	• Sedation and hypotension +++ • Less EPS • Anticholinergic • Minimal effect on prolactin • Agranulocytosis • Precipitate seizures, weight gain • Hypersalivation • Reserve drug for resistant cases
Olanzapine	Potent 5-HT ₂ blockade D ₂ - (weak), M, H ₁ and α-blockade	• Sedation +, hypotension ++ • Less EPS • Minimal effect on prolactin • Potent anticholinergic • Precipitates seizures, weight gain • Hyperglycaemia
Risperidone	5-HT ₂ blockade D ₂ -, M, H ₁ and α-blockade	• Sedation, hypotension ++ • Low doses (< 6 mg/d) less EPS • Increases prolactin levels • Less likely to cause seizures
Ziprasidone	5-HT ₂ , D ₂ -blockade	• Less EPS
Aripiprazole	5-HT ₂ blockade D ₂ partial agonist	• Minimal effect on prolactin • Less weight gain • Less hyperglycaemia
Quetiapine	5-HT _{1A} , 5-HT ₂ , D ₂ -blockade	• Sedation +++ • QT prolongation
Amisulpride	D ₂ -blockade	• Less EPS (atypical antipsychotic) • No sedation • QT prolongation

Clozapine and Olanzapine

1. Atypical antipsychotic drugs.
2. Mainly block 5-HT₂ receptors.
3. Have weak D₂-blocking effect.
4. Also block α_1 -receptors, H₁- and muscarinic receptors.
5. Cause sedation and hypotension.
6. Rarely cause EPS.

Adverse Effects (Table 5.17) Side effects of clozapine are sedation, salivation, seizures, weight gain and hypotension. The dangerous side effect is agranulocytosis; hence, regular monitoring of blood counts is required during clozapine therapy. Side effects of olanzapine are dry mouth, constipation, weight gain and rarely EPS. It does not cause agranulocytosis.

Uses. Clozapine is a reserve drug for the treatment of schizophrenia because of the risk of agranulocytosis. Olanzapine is used for the treatment of schizophrenia and mania associated with bipolar disorder. They suppress both positive symptoms (thought disorder, hallucinations, delusions, etc.) and negative symptoms (social withdrawal, lack of motivation and flattening of emotions) of schizophrenia.

Risperidone

1. Atypical antipsychotic drug.
2. Blocks D₂-, 5-HT₂, α_1 -adrenergic and H₁-receptors.
3. EPS is rare at low doses.
4. Used for the treatment of schizophrenia and short-term treatment of mania associated with bipolar disorder.

Other atypical antipsychotics are aripiprazole, ziprasidone, quetiapine and amisulpride (Table 5.17).

Therapeutic Uses

1. **Schizophrenia:** The neuroleptics are the only efficacious drugs available for the treatment of schizophrenia (for effects in schizophrenia, see p. 218).
The atypical antipsychotics are commonly prescribed owing to the lower risk of EPS. Risperidone, olanzapine, aripiprazole, ziprasidone and quetiapine are frequently used. Clozapine is reserved for resistant cases of schizophrenia. Of the older agents, haloperidol and fluphenazine are commonly used.
2. **Mania:** Acute mania can be treated with a neuroleptic (chlorpromazine or haloperidol); lithium is used for maintenance therapy. Atypical antipsychotics like olanzapine, risperidone, quetiapine and aripiprazole are commonly used for acute mania. If parenteral therapy is required, older agents like chlorpromazine or haloperidol are used.
3. **As antiemetic:** These drugs (phenothiazines, haloperidol, etc.) produce antiemetic effect by blocking D₂-receptors in CTZ. However, they are not routinely used as antiemetics because of their side effects. Phenothiazine, such as prochlorperazine, is useful for prevention and treatment of nausea and vomiting associated with migraine or emesis due to anticancer drugs.
4. **Intractable hiccough** has been treated with chlorpromazine.
5. As adjuvant with selective serotonin reuptake inhibitors (SSRIs) in anxiety.

Antianxiety Agents

PH.19

1. **Benzodiazepines (BZDs):** BZDs are the preferred anxiolytic drugs. Chlordiazepoxide, diazepam, lorazepam, oxazepam, alprazolam, nitrazepam, flurazepam,

etc. are used as anxiolytic agents. They act on limbic system and facilitate the inhibitory effect of GABA. BZDs are mainly useful for short-term treatment of anxiety. They act rapidly and are most commonly used for acute anxiety. Adverse effects are sedation, impairment of memory, confusion and dependence. Tolerance may develop to anxiolytic effect on long-term use.

2. **Buspirone:** Buspirone is a partial agonist of 5-HT_{1A} receptor and causes selective anxiolytic effect. It has no sedative, anticonvulsant or muscle relaxant effects. It does not potentiate the central effects of alcohol or other CNS depressants. There is no tolerance or drug dependence. It does not affect GABA transmission. Buspirone is well absorbed from GI tract; but bioavailability is low because of first-pass metabolism. It produces active metabolites. Enzyme inducers (rifampin) and inhibitors (erythromycin) alter its plasma levels. It is mainly used in the treatment of generalized anxiety states. But its effect is delayed and may take 2 weeks to fully develop. So, it is not effective for acute cases.
3. **β-Blockers:** Propranolol and other nonselective β-blockers are used mainly to reduce the symptoms of anxiety, such as tachycardia, palpitation, tremor and sweating.
4. **SSRIs and serotonin and noradrenaline reuptake inhibitor (SNRI, venlafaxine):** These are the preferred agents for most of the anxiety disorders, except acute anxiety. Response is delayed.
5. **H₁-blocker:** Hydroxyzine is a highly sedative first-generation H₁-blocker; it has selective antianxiety action. It also has antiallergic, antiemetic and anticholinergic actions.

Antidepressants

PH1.19

Depression is a common clinical condition associated with feeling of sadness, loss of interest, self-neglect, anorexia, sleep disturbances, suicidal feelings in severe cases, etc. Various hypotheses have been proposed for pathogenesis of depression.

- Decrease in levels or function of monoamines (5-HT, NE, DA) in cortical and limbic system.
- Decrease in brain-derived neurotrophic factor (BDNF).
- Abnormalities in HPA axis, thyroid function and sex steroid levels.

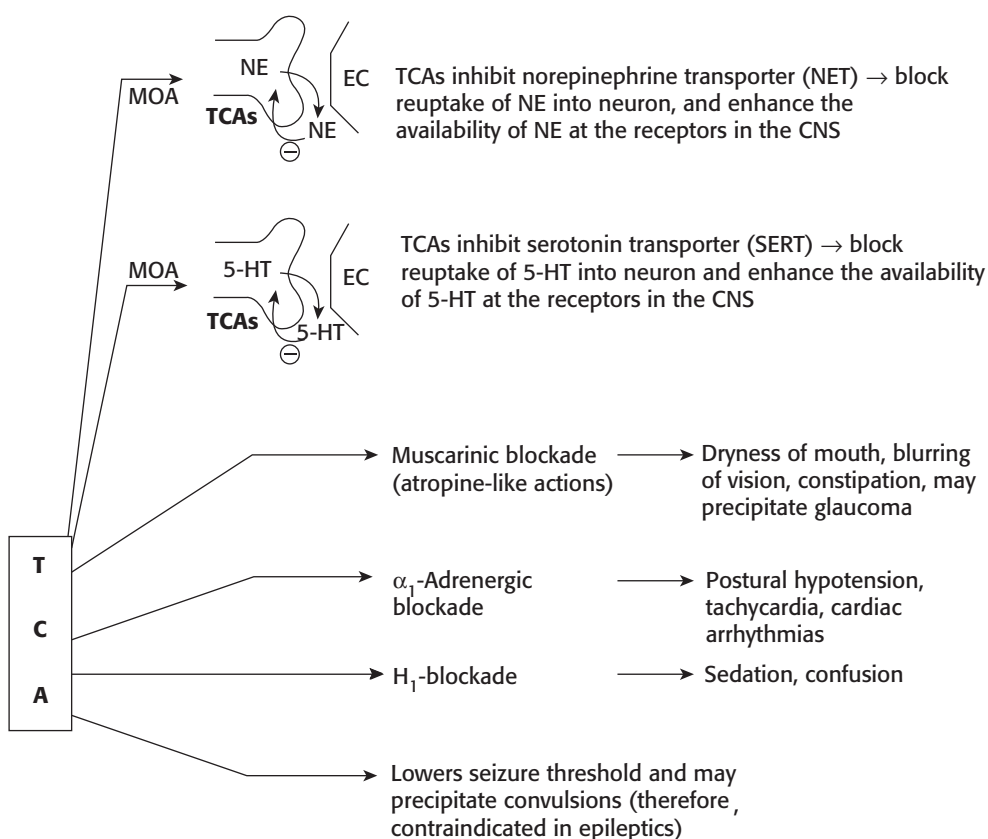
CLASSIFICATION

1. Tricyclic antidepressants (mnemonic: ANTI-DEP C)

Amitriptyline, Amoxapine	Doxepin, Desipramine, Dothiepin
Nortriptyline	E—————
Trimipramine	Protriptyline
Imipramine	Clomipramine
2. **Selective serotonin (5-HT) reuptake inhibitors (SSRIs):** Fluoxetine, fluvoxamine, citalopram, escitalopram, sertraline, paroxetine, dapoxetine.
3. **SNRIs:** Duloxetine, venlafaxine.
4. **Atypical antidepressants:** Trazodone, bupropion, mianserin, mirtazapine, atomoxetine.
5. **MAO-A inhibitors:** Moclobemide, clorgyline.

Tricyclic Antidepressants

Mechanism of action and actions are described in [Fig. 5.16](#)



All types of antidepressants take at least 2–3 weeks to produce beneficial effects. $\uparrow$ 5HT/NE in synaptic cleft $\rightarrow$ stimulation of presynaptic 5-HT_{1A}/ α_2 -receptors initially. Later, receptor desensitization occurs. The antidepressant effect coincides with desensitization of various receptors (presynaptic α_2 -adrenergic and 5-HT_{1A} receptors), which mediate negative feedback control on transmitter release.

Fig. 5.16 Mechanism of action, pharmacological actions and adverse effects of tricyclic antidepressants (TCAs). MOA, Mechanism of action; EC, effector cell; NE, norepinephrine; 5-HT serotonin; CNS, central nervous system.

Pharmacokinetics. TCAs are well absorbed through the GI tract and are highly bound to plasma proteins. They are widely distributed in tissues including CNS. They are metabolized in liver. Some of them (imipramine, amitriptyline, etc.) produce active metabolites which are responsible for the long duration of action of these drugs. These drugs are excreted mainly in urine as inactive metabolites.

Adverse Effects and Contraindications of Tricyclic Antidepressants (Fig. 5.16)

1. 'Atropine-like' side effects: Dryness of mouth, blurring of vision, constipation, urinary retention, etc.
2. α_1 -Adrenergic blocking effects: Postural hypotension, tachycardia, cardiac arrhythmias, etc.
3. H_1 -blocking effects: Sedation and confusion.
4. Other effects: Increased appetite, weight gain and may precipitate convulsions (seizure threshold is lowered).

TCAs are contraindicated in patients with glaucoma, epilepsy, ischaemic heart disease and enlarged prostate.

Other antidepressants are shown in [Table 5.18](#).

MAO Inhibitors

MAO is a mitochondrial enzyme involved in the metabolism of biogenic amines. There are two isoforms of MAO. MAO-A is responsible mainly for the metabolism of NA, 5-HT and tyramine. MAO-B is more selective for dopamine metabolism.

Moclobemide. A selective and reversible inhibitor of MAO-A (RIMA) is relatively free of food and drug interactions. Hence, cheese reaction is rare. It is also devoid of anticholinergic, α_1 -adrenergic blocking and sedative effects.

Table 5.18 ■ Comparative features of antidepressants

Drug	MOA	Other points
1. Tricyclic antidepressants	See Fig. 5.16	See Fig. 5.16
2. Selective serotonin reuptake inhibitors (SSRIs): • Fluoxetine • Fluvoxamine • Citalopram • Escitalopram • Paroxetine • Sertraline • Dapoxetine	Inhibit serotonin transporter (SERT) → block reuptake of 5-HT into the neuron → increase the availability of 5-HT at receptors in the CNS and enhance serotonergic activity	• No anticholinergic effects • No hypotension • No sedation • No weight gain • Do not precipitate convulsions • Do not cause cardiac arrhythmias • Orally effective • Fluoxetine and sertraline produce active metabolites • Fluoxetine is the longest acting SSRI (half-life: 48–72 hours) • Adverse effects: GI symptoms like nausea, vomiting and diarrhoea, headache, insomnia, sexual dysfunction, impotence, loss of libido; SSRIs inhibit drug-metabolizing enzymes and cause interactions with other drugs; sertraline, citalopram and escitalopram have less potential for interactions
3. Serotonin and noradrenaline reuptake inhibitors (SNRIs) • Venlafaxine • Duloxetine	Inhibit the reuptake of serotonin and noradrenaline into the neuron (serotonin and norepinephrine reuptake inhibitors)	• No anticholinergic effects • No sedation • No weight gain • Do not precipitate convulsions • Orally effective • Adverse effects: nausea, sweating, sexual dysfunction, anxiety, hypertension
4. Atypical antidepressants • Bupropion	Inhibits the reuptake of DA and NA into the neuron	• Useful for smoking cessation • No anticholinergic effects • No hypotension • No sedation • May precipitate seizures • Adverse effects: dry mouth, tremor, sweating, convulsions

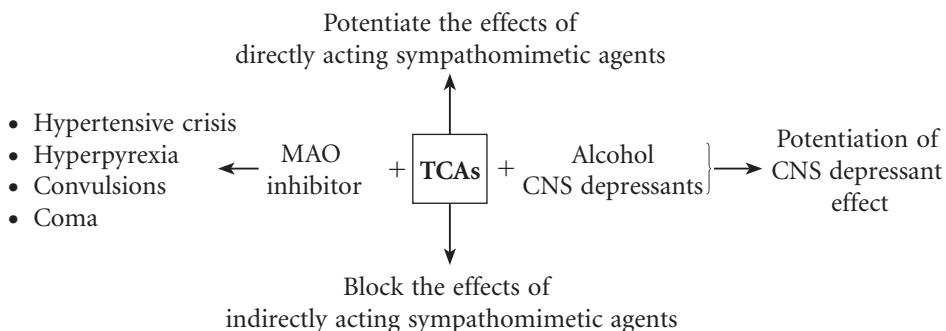
Table 5.18 ■ Comparative features of antidepressants—cont'd

Drug	MOA	Other points
Mirtazapine	Blocks α_2 -autoreceptors on noradrenergic neurons and heteroreceptors on 5-HT neurons; increases NA and 5-HT release; also blocks H_1 -receptors	- Mirtazapine (noradrenergic and specific serotonergic antidepressant – NaSSA) - Adverse effects: sedation, weight gain
Trazodone	Blocks 5-HT reuptake and 5-HT ₂ antagonist; blocks α_1 -adrenergic receptors	Adverse effects: sedation, hypotension, priapism (painful erection of penis)
Mianserin	Increases NA release by blocking presynaptic α_2 -receptors	- Has antianxiety action - Can precipitate seizures - Anticholinergic and cardiac side effects may occur rarely - Causes sedation

Note: Atomoxetine (see p. 217).

Drug Interactions

(a) Involving TCAs.



- (b) Serotonin syndrome: Concomitant administration of SSRIs with MAO inhibitors produces severe undesirable effects like tremor, restlessness, muscle rigidity, hyperthermia, sweating, shivering, seizures and coma due to increased serotonin levels at the synapses, which is termed serotonin syndrome.
- (c) SSRIs inhibit metabolism of a number of drugs such as TCAs, antipsychotics, β -blockers, phenytoin and carbamazepine, and increase their plasma levels.

CHEESE REACTION

Normally, tyramine in food is metabolized by MAO present in the gut and liver. So, very little tyramine reaches systemic circulation. When a patient on MAO inhibitor consumes food stuff rich in tyramine, it may result in fatal hypertensive crisis and cerebrovascular accidents. The reaction can be treated with i.v. phentolamine (Fig. 5.17).

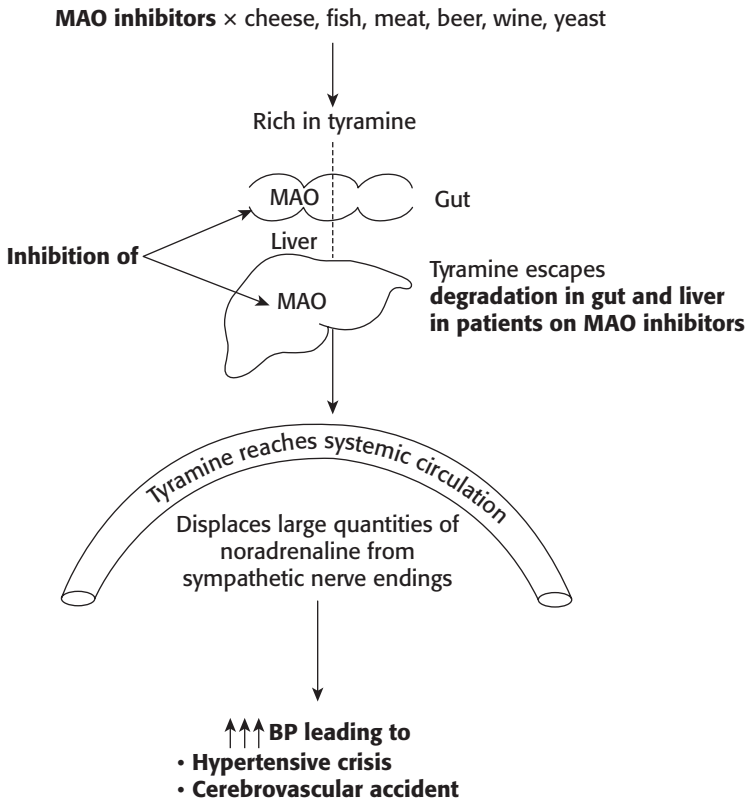


Fig. 5.17 Cheese reaction. MAO, Monoamine oxidase; BP, blood pressure.

USES OF ANTIDEPRESSANTS

1. Depression: Antidepressants are used in the treatment of endogenous depression (major depression) and during the phase of depression in bipolar illness. Patient starts taking interest in daily activities, mood is elevated, concentration improves and agitation decreases. Patient becomes more responsive. SSRIs are preferred to TCAs because of:
 - (a) Better tolerability.
 - (b) Less side effects (do not cause hypotension and sedation; do not have anticholinergic effects and no precipitation of convulsions, do not cause cardiac arrhythmias).
 - (c) Longer duration of action.
2. Anxiety disorders: SSRIs are used for the treatment of generalized anxiety disorder. Onset of action is slow; hence, BZDs are co-administered for a short period to control anxiety during this period. SNRIs like venlafaxine and duloxetine are also useful in anxiety.
3. Obsessive compulsive disorder (OCD): Clomipramine (TCA) and fluvoxamine (SSRI) are highly effective.
4. ADHD: TCAs (imipramine, nortriptyline, etc.) are used in ADHD. Atomoxetine, methylphenidate and dextroamphetamine can also be used in this disorder.
5. Nocturnal enuresis: Imipramine is effective.

6. Prophylaxis of migraine: Amitriptyline is effective.
7. Chronic pain including neuralgias: TCAs are effective in trigeminal, herpetic and postherpetic neuralgias. Venlafaxine and duloxetine (SNRIs) are used in the treatment of fibromyalgia.
8. Atopic dermatitis: Topical doxepin is useful; it has antipruritic action.
9. Premature ejaculation: SSRIs like paroxetine, fluoxetine, sertraline, citalopram and dapoxetine are effective. Dapoxetine is taken 1 hour before intercourse as it acts rapidly. If SSRIs are not tolerated, TCA like clomipramine can be used.

Drugs for Bipolar Disorder

PH1.19

Bipolar disorder (manic-depressive illness) is a psychiatric disorder in which depression alternates with mania. Mania is an affective disorder that manifests as elation, agitation, hyperactivity, uncontrolled thought and speech.

Drugs used in bipolar disorder are lithium, carbamazepine, sodium valproate, olanzapine, risperidone, haloperidol, etc.

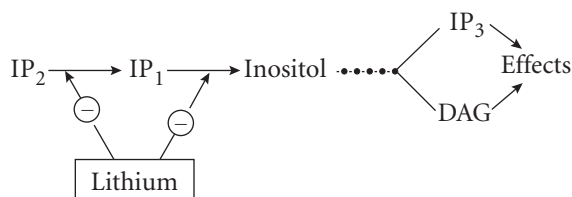
LITHIUM

Lithium was the first drug used for the treatment of mania. The antiepileptic drugs such as carbamazepine, sodium valproate and gabapentin have been approved for the treatment of bipolar disorder.

Actions and Mechanism

Lithium reduces motor activity, decreases euphoria, relieves insomnia and stabilizes the mood in patient with bipolar disorder.

In the **neuronal membrane**:



IP₂, inositol bisphosphate; IP₁, inositol monophosphate; IP₃, inositol triphosphate, DAG, diacylglycerol.

1. Lithium, by inhibiting the above steps, reduces the release of IP₃ and DAG, which are second messengers for both α -adrenergic and muscarinic transmission.
2. Lithium is a monovalent cation that can mimic the role of Na⁺.
3. Lithium also decreases the release of NA and DA in the brain.

Other Actions

- Lithium may produce nephrogenic diabetes insipidus by blocking the action of ADH on collecting duct.
- Increases total WBC count (leukocytosis).
- Inhibits the release of thyroid hormones (T₃ and T₄).

Pharmacokinetics

Lithium carbonate is effective orally, does not bind to plasma proteins and is distributed throughout the total body water. It is not metabolized and gets excreted in urine, saliva, sweat, etc. Lithium is a monovalent cation. The kidney handles lithium in the same way as Na^+ . About 80% of the filtered lithium is reabsorbed in the proximal tubules. Sodium depletion reduces the rate of excretion of lithium and increases its toxicity. Lithium has low therapeutic index; hence, therapeutic drug monitoring (TDM) is essential for optimal therapy (normal levels: 0.5–1.5 mEq/L). Estimation of salivary concentration can be used for noninvasive monitoring of lithium.

Adverse Effects

1. **GIT:** Nausea, vomiting and diarrhoea.
2. **CNS:** Tremor, ataxia, drowsiness, headache, muscular weakness and slurred speech.
3. **Renal:** Polyuria, polydipsia due to inhibition of ADH action.
4. **Goitre** with hypothyroidism may occur.
5. **Acute lithium toxicity** manifests as confusion, convulsions, cardiac arrhythmias, coma and death.

Treatment

1. Lithium should be stopped immediately, and its serum level is estimated.
2. i.v. mannitol to promote lithium excretion.
3. i.v. normal saline to restore Na^+ levels, which in turn promotes the excretion of lithium.
4. Haemodialysis is indicated if the serum levels are very high (>4 mEq/L).

Uses of Lithium

It is used as a prophylactic agent for bipolar disorder. It decreases the frequency and severity of both manic and depressive attacks; hence, it is called mood stabilizer. Lithium has a slow onset of action, hence not used for acute mania. Lithium is also useful in the prophylaxis of unipolar depression.

Drug Interactions

1. **Lithium $\times$ thiazides/furosemide:** Thiazides and furosemide cause hyponatraemia. As a result, there will be a compensatory increase in the reabsorption of Na^+ in PCT. Along with Na^+ , reabsorption of lithium is also increased leading to toxicity.
2. Neuromuscular blockade induced by depolarizing (succinylcholine) and nondepolarizing (pancuronium) **neuromuscular blockers** is prolonged in patients on lithium.
3. **Lithium $\times$ haloperidol:** Long-term lithium therapy may cause rigidity and potentiates the EPS of haloperidol.

Other Drugs Used in Mania and Bipolar Disorder

- **Sodium valproate:** It is the preferred drug for treatment of acute mania because of its rapid action, wider therapeutic index and better tolerability than lithium. It is also used prophylactically for bipolar disorder. It is used in combination with lithium or an antipsychotic. Divalproex can also be used.
- **Carbamazepine:** Carbamazepine, an antiepileptic drug, has mood-stabilizing effect and is used in the treatment of bipolar disorder. It may be used alone or in

combination with lithium or valproate. It is less effective than valproate/lithium. It is used prophylactically in bipolar disorder as adjunct to lithium.

- **Antipsychotics:** Olanzapine, risperidone, aripiprazole, quetiapine, etc. are preferred agents to control acute attack of mania. They can be used alone or combined with BZD/sodium valproate/lithium in acute mania. Conventional antipsychotics like haloperidol and fluphenazine are also useful.
- Lamotrigine, newer antiepileptic agent, is found to be useful only for prophylaxis of depression in bipolar disorder. It can also be used with lithium.
- **BZDs** like lorazepam or clonazepam are used as adjuncts if patient is agitated.

Autacoids and Respiratory System

Autacoids are produced by cells and act locally. Hence, they are also called 'local hormones'. Various autacoids are histamine, serotonin (5-hydroxytryptamine [5-HT]), prostaglandins (PGs), leukotrienes, angiotensin, kinins and platelet-activating factor (PAF).

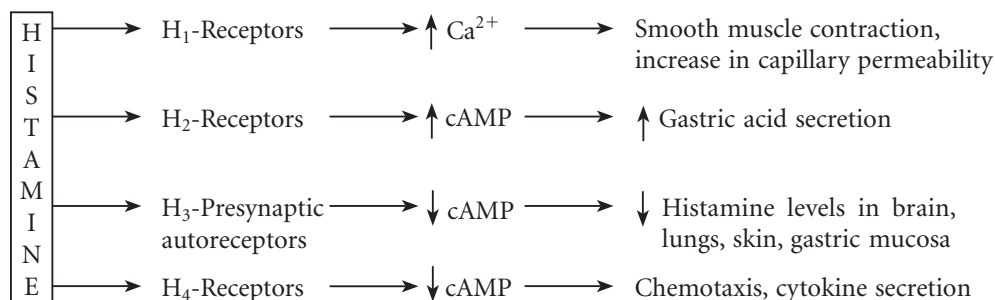
Histamine and Antihistamines

PH1.16

Histamine is a biogenic amine present in many animal and plant tissues. It is also present in venoms and stinging secretions. It is synthesized by decarboxylation of the amino acid, histidine. It is mainly present in storage granules of mast cells in tissues like skin, lungs, liver, gastric mucosa and placenta. It is one of the mediators involved in inflammatory and hypersensitivity reactions.

MECHANISM OF ACTION AND EFFECTS OF HISTAMINE

Histamine exerts its effects by binding to histamine (H) receptors.



HISTAMINE LIBERATORS

Many agents release histamine from mast cells (Fig. 6.1).

Uses

Histamine has no valid clinical use.

BETAHISTINE

It is a histamine analogue that is used orally to treat vertigo in Meniere's disease. It probably acts by improving blood flow in the inner ear. The side effects are nausea, vomiting, headache and pruritus. It should be avoided in patients with asthma and peptic ulcer.

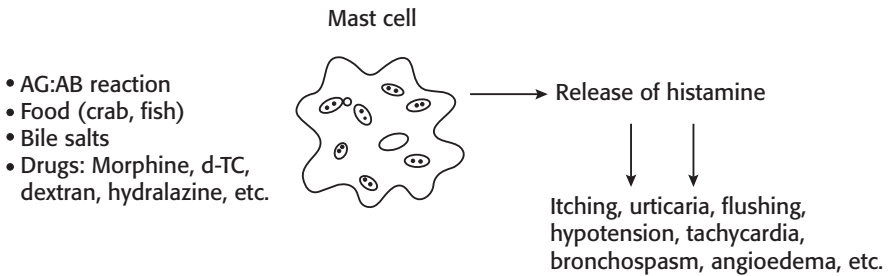
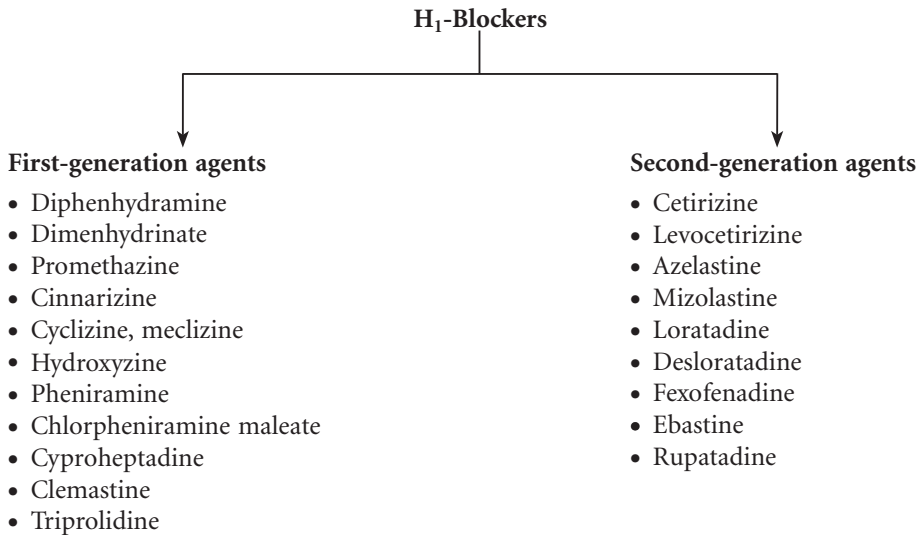


Fig. 6.1 Histamine liberators and its effects.

H₁-Receptor Antagonists (H₁-Blockers, Antihistamines)

PH1.16

CLASSIFICATION



MECHANISM OF ACTION OF H₁-BLOCKERS

H₁-antihistamines antagonize the effects of histamine by competitively blocking the H₁-receptors (competitive antagonism).



FIRST-GENERATION H₁-BLOCKERS

They are conventional antihistamines.

Pharmacological Actions

1. H₁-blockers cause CNS depression, sedation and drowsiness. Certain antihistamines have antiemetic, local anaesthetic and anti-parkinsonian effects.

2. They have antiallergic action; hence, most of the manifestations of type I reactions are suppressed.
3. They have anticholinergic actions – cause dryness of mouth, blurring of vision, constipation, urinary retention.

Pharmacokinetics

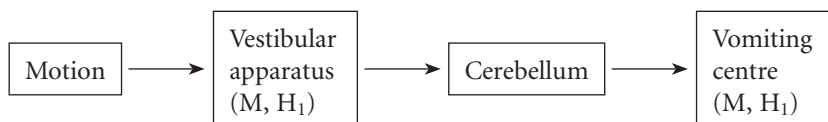
H₁-antihistamines are well absorbed after oral and parenteral administration. They are distributed widely throughout the body, metabolized extensively in liver and excreted in urine.

Adverse Effects

1. The common adverse effects are sedation, drowsiness, lack of concentration, headache, fatigue, weakness, lassitude, psychomotor incoordination, etc. Hence, H₁-antihistamines should be avoided while driving or operating machinery. These adverse effects are rare with second-generation antihistamines.
2. Gastrointestinal side effects are nausea, vomiting, loss of appetite and epigastric discomfort.
3. Anticholinergic side effects such as dryness of mouth, blurring of vision, constipation and urinary retention. These effects are not seen with second-generation antihistamines.
4. Teratogenic effects of some H₁-blockers have been observed in animals.
5. Allergic reactions may occur rarely with these agents, especially contact dermatitis on topical application.

Uses

1. **Allergic diseases:** H₁-antihistamines are used to prevent and treat symptoms of allergic reactions. For example, pruritus, urticaria, dermatitis, rhinitis, conjunctivitis and angioedema of lips respond to these drugs.
2. **Common cold:** They produce symptomatic relief by sedative and anticholinergic actions.
3. **Preanaesthetic medication:** Promethazine is used for its sedative and anticholinergic effects.
4. **As antiemetic:** Promethazine, diphenhydramine, dimenhydrinate, etc. are useful for prophylaxis of motion sickness because of their anticholinergic action. They act probably on the vestibular apparatus or cortex. Sedative effect also contributes to their beneficial effect. These drugs are useful in drug-induced and postoperative vomiting. Promethazine, in combination with other antiemetics, is used to control vomiting due to cancer chemotherapy and radiation therapy.



5. **Parkinsonism:** Imbalance between dopamine (DA) and acetylcholine ($\downarrow$ DA or $\uparrow$ ACh) in the basal ganglia produces parkinsonism. Promethazine, diphenhydramine or orphenadrine are used to control tremor, rigidity (central action) and sialorrhoea of parkinsonism due to their anticholinergic and sedative properties. Promethazine and diphenhydramine are useful for the treatment of idiopathic and drug-induced parkinsonism.
6. **H₁-blockers** are used to control mild blood transfusion and saline infusion reactions (chills and rigors) and as adjunct in anaphylaxis.

7. Cinnarizine, dimenhydrinate and meclizine are effective for controlling **vertigo** in Meniere's disease and other types of vertigo. Their antihistaminic and anticholinergic actions are useful in this condition.
8. **Sedative and hypnotic:** H₁-antihistamines (e.g. promethazine and diphenhydramine) are used to induce sleep, especially in children during minor surgical procedures.

SECOND-GENERATION H₁-BLOCKERS (Table 6.1)

Cetirizine, levocetirizine, loratadine, desloratadine, azelastine, fexofenadine, etc. are highly selective for H₁-receptors and have the following properties. They:

1. Have no anticholinergic effects.
2. Lack antiemetic effect.
3. Do not cross blood–brain barrier (BBB), hence cause minimal/no drowsiness.
4. Do not impair psychomotor performance.
5. Are relatively expensive.

Cetirizine is one of the commonly used second-generation antihistamines. In addition to H₁-blocking effect, it can also inhibit the release of histamine. It causes minimal/ or no drowsiness. It is not metabolized in the body. Incidence of cardiac arrhythmias is rare with this drug.

Table 6.1 ■ Second-generation H₁-blockers

Drug	Route and duration of action	Important features
Cetirizine	p.o., 12–24 hours	• H₁-blocker; inhibits histamine release; achieves good concentration in the skin; poorly crosses BBB; may cause drowsiness • Drug interactions rare
Levocetirizine	p.o., 12–24 hours	More potent and produces less adverse effects than cetirizine
Loratadine Desloratadine Mizolastine Ebastine	p.o., 24 hours }	• Long acting, nonsedating agents • Cardiac arrhythmias have been noticed in animals treated with ebastine • No cardiac arrhythmias with loratadine and desloratadine • Loratadine may rarely cause seizures
Fexofenadine	p.o., 12–24 hours	• Active metabolite of terfenadine • Nonsedating agent • Arrhythmias rare; avoid in patients with prolonged QT interval
Azelastine	Topical (nasal spray, eye drops), 12–24 hours	• H₁-blocker; inhibits histamine release • Produces active metabolite • Has a rapid onset and long duration of action • Taste alteration, burning sensation in the nose, drowsiness
Rupatadine	p.o.	H ₁ -blocker + blocks actions of platelet-activating factor

Uses

Second-generation H₁-blockers are used in various allergic disorders, e.g. rhinitis, dermatitis, conjunctivitis, urticaria, eczema, drug and food allergies. For allergic rhinitis or hay fever, fexofenadine, cetirizine, mizolastine or rupatadine are used orally. Azelastine is used as nasal spray in allergic rhinitis. For urticaria, atopic dermatitis and other skin allergies, fexofenadine, cetirizine, mizolastine, loratadine and ebastine are useful. Azelastine and levocabastine are available as eye drops for allergic conjunctivitis.

ANTIVERTIGO DRUGS

Vertigo is a sensation of rotation or movement of one's self or of one's surrounding in any plane. Antivertigo drugs are cinnarizine, promethazine and diphenhydramine (H₁-blockers), hyoscine (anticholinergic), prochlorperazine (phenothiazine), betahistine (H₁-analogue), acetazolamide, thiazides and furosemide (diuretics), diazepam (benzodiazepine), amitriptyline (tricyclic antidepressant [TCA]), glucocorticoids, etc. Cinnarizine is a first-generation H₁-blocker. It decreases entry of calcium into vestibular cells and relieves vertigo. Antihistaminics, anticholinergics and prochlorperazine act as labyrinthine suppressants. Corticosteroids decrease oedema in the labyrinth.

5-Hydroxytryptamine: Agonists and Antagonists

PH1.16

5-HT (serotonin) is an important neurotransmitter, widely distributed in plants and animals. It is synthesized from an amino acid, tryptophan. High concentration of 5-HT is found in the intestine, platelets and brain. 5-HT is involved in several conditions such as migraine, affective disorders, psychoses, GI disorders and sleep. There are seven subtypes of serotonin receptors (1–7). All of them are G-protein-coupled receptors, except 5-HT₃ (ligand-gated ion channel). The serotonin receptor subtypes are shown in [Table 6.2](#).

5-HT ANTAGONISTS

Cyproheptadine

- H₁-receptor and 5-HT_{2A} blocker
- Has sedative, antipruritic and anticholinergic effects
- Increases appetite
- Useful in carcinoid and postgastrectomy dumping syndrome (to control GI manifestations)
- Dry mouth, drowsiness, weight gain are some of the side effects

Ketanserin

- 5-HT_{2A} antagonist and α_1 -blocker
- Has antihypertensive effect

Ondansetron and Granisetron

They are 5-HT₃ receptor antagonists used as antiemetics.

Atypical Antipsychotics

Clozapine, olanzapine, quetiapine, risperidone, etc. are 5-HT₂ blockers used in schizophrenia.

Table 6.2 ■ Serotonin receptor subtypes

Receptor	Location	Important actions	Drugs
5-HT ₁	CNS, cranial blood vessels	• Autoreceptors: Decrease 5-HT release from nerve endings • Constriction of cranial blood vessels • Decreased release of peptides from nerve endings	• <i>Buspirone</i> (5-HT_{1A} partial agonist) • <i>Triptans</i> (Selective 5-HT_{1B/1D} agonists) • <i>Ergotamine</i> (antagonist/partial agonist at all subtypes of 5-HT₁ receptors)
5-HT ₂	• Platelets • Smooth muscles • Cerebral cortex (5-HT_{2A}) • Fundus of the stomach (5-HT_{2B}) • Choroid (5-HT_{2C})	• Platelet aggregation • Contraction of smooth muscles • Activation of neurons • Contraction • CSF production	• <i>Ketanserin</i> (5-HT_{2A} antagonist) • <i>Cyproheptadine</i> (5-HT_{2A} antagonist) • <i>Methysergide</i> (5-HT_{2A/2C} antagonist) • <i>Atypical anti-psychotics</i> (5-HT_{2A} antagonists)
5-HT ₃	CTZ, NTS, parasympathetic nerve terminals (GIT)	• Vomiting • Peristalsis	Ondansetron, granisetron (5-HT ₃ antagonists)
5-HT ₄	GIT, CNS	Peristalsis	Metoclopramide, prucalopride (5-HT ₄ agonists)
5-HT ₅₋₇	CNS	—	—

Methysergide

- 5-HT_{2A/2C} antagonist.
- It was used for prophylaxis of migraine.
- Long-term use causes abdominal and pulmonary fibrosis.

Ergot Alkaloids

Ergot alkaloids occur naturally in a fungus, *Claviceps purpurea*. The most important compounds and their therapeutic uses are given in [Table 6.3](#).

Ergot alkaloids are contraindicated in ischaemic heart disease, hypertension, peripheral vascular disease and renal disease.

DRUG THERAPY OF MIGRAINE

PH1.16

Migraine is a common and debilitating condition, the cause of which is not clear. A migraine attack consists of an initial visual disturbance (the aura), severe throbbing headache often with photophobia, nausea and vomiting.

Drugs for Acute Attack of Migraine

Nonsteroidal Anti-inflammatory Drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used alone or in combination. They provide symptomatic relief but should not be

Table 6.3 ■ Ergot alkaloids and their derivatives

Drug	Action on receptor	Effects	Use with route	Adverse effects
Ergotamine (natural alkaloid)	Partial agonist/antagonist at α , 5-HT ₁ and 5-HT ₂ receptors	Contraction of smooth muscles – blood vessels, uterus, gut and other viscera	Acute migraine (oral, sublingual, rectal)	Vomiting, diarrhoea; overdosage – severe vaso-spasm → gangrene
Dihydroergotamine (semi-synthetic)	• Predominant α-blockade • Weak 5-HT and α-agonistic action	• Smooth muscle contraction less than ergotamine • Less vasoconstrictor effect (safer than ergotamine for parenteral use)	Acute migraine (oral, i.m., s.c.)	Nausea, vomiting
Ergometrine (ergonovine; natural alkaloid)	• Partial agonist at 5-HT₂ and weak action at α-receptors • No α-antagonistic action	• Major action – contraction of myometrium • Vasoconstriction is minimal	Postpartum haemorrhage (i.m., i.v.)	Nausea, vomiting, rise in BP
Bromocriptine (semi-synthetic)	D ₂ -agonist	Decreases prolactin release	• Parkinsonism • Galactorrhoea (oral)	Vomiting, hypotension

taken on a long-term basis, e.g. paracetamol, aspirin, ibuprofen, naproxen, diclofenac and mefenamic acid. They are useful in mild and moderate migraine.

Antiemetics (Oral or Parenteral). They are used to treat nausea and vomiting associated with the attack. They also improve absorption of oral medications used to treat migraine, e.g. metoclopramide, domperidone, prochlorperazine, promethazine and diphenhydramine.

Ergot Preparations

Ergotamine. Oral/sublingual/suppository preparation is used at the onset of pain or warning symptoms. It is used in moderate to severe migraine.

Mechanism of Action. It acts as a partial agonist at 5-HT_{1B/1D} receptors in cranial blood vessels → constriction of dilated cranial blood vessels, decreases inflammation and extravasation of plasma into perivascular space.

Ergotamine is available in combination with caffeine. Caffeine increases absorption of ergotamine. It also has vasoconstrictor effect on cranial blood vessels like ergotamine.

Dihydroergotamine. It is administered parenterally (i.m., i.v., s.c.) at the time of attack. It is safer for parenteral use than ergotamine.

Triptans. Selective 5-HT_{1B/1D} agonists, include sumatriptan, rizatriptan, eletriptan, almotriptan, zolmitriptan, naratriptan, frovatriptan, etc. They are used in moderate and severe migraine.

Mechanism of Action of Triptans (Selective 5-HT_{1B/1D} Agonists)

Abnormal dilatation of cranial blood vessels $\implies$ Cerebral ischaemia $\implies$ Migraine attack

- Triptans $\implies$ Selective 5-HT_{1B/1D} agonists $\implies$ Constrict dilated cranial blood vessels and arteriovenous shunts $\implies$ Restore cerebral blood flow
- Decrease 5-HT and vasoactive peptide release by acting on 5-HT_{1B/1D} receptors on presynaptic nerve endings
- Inhibit extravasation of plasma proteins in the perivascular space

By inhibiting the release of inflammatory peptides from the nerve endings in the perivascular space, they decrease inflammation. They are the preferred drugs for acute attack of migraine. All triptans are administered orally. Sumatriptan can also be administered by s.c. and nasal routes; zolmitriptan can also be given by nasal route. Sumatriptan is rapid acting and has a half-life of 2 hours. Other triptans have a higher oral bioavailability than sumatriptan. Frovatriptan and naratriptan have longer half-life than sumatriptan.

Adverse Effects and Contraindications of Triptans. They include paraesthesia, tightness in the chest, flushing and dizziness. Nausea may occur. Pain at the site of injection is common. They may cause a rise in BP and coronary vasospasm. Triptans are contraindicated in pregnancy, patients with ischaemic heart disease, and those with peripheral vascular disease, hypertension and risk factor for coronary artery disease. Triptan and ergot preparations should not be coadministered; neither should triptans be taken within 24 hours of an ergot derivative.

Prophylaxis of Migraine (Note ABCD)

Prophylactic treatment may be required if migraine headaches occur two/three or more times in a month or if there is significant functional impairment during the attack. The drugs used are as follows:

1. **Beta-blockers:** Propranolol, timolol, atenolol, metoprolol, etc. Propranolol is more effective than other β -blockers; requires prolonged treatment. The mechanism of action is unknown.
2. **Antidepressants:** TCAs like amitriptyline help to reduce attacks of migraine; exact mechanism of action of antimigraine effect is not clear. TCAs produce undesirable side effects on prolonged therapy.
3. **Calcium channel blockers (CCBs):** For example, verapamil and flunarizine. They reduce the frequency of attacks. Flunarizine is selective for cerebral calcium channels; it also has Na⁺ channel-blocking effect. CCBs should not be co-administered with β -blockers.
4. **Anticonvulsants:** For example, gabapentin, sodium valproate and topiramate are used for migraine prophylaxis.

Others: Methysergide and cyproheptadine are rarely used for prophylaxis of migraine.

Prostaglandins and Leukotrienes (Eicosanoids)

PH1.16

PROSTAGLANDINS

PGs are the products of long-chain fatty acids. Arachidonic acid is the precursor for biosynthesis of all PGs. The enzyme involved in the formation of PGs from arachidonic acid is cyclooxygenase (COX). The main PGs are PGE₂, PGF_{2α} and PGI₂. Another class of substances obtained from arachidonic acid by the action of lipoxygenase is leukotrienes.

There are two forms of COX, called COX-1 and COX-2 (Fig. 6.2). COX-1 is constitutive (it is always present) and is widely distributed. It participates in various physiological functions such as protection of gastric mucosa, homeostasis and regulation of cell division. COX-2 is induced during inflammation by cytokines and endotoxins.

Pharmacological Actions and Uses (Fig. 6.3)

1. **GI tract:** PGE₂ and PGI₂ reduce acid secretion and increase the secretion of mucus in the stomach (cytoprotective action). Misoprostol (PGE₁ analogue) is used for the prevention of NSAID-induced ulcers (Table 6.4).
2. **Cardiovascular system:** PGD₂, PGE₂ and PGI₂ cause vasodilatation. PGF_{2α} constricts pulmonary veins and arteries. TXA₂ is a vasoconstrictor.
(a) PGE₁ (alprostadil) is used to maintain the patency of ductus arteriosus before surgery.

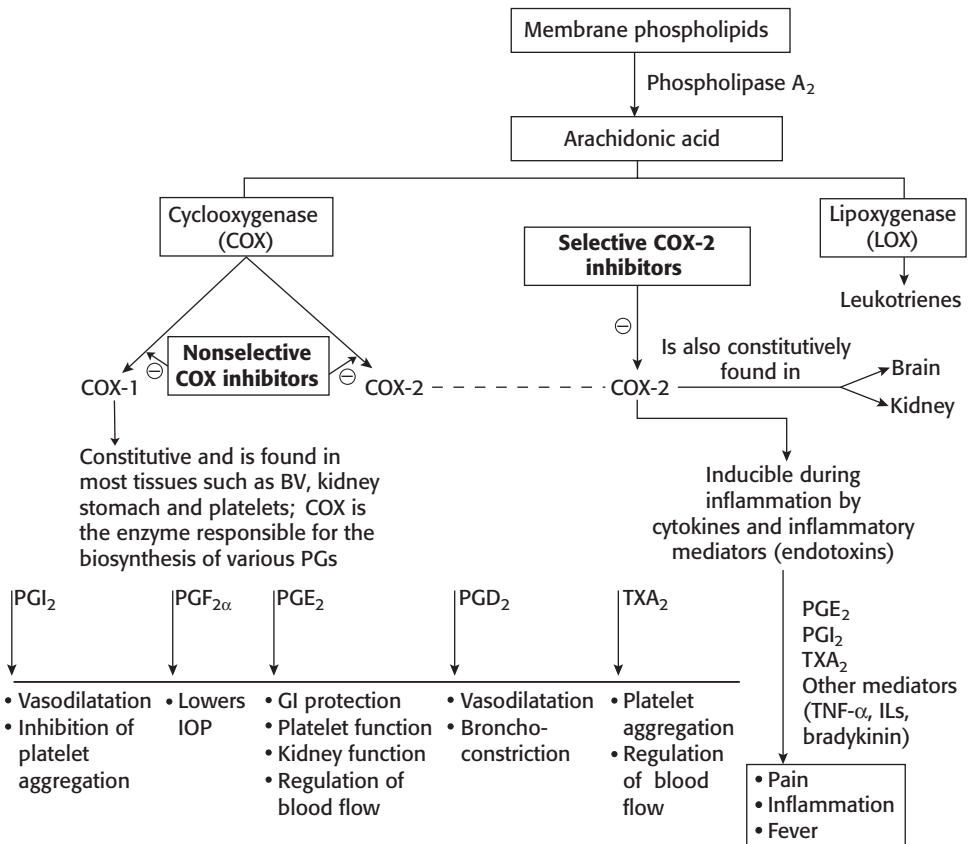


Fig. 6.2 The different roles of cyclooxygenases (COX-1 and COX-2) and the drugs inhibiting them. BV, blood vessels; IOP, intraocular pressure.

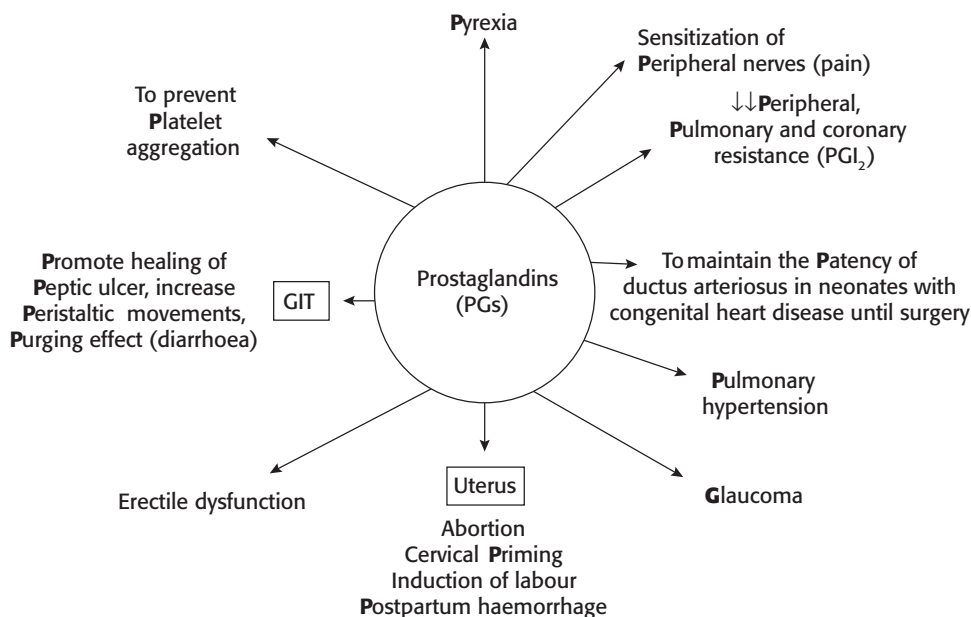


Fig. 6.3 Effects and uses of prostaglandins.
Note: **PGs** – in the figure, actions/uses with plenty of ‘P’s and a single ‘G’.

Table 6.4 ■ Preparations, formulations and uses of prostaglandin analogues

Preparations	Formulations/route	Uses
• Dinoprostone (PGE_2)	• Vaginal tab • Vaginal gel	• Induction of labour • Mid-term abortion • Termination of pregnancy
• Dinoprost ($\text{PGF}_{2\alpha}$)	Intra-amniotic injection	Mid-term abortion
• Carboprost (15-methyl $\text{PGF}_{2\alpha}$)	i.m.	• Mid-term abortion • Control of PPH
• Gemeprost (PGE_1)	Vaginal pessary	Cervical priming in early pregnancy
• Alprostadil (PGE_1)	• Intravenous infusion • Intracavernous injection	• To maintain the patency of ductus arteriosus in neonates with congenital heart disease until surgery • Erectile dysfunction
• Misoprostol (PGE_1)	Oral, vaginal pessary	• Peptic ulcer • Abortion, PPH
• Epoprostenol (PGI_2) • Treprostinil (PGI_2) • Iloprost (PGI_2)	Intravenous infusion	Pulmonary hypertension
• Latanoprost ($\text{PGF}_{2\alpha}$) • Bimatoprost ($\text{PGF}_{2\alpha}$) • Unoprostone ($\text{PGF}_{2\alpha}$) • Travoprost ($\text{PGF}_{2\alpha}$)	Topical (eye drops)	Glaucoma

- (b) Prostacyclin (PGI_2) decreases peripheral, pulmonary and coronary resistance. PGI_2 (epoprostenol) is used to treat pulmonary hypertension. Other PGI_2 analogues useful in this condition are treprostinil and iloprost.
- 3. **Platelets:** PGI_2 inhibits platelet aggregation. Hence, it is useful during haemodialysis to prevent platelet aggregation.
- 4. **Eye:** $\text{PGF}_{2\alpha}$ has been found to decrease intraocular tension. Its analogues, e.g. latanoprost, bimatoprost, travoprost and unoprostone, are used in glaucoma.
- 5. **Uterus:**
 - (a) PGE_2 (low concentration) and $\text{PGF}_{2\alpha}$ contract pregnant uterus; PGs are mainly used in mid-trimester abortion, missed abortion and in hydatidiform mole (Table 6.4).
 - (b) Induction of labour: PGE_2 and $\text{PGF}_{2\alpha}$ can induce labour at term.
 - (c) Cervical priming: PGE_2 , PGE_1 and $\text{PGF}_{2\alpha}$ promote ripening of the cervix; make the cervix favourable for induction and facilitation of labour.
 - (d) Postpartum haemorrhage (PPH): PGs increase tone as well as amplitude of uterine contractions. Carboprost (15-methyl $\text{PGF}_{2\alpha}$) can be used to control PPH.
- 6. **Male reproductive system:** PGE_1 (alprostadil) is useful in the treatment of erectile dysfunction.

Therapeutic Uses of Prostaglandins in Obstetrics

- 1. **Abortion:** PGs stimulate uterine contractions and cause ripening of the cervix.
 - Dinoprostone (vaginal) is used for induction of mid-trimester abortion, missed abortion and hydatidiform mole.
 - Misoprostol (oral or vaginal) can be used in combination with mifepristone or methotrexate to induce abortion in early pregnancy.
 - Carboprost (i.m.) is used to induce abortion in second trimester of pregnancy.
 - Gemeprost (PGE_1) and dinoprost ($\text{PGF}_{2\alpha}$) are also useful for inducing abortion.
- 2. **Induction of labour:** PGs can be used to soften the cervix for induction of labour. PGE_2 can facilitate labour by softening and dilatation of cervix.
- 3. **PPH:** Carboprost (i.m.) and misoprostol (oral) can be used to control PPH.

Adverse Effects

They are nausea, vomiting, diarrhoea, fever, flushing, hypotension and backache due to uterine contractions. Injections are painful due to sensitization of nerve endings.

LEUKOTRIENES

These are obtained from arachidonic acid by the action of lipoxygenase.

Leukotriene Antagonists (See p. 259)

Nonsteroidal Anti-Inflammatory Drugs

PH1.16

CLASSIFICATION

- 1. **Nonselective COX inhibitors**
 - (a) *Salicylates*: Aspirin, diflunisal.
 - (b) *Propionic acid derivatives*: Ibuprofen, naproxen, ketoprofen, flurbiprofen.
 - (c) *Fenamic acid derivatives*: Mefenamic acid, flufenamic acid.
 - (d) *Acetic acid derivatives*: Ketorolac, indomethacin.
 - (e) *Enolic acid derivatives*: Piroxicam, tenoxicam, lornoxicam.

2. **Preferential COX-2 inhibitors:** Diclofenac, aceclofenac, nimesulide, meloxicam.
3. **Highly selective COX-2 inhibitors:** Etoricoxib, parecoxib.
4. **Analgesic and antipyretics having weak anti-inflammatory effect:** Paracetamol, nefopam.

MECHANISM OF ACTION

COX is the enzyme responsible for biosynthesis of various PGs. There are two well-recognized isoforms of COX: COX-1 and COX-2. COX-1 is constitutive, found in most tissues such as blood vessels, stomach and kidney. PGs have important physiological role in many tissues (Fig. 6.2). COX-2 is induced during inflammation by cytokines and endotoxins and is responsible for the production of prostanoid mediators of inflammation.

Aspirin and most of the NSAIDs inhibit both COX-1 and COX-2 isoforms; thereby decrease PGs and thromboxane synthesis. The anti-inflammatory effect of NSAIDs is mainly due to inhibition of COX-2. Aspirin causes irreversible inhibition of COX activity. Rest of the NSAIDs causes reversible inhibition of the enzyme.

PHARMACOLOGICAL ACTIONS OF ASPIRIN AND OTHER NSAIDs

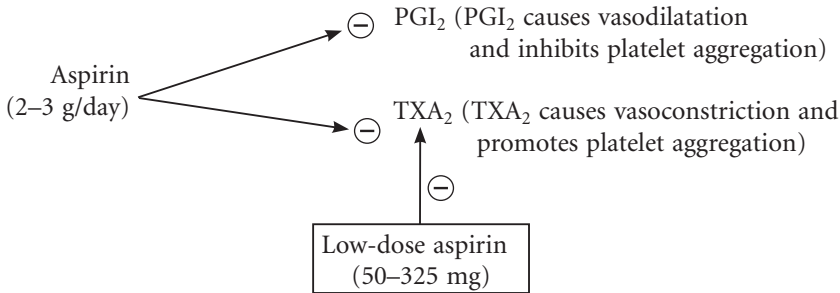
Aspirin (acetylsalicylic acid) is the prototype drug. The other nonselective NSAIDs vary mainly in their potency, analgesic, anti-inflammatory effects and duration of action.

1. **Analgesic effect:** NSAIDs are mainly used for relieving musculoskeletal pain, dysmenorrhoea and pain associated with inflammation or tissue damage. Analgesic effect is mainly due to peripheral inhibition of PG production. They prevent sensitization of peripheral nerve endings by inflammatory mediators. They also increase pain threshold by acting at subcortical site. These drugs relieve pain without causing sedation, respiratory depression, tolerance or dependence. They are less efficacious than opioids as analgesics. Aspirin produces analgesia at doses of 2–3 g/day.
2. **Antipyretic effect:** The thermoregulatory centre is situated in the hypothalamus. Fever occurs when there is a disturbance in hypothalamic thermostat. NSAIDs reset the hypothalamic thermostat and reduce the elevated body temperature during fever. They promote heat loss by causing cutaneous vasodilatation and sweating. They do not affect normal body temperature. The antipyretic effect is mainly due to inhibition of PGs in the hypothalamus. The dose of aspirin for antipyretic effect is 2–3 g/day.
3. **Anti-inflammatory effect:** Anti-inflammatory effect is seen at high doses (aspirin: 4–6 g/day in divided doses). These drugs produce only symptomatic relief. They suppress signs and symptoms of inflammation such as pain, tenderness, swelling, vasodilatation and leukocyte infiltration but they do not affect the progression of underlying disease.

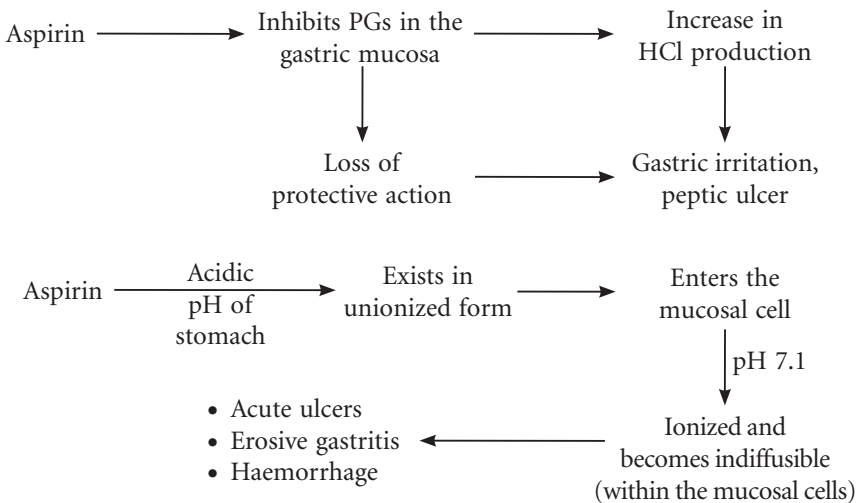
The anti-inflammatory action of NSAIDs is mainly due to inhibition of PG synthesis at the site of injury. They also affect other mediators of inflammation (bradykinin, histamine, serotonin, etc.), thus inhibit granulocyte adherence to the damaged vasculature. NSAIDs also cause modulation of T-cell function, stabilization of lysosomal membrane and inhibition of chemotaxis.

4. **Antiplatelet (antithrombotic) effect:** Aspirin in low doses (50–325 mg/day) irreversibly inhibits platelet TXA₂ synthesis and produces antiplatelet effect, which lasts for 8–10 days, i.e. the life time of the platelets. Aspirin in high doses

(2–3 g/day) inhibits both PGI_2 and TXA_2 synthesis, hence antiplatelet effect is lost. Aspirin should be withdrawn 1 week prior to elective surgery because of the risk of bleeding.



5. **Acid–base and electrolyte balance:** In therapeutic doses, salicylates cause respiratory alkalosis, which is compensated by excretion of bicarbonate (compensated respiratory alkalosis). In toxic doses, the respiratory centre is depressed and can lead to respiratory acidosis. Later, there is uncompensated metabolic acidosis.
6. **GIT:** Aspirin irritates the gastric mucosa and produces nausea, vomiting and dyspepsia. The salicylic acid formed from aspirin also contributes to these effects. Aspirin also stimulates CTZ and produces vomiting (Fig. 6.4).



7. **CVS:** Prolonged use of aspirin and other NSAIDs causes sodium and water retention. They may precipitate CCF in patients with low cardiac reserve. They may also decrease the effect of antihypertensive drugs.
8. **Urate excretion:** Salicylates, in therapeutic doses, inhibit urate secretion into the renal tubules and increase the plasma urate levels. In high doses, salicylates inhibit the reabsorption of uric acid in the renal tubules and produce uricosuric effect.

PHARMACOKINETICS

Salicylates are rapidly absorbed from the upper GI tract. They are highly bound to plasma proteins but the binding is saturable. Salicylates are well distributed throughout

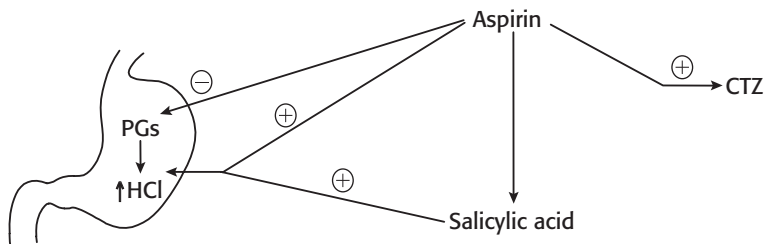


Fig. 6.4 Action of aspirin on stomach and CTZ. ⊕, Stimulation; ⊖, inhibition; PGs, prostaglandins.

the tissues and body fluids; metabolized in liver by glycine and glucuronide conjugation. In low doses, elimination follows first-order kinetics and with high doses as the metabolizing enzymes get saturated, it switches over to zero-order kinetics. After this, an increase in salicylate dosage increases its plasma concentration markedly and severe toxicity can occur. Alkalinization of urine increases the rate of excretion of salicylates.

DOSAGE REGIMEN FOR ASPIRIN

Analgesic dose: 2–3 g/day in divided doses after food.

Anti-inflammatory dose: 4–6 g/day in divided doses after food.

Antiplatelet dose: 50–325 mg/day (low-dose aspirin).

ADVERSE EFFECTS

- GIT:** Nausea, vomiting, dyspepsia, epigastric pain, acute gastritis, ulceration and GI bleeding. Ulcerogenic effect is the major drawback of NSAIDs, which is prevented/minimized by taking:
 - NSAIDs after food.
 - Buffered aspirin (preparation of aspirin with antacid).
 - Proton-pump inhibitors/H₂-blockers/misoprostol with NSAIDs.
 - Selective COX-2 inhibitors.
- Hypersensitivity:** It is relatively more common with aspirin. The manifestations are skin rashes, urticaria, rhinitis, bronchospasm, angioneurotic oedema and rarely anaphylactoid reaction. Bronchospasm (aspirin-induced asthma) is due to increased production of leukotrienes. Incidence of hypersensitivity is high in patients with asthma, nasal polyps, recurrent rhinitis or urticaria. Therefore, aspirin should be avoided in such patients.
- In people with G6PD deficiency, administration of salicylates may cause **haemolytic anaemia**.
- Prolonged use of salicylates **interfere with action of vitamin K** in the liver → decreased synthesis of clotting factors (hypoprothrombinaemia) → predisposes to bleeding (can be treated by administration of vitamin K).
- Reye's syndrome:** Use of salicylates in children with viral infection may cause hepatic damage with fatty infiltration and encephalopathy – Reye's syndrome. Hence, salicylates are contraindicated in children with viral infection.
- Pregnancy:** These drugs inhibit PG synthesis, thereby delay onset of labour and increase chances of PPH. In the newborn, inhibition of PG synthesis results in premature closure of ductus arteriosus.

7. **Analgesic nephropathy:** Slowly progressive renal failure may occur on chronic use of high doses of NSAIDs. Renal failure is usually reversible on stoppage of therapy but rarely NSAIDs may cause irreversible renal damage.

Salicylism

Salicylate intoxication may be mild or severe. The mild form is called salicylism. The symptoms include headache, tinnitus, vertigo, confusion, nausea, vomiting, diarrhoea, sweating, hyperpnoea, electrolyte imbalance, etc. These symptoms are reversible on stoppage of therapy.

Acute Salicylate Poisoning

It is common in children. Manifestations are vomiting, dehydration, acid–base and electrolyte imbalances, hyperpnoea, restlessness, confusion, coma, convulsions, cardiovascular collapse, pulmonary oedema, hyperpyrexia and death.

Treatment. There is no specific antidote for salicylate poisoning. Treatment is symptomatic.

1. Hospitalization.
2. Gastric lavage followed by administration of activated charcoal (activated charcoal adsorbs the toxic material – *physical antagonism*).
3. Maintain fluid and electrolyte balance. Correct acid–base disturbances.
4. Intravenous sodium bicarbonate to treat metabolic acidosis. It also alkalinizes the urine and enhances renal excretion of salicylates (since salicylates exist in ionized form in alkaline pH).
5. External cooling.
6. Haemodialysis in severe cases.
7. Vitamin K₁ and blood transfusion if there is bleeding.

DRUG INTERACTIONS

1. NSAIDs × glucocorticoids: Potentiation of GI complications – nausea, vomiting, dyspepsia, epigastric pain, acute gastritis, ulceration and GI bleeding.
2. NSAIDs potentiate the effects of oral anticoagulants, oral hypoglycaemic agents (sulphonylureas) and methotrexate by displacing them from plasma protein binding sites.
3. Some of the NSAIDs (e.g. piroxicam) can impair the clearance of lithium leading to its toxicity.
4. NSAIDs × thiazides/furosemide: NSAIDs by inhibiting PG synthesis promote Na⁺ and water retention on chronic use. Thus, they decrease the diuretic efficacy of thiazides/furosemide.
5. NSAIDs × antihypertensives: NSAIDs by inhibiting PG synthesis promote Na⁺ and water retention on chronic use. Thus, they decrease the efficacy of antihypertensives.

CLINICAL USES OF NSAIDs (FOR BASIS AND EXPLANATION, SEE 'PHARMACOLOGICAL ACTIONS')

1. **As analgesic:** In painful conditions like headache, toothache, backache, body ache, muscle pain, joint pain, bursitis, neuralgias and dysmenorrhoea.
2. **As antipyretic:** To reduce elevated body temperature in fever, paracetamol is preferred because:
 - (a) Gastrointestinal symptoms are rare.
 - (b) It does not cause Reye syndrome in children.

3. **Osteoarthritis:** In mild cases, paracetamol is used. In severe cases of osteoarthritis, other NSAIDs are more effective than paracetamol. Topical agents like methyl salicylate, diclofenac gel and capsaicin cream can also be used.
4. **Rheumatoid arthritis (RA):** NSAIDs have anti-inflammatory effects and can produce only symptomatic relief but they do not alter the progression of disease.
5. **Acute rheumatic fever:** Aspirin is the preferred drug. It reduces fever, relieves swelling and joint pain, but does not affect the normal course of the disease.
6. **Thromboembolic disorders:** The antiplatelet effect of low-dose aspirin is made use of in the prophylactic treatment of various thromboembolic disorders, such as
 - (a) Transient ischaemic attacks
 - (b) Myocardial infarction (MI)
 - (i) To reduce incidence of recurrent MI
 - (ii) To decrease mortality in post-MI patients
7. **Other uses:**
 - (a) Medical closure of patent ductus arteriosus (indomethacin is preferred).
 - (b) Colon and rectal cancer: Regular use of aspirin is reported to reduce the risk of cancer.
 - (c) Aspirin is reported to reduce the risk and retard the onset of Alzheimer's disease.
 - (d) To control radiation-induced diarrhoea.
 - (e) To control pruritus and flushing associated with the use of nicotinic acid.
 - (f) Low dose of aspirin may be useful in preeclampsia.

Aspirin *per se* is rarely used at present because of the following disadvantages:

1. It has a short duration of action, requires large doses and frequent administration.
2. Gastric irritation and ulcerogenic effect are the main drawbacks of NSAIDs. The incidence is high with aspirin.
3. Salicylates should be avoided in children with viral infection.
4. NSAIDs may precipitate bronchospasm in patients with bronchial asthma (aspirin-induced asthma).

OTHER NSAIDs (Table 6.5)

They have similar mechanism of action, pharmacological actions, therapeutic uses and adverse effects. They vary mainly in their potency, duration of action, analgesic and anti-inflammatory effects.

Nimesulide

- Preferential COX-2 inhibitor
- Has analgesic, antipyretic and anti-inflammatory effects
- Used in dysmenorrhoea, osteoarthritis, skin, soft tissue and bone inflammatory conditions, etc.

Table 6.5 ■ Nonsteroidal anti-inflammatory drugs and their important features

Drug	Route and formulations with oral dose	Other points
1. Ibuprofen	Oral and topical gel Dose: 400–600 mg t.d.s.	• It has moderate anti-inflammatory effect • It is better tolerated than aspirin • It can be used in children

Continued

Table 6.5 ■ Nonsteroidal anti-inflammatory drugs and their important features—cont'd

Drug	Route and formulations with oral dose	Other points
2. Diclofenac	Oral, i.m., rectal, topical gel and ophthalmic preparation (eye drops) Dose: 50 mg b.d. or 100 mg sustained release preparation o.d.	• It has potent anti-inflammatory effect • It gets concentrated in synovial fluid, hence preferred in inflammatory conditions (arthritis) of joint • Incidence of hepatotoxicity is more • Combination of diclofenac with misoprostol (PGE₁ analogue) is available, which reduces GI irritation and peptic ulcer
3. Aceclofenac	Oral Dose: 100 mg b.d. or 200 o.d.	Same as diclofenac
4. Indomethacin Note: It has • <i>Extra</i> mechanism of action • <i>Extra</i> uses • <i>Extra</i> side effects	Oral, eye drops and suppository Dose: 50 mg t.d.s.	• It is a nonselective COX inhibitor • It has potent anti-inflammatory effect • It inhibits migration of neutrophils to inflamed area • It is very effective in ankylosing spondylitis, acute gout and psoriatic arthritis • It has prominent GI side effects • CNS side effects are severe headache, confusion, hallucinations, etc. • It is contraindicated in epileptics, psychiatric patients and drivers
5. Piroxicam	Oral, i.m. and topical gel Dose: 20 mg o.d.	• It has potent anti-inflammatory effect • It is long acting • Increased incidence of peptic ulcer and bleeding
6. Ketorolac	Oral, i.m., i.v., ophthalmic preparation and transdermal patch Dose: 10–20 mg q.i.d.	• It has potent analgesic effect and efficacy is almost equal to morphine • It relieves pain without causing respiratory depression, hypotension and drug dependence • It is used in renal colic, postoperative and metastatic cancer pain
7. Mefenamic acid	Oral Dose: 250–500 mg t.i.d.	• It has analgesic, antipyretic and weak anti-inflammatory effect • It is used in dysmenorrhoea, osteoarthritis, rheumatoid arthritis
8. Naproxen	Oral 500 mg b.d.	• Potent anti-inflammatory action • Inhibits migration of leukocytes • Long acting • Better tolerated • It is used in rheumatoid arthritis, acute gout
9. Flurbiprofen	Oral Topical (eye drops)	It is used in osteoarthritis, rheumatoid arthritis and ocular inflammation

- Adverse effects: GI irritation is less than aspirin and other NSAIDs; skin rashes, itching, hepatotoxicity has been reported – hence is banned for paediatric use in India

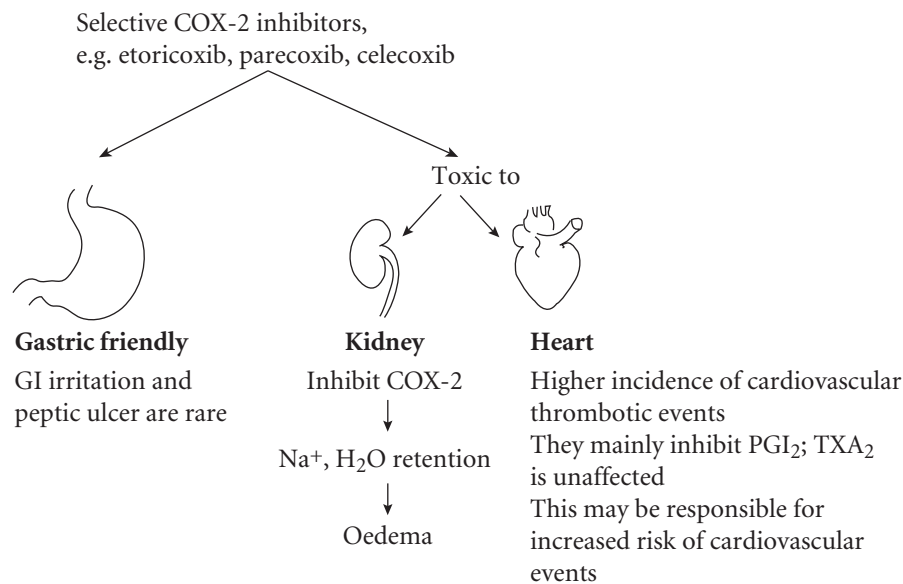
Meloxicam

- Preferential COX-2 inhibitor
- Has analgesic, antipyretic and anti-inflammatory effects
- Is long acting

SELECTIVE COX-2 INHIBITORS

Some of the COX-2 inhibitors are parecoxib, etoricoxib, etc.

Parecoxib is a prodrug of valdecoxib and is administered parenterally; celecoxib and etoricoxib are given by enteral route (Table 6.6).



Paracetamol (Acetaminophen)

Paracetamol is effective by oral and parenteral routes. It is well absorbed, widely distributed all over the body, metabolized in liver by sulphate and glucuronide conjugation. The metabolites are excreted in urine (Table 6.7).

Table 6.6 ■ Differences between nonselective COX and selective COX-2 inhibitors

Nonselective COX inhibitors	Selective COX-2 inhibitors
• Analgesic effect + • Antipyretic effect + • Anti-inflammatory effect + • Antiplatelet effect + • GI side effects are marked ++ • Renal toxicity + (sodium and water retention)	• Analgesic effect + • Antipyretic effect + • Anti-inflammatory effect + • No antiplatelet effect • GI side effects are less (less ulcerogenic potential) • Renal toxicity +

Note: +, present; ++, effect is more.

Table 6.7 ■ Differences between aspirin and paracetamol

Aspirin	Paracetamol (acetaminophen)
1. It is a salicylate derivative 2. It has analgesic, antipyretic and potent anti-inflammatory effects 3. It causes GI irritation (nausea, vomiting, peptic ulcer and bleeding) 4. In large doses, it produces acid–base and electrolyte imbalances 5. It has antiplatelet action 6. It has no specific antidote 7. It is contraindicated in peptic ulcer, people with bleeding tendency, bronchial asthma and in children with viral infection	1. It is a <i>para</i>-aminophenol derivative 2. It has potent antipyretic and analgesic effects with poor anti-inflammatory activity 3. It usually does not produce gastric irritation 4. It does not produce acid–base and electrolyte imbalances 5. It has no antiplatelet action 6. <i>N</i>-acetylcysteine is the antidote 7. Paracetamol is the preferred analgesic and antipyretic in patients with peptic ulcer, bronchial asthma and in children

Uses

1. As antipyretic: To reduce body temperature during fever.
2. As analgesic: To relieve headache, toothache, myalgia, dysmenorrhoea, etc.
3. It is the preferred analgesic and antipyretic in patients with peptic ulcer, haemophilia, bronchial asthma and children.

Adverse Effects

1. Side effects are rare, occasionally causes skin rashes and nausea.
2. Hepatotoxicity: With acute overdose or chronic use.
3. Nephrotoxicity is commonly seen on chronic use.

Acute Paracetamol Poisoning. Acute overdosage mainly causes hepatotoxicity – the symptoms are nausea, vomiting, diarrhoea, abdominal pain, hypoglycaemia, hypotension, hypoprothrombinaemia, coma, etc. Death is usually due to hepatic necrosis.

Mechanism of Toxicity and Its Treatment (Fig. 6.5)

- The toxic metabolite of paracetamol is detoxified by conjugation with glutathione and gets eliminated.
- High doses of paracetamol cause depletion of glutathione levels. In the absence of glutathione, toxic metabolite (N-acetyl-p-benzo-quinoneimine [NAPQI]) binds covalently with proteins in the liver and kidney and causes necrosis.
- Alcoholics and premature infants are more prone to hepatotoxicity.
- N-acetylcysteine or oral methionine replenishes the glutathione stores of the liver and protects liver cells.
- Activated charcoal is administered to decrease the absorption of paracetamol from the gut.
- Haemodialysis may be required in cases with acute renal failure.

TOPICAL NSAIDs

Topical formulations of NSAIDs are available. Systemic toxicity is minimal. Diclofenac, ibuprofen, naproxen, etc. are useful topically for musculoskeletal pain. They are used in backache, osteoarthritis, sprain, etc. Flurbiprofen and diclofenac eye drops are used in ophthalmic practice.

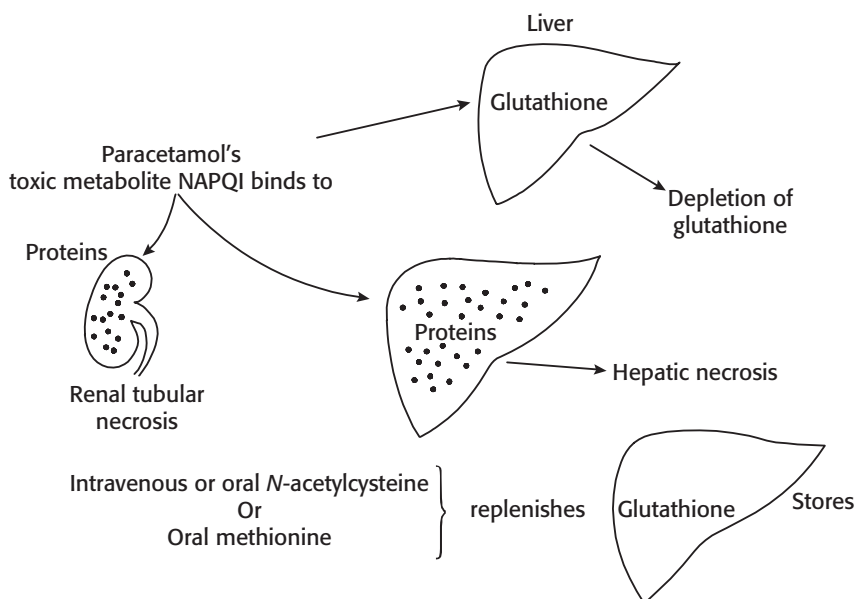


Fig. 6.5 Mechanism of paracetamol toxicity and its treatment. NAPQI, N-acetyl-p-benzo-quinoneimine.

Drugs Used in the Treatment of Gout

PH1.16

Gout is a disorder of purine metabolism in which plasma urate concentration is raised either due to overproduction or impaired excretion of uric acid. It is characterized by intermittent attacks of acute arthritis produced by deposition of sodium urate crystals in joints.

Primary hyperuricaemia may be idiopathic or due to enzyme defects. Secondary hyperuricaemia can occur in leukaemias, chronic renal failure and during drug therapy (thiazides, loop diuretics, pyrazinamide, levodopa, cytotoxic agents, etc.).

CLASSIFICATION

1. Acute gout

- (a) NSAIDs: Indomethacin, naproxen, diclofenac, aceclofenac, piroxicam, sulindac, etoricoxib
- (b) Colchicine
- (c) Glucocorticoids: Prednisolone, methylprednisolone, triamcinolone

2. Long-term control of gout or hyperuricaemia

- (a) Uricosuric agents: Probenecid, sulphinpyrazone
- (b) Uric acid synthesis inhibitors: Allopurinol, febuxostat

TREATMENT OF ACUTE ATTACK OF GOUT

Nonsteroidal Anti-Inflammatory Drugs

To relieve an acute attack, NSAIDs like naproxen, indomethacin, piroxicam, diclofenac, aceclofenac and etoricoxib are used. They are better tolerated than colchicine.

Colchicine. It is an alkaloid. It is neither an analgesic nor a uricosuric agent, although it relieves pain in acute attack of gout. Deposition of urate crystals in the joint → chemotactic factors produced → migration of neutrophils into the joint → release factors which contribute to inflammation. Colchicine prevents release of chemotactic factors and inhibits migration of neutrophils to the affected area. It is administered either orally or intravenously. It is rapid acting but poorly tolerated. They are nausea, vomiting, diarrhoea and abdominal pain. Chronic use may lead to myopathy, alopecia, aplastic anaemia and agranulocytosis.

Glucocorticoids. Glucocorticoids are effective, produce rapid response and are reserved for cases not responding to NSAIDs and colchicine. Prednisolone and methylprednisolone are used systemically in gout. If a single joint is affected, then intra-articular triamcinolone is effective.

TREATMENT OF CHRONIC GOUT

Uricosuric Agents

They inhibit active tubular reabsorption of uric acid in proximal tubules and increase excretion of uric acid, e.g. probenecid and sulphinpyrazone. They are rapid acting but poorly tolerated. High fluid intake is advised to prevent formation of urate crystals in urine. Sulphinpyrazone is an alternative to probenecid. Uricosuric drugs should not be given within 3 weeks of an acute attack of gout. They mobilize uric acid from tophaceous deposits, hence there is fluctuation in serum uric acid levels which can precipitate an acute attack. These drugs are contraindicated in patients with renal failure. Side effects are rare, but GI toxicity (nausea, vomiting) and skin rashes may occur.

DRUG INTERACTIONS

Probenecid × β -Lactam Antibiotics (Penicillins, Cephalosporins)

They are excreted by active tubular secretion. When they are administered simultaneously, probenecid competes with penicillins/cephalosporins and blocks the tubular secretion of β -lactam antibiotics. Therefore, plasma levels of β -lactam antibiotics and their duration of action increases. Thus, the treatment becomes more effective.

Uric Acid Synthesis Inhibitors



Allopurinol. Allopurinol prevents the synthesis of uric acid by inhibiting the enzyme xanthine oxidase, thus reduces the plasma urate levels. Its active metabolite, alloxanthine, is a noncompetitive inhibitor of xanthine oxidase enzyme. It reduces urate crystals in the kidney, joints and soft tissue. There is an increase in the levels of xanthine and hypoxanthine in plasma which are effectively excreted in urine.

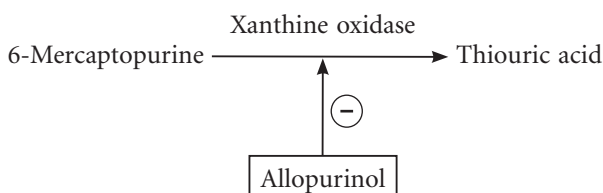
Allopurinol is administered orally and is the drug of choice for asymptomatic gout. It is used in chronic gout as well as hyperuricaemia associated with cancer chemotherapy, radiation or renal disease. It should not be started within 3 weeks of an acute attack of gout, as it may precipitate another attack. Allopurinol is also useful in kala-azar.

Adverse Effects

1. Hypersensitivity: Skin rashes, itching, erythema, headache, fever and rarely Stevens–Johnson syndrome may occur.
2. GIT: Nausea, vomiting, diarrhoea and occasionally hepatotoxicity may also occur. Allopurinol is contraindicated in children, pregnancy, lactation, patients with liver and kidney diseases.

Drug Interactions

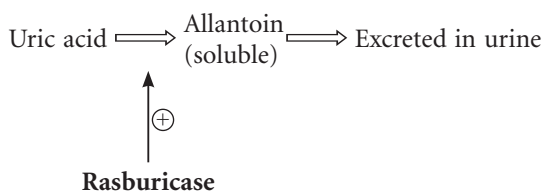
Allopurinol × *6-mercaptopurine*



Allopurinol interferes with the metabolism of 6-mercaptopurine by inhibiting the enzyme xanthine oxidase and increases its effect. Therefore, allopurinol is commonly used in cancer patients receiving chemotherapy to reduce hyperuricaemia, decrease the dose of 6-mercaptopurine and its side effects.

Febuxostat. It is a xanthine oxidase inhibitor → decreases formation of uric acid. It is administered orally (once daily dose is used) for chronic gout. Adverse effects include diarrhoea, headache and hepatotoxicity. Febuxostat can be used in gout in patients intolerant to allopurinol.

Rasburicase. It is a urate oxidase produced by recombinant technology. It converts uric acid to soluble allantoin.



It is infused to decrease serum uric acid levels in children with leukaemia on anticancer drug therapy. Haemolysis, gastrointestinal disturbances, hypersensitivity reactions may occur.

Pegloticase. It converts uric acid to allantoin which is soluble and easily excreted in urine. It is administered as i.v. infusion in cases not responding to other drugs. Anaphylaxis can occur.

Drugs Used in the Treatment of Rheumatoid Arthritis PH1.16

Rheumatoid arthritis (RA) is a chronic multisystem autoimmune disease of unknown cause. Although there are a variety of systemic manifestations, the main characteristic feature is persistent inflammatory synovitis of peripheral smaller joints. The course of the disease is prolonged with exacerbation and remissions. Pain and swelling of the

joints are mainly due to PGs, whereas cytokines are responsible for progressive damage to the joints leading to deformity.

Drugs used in the treatment of RA:

1. Disease-modifying antirheumatic drugs (DMARDs)

(i) *Nonbiologics*

Methotrexate, azathioprine, cyclophosphamide, cyclosporine, chloroquine, hydroxychloroquine, sulphasalazine, leflunomide, gold salts, d-penicillamine.

(ii) *Biologics*

(a) TNF- α antagonists: Etanercept, infliximab, adalimumab

(b) IL-1 antagonist: Anakinra

(c) T-cell modulating agent: Abatacept

(d) B-lymphocyte depleter: Rituximab

2. NSAIDs: Aspirin, ibuprofen, diclofenac, naproxen, piroxicam, etoricoxib.

3. Glucocorticoids: Prednisolone, triamcinolone, methylprednisolone.

M – Methotrexate

A – Anakinra, abatacept

E – Etanercept

L – Leflunomide

D – D-Penicillamine

S – Sulphasalazine

I – Infliximab

R – Rituximab

C – Chloroquine and hydroxychloroquine

Gold compounds

Note: Mnemonic for DMARDs – M E D I C A L S R Gold (E, I, A and R are biologics).

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Rapidly produce symptomatic relief – they reduce inflammation, pain, stiffness and swelling but they have little effect on the progression of bone and cartilage destruction.

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Nonbiologics

They relieve symptoms as well as reduce disease activity in RA. The effects of DMARDs may take few weeks to several months to become evident. Once a diagnosis of RA is made, the patient should be started on a DMARD.

Methotrexate

It is the preferred DMARD in the treatment of RA. It has relatively more rapid onset of action than other DMARDs. It is a folate antagonist. The dose of methotrexate used in RA is much lower than the dose needed in cancer chemotherapy. It exerts anti-inflammatory effect. It inhibits chemotaxis of neutrophils and decreases production of proinflammatory cytokines by activated T cells. Methotrexate is administered orally starting with a dose of 7.5–15 mg once weekly and increasing the dose by 2.5 mg weekly if there is no improvement. It can also be used in psoriasis, polymyositis, giant cell arteritis, dermatomyositis, etc.

Adverse Effects. They include nausea, vomiting, mucosal ulcers and dose-dependant hepatotoxicity. Hence, hepatic function should be monitored periodically. The adverse effects can be minimized by administration of folic acid or folinic acid. Methotrexate is contraindicated in pregnancy, liver disease and peptic ulcer.

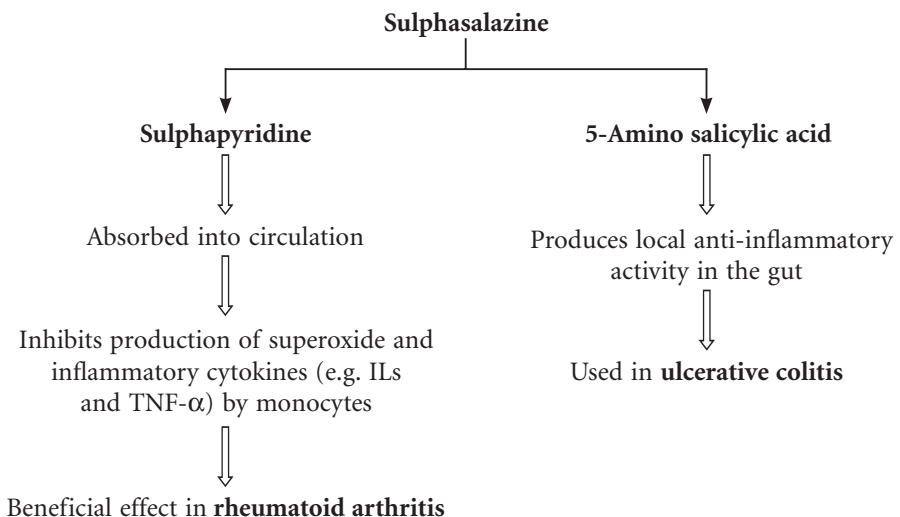
Chloroquine and Hydroxychloroquine

These are antimalarial drugs – also useful in RA. The exact mechanism of action of these drugs in RA is not clear. They decrease release of lysosomal enzymes and scavenge

free radicals. They are well tolerated. They are administered orally, highly bound to tissue proteins and deposited in melanin containing tissues, especially eye. Prolonged administration may cause corneal opacity and retinal damage. Hence, ophthalmologic examination should be done at least once a year in patients on chloroquine/hydroxychloroquine. The other side effects are nausea, vomiting and skin rashes. The drug is relatively safe in pregnancy. They are used alone in patients with mild disease or in combination with methotrexate and/or sulphasalazine.

Sulphasalazine

It is used alone in mild disease or in combination with other drugs in severe cases. It causes remission in active RA and is also used for chronic inflammatory bowel disease. It is administered orally and is split in the gut by colonic bacteria. Common side effects are nausea, vomiting, diarrhoea, headache, skin rashes and leukopaenia.



Leflunomide

Its active metabolite inhibits dihydroorotate dehydrogenase, thus decreases pyrimidine synthesis. It inhibits T-cell proliferation. Leflunomide is used alone or in combination with methotrexate for the treatment of RA. It is as effective as methotrexate. It is completely absorbed after oral administration and has a long plasma half-life of about 2–3 weeks. Hence, a loading dose is given. Adverse effects include loose stools (diarrhoea), loss of hair, liver toxicity (hepatotoxicity), leukopaenia and skin rashes. It is contraindicated in children, in pregnant women and lactating mothers. (**Note 'L's.**)

Gold Compounds

They are not used because of their toxicity.

D-Penicillamine

It is a metabolite of penicillin and rarely used now because of toxicity.

Adverse effects are proteinuria, pruritus, pancytopenia, pemphigus-like skin rashes, thrombocytopenia and GI side effects.

Table 6.8 ■ **Biologics and their important features**

Drug	Route	MOA	Adverse effects	Uses
• Etanercept • Infliximab • Adalim-umab • Golimumab	s.c.	TNF- α antagonists	Opportunistic infections including tuberculosis	Rheumatoid arthritis, psoriasis, Crohn disease, ankylosing spondylitis
Anakinra	s.c.	IL-1 antagonist	Opportunistic infections, mainly respiratory	Rheumatoid arthritis
Abatacept	i.v. infusion	Inhibits T-cell activation	Opportunistic infections	Rheumatoid arthritis
Rituximab	i.v. infusion	Depletes peripheral B lymphocytes	Skin rashes	Used with methotrexate in resistant cases of rheumatoid arthritis

Note: MOA, mechanism of action.

Biologics

Biologics are preparations made from microorganisms, animals or human or their products. They are administered parenterally. These agents are used in case of RA not responding to nonbiological agents. They are also useful in other autoimmune disorders like psoriasis, Crohn disease, ankylosing spondylitis and scleroderma (Table 6.8).

Prolonged use may produce opportunistic infections like tuberculosis, *P. jiroveci* infection and urinary tract infection.

GLUCOCORTICOIDS

These are adjuvant drugs in RA. Their effects are prompt and they suppress inflammation quickly. They are administered either systemically or topically (intra-articular). Glucocorticoids are also used for certain serious extra-articular manifestations or during periods of exacerbation. Prolonged use of glucocorticoids leads to adverse effects.

Respiratory System

PH1.33

DRUGS USED IN THE TREATMENT OF COUGH

Cough is a protective reflex, intended to remove irritants and accumulated secretions from the respiratory passages. The drugs used in the symptomatic treatment of cough are as follows:

1. **Antitussives:** Codeine, pholcodine, noscapine, dextromethorphan, prenoxidazine, chlophedianol and antihistamines.
2. **Pharyngeal demulcents:** Lozenges, syrups, liquorice.

3. **Expectorants:** Sodium and potassium citrate, potassium iodide, guaiphenesin, ammonium chloride.
4. **Mucolytics:** Bromhexine, acetylcysteine, carbocisteine, ambroxol.

Cough may be:

1. Productive cough: Helps to clear the airway. Suppression of productive cough is harmful as it may lead to infections. Treatment includes antibiotics for infection, expectorants and mucolytics for cough.
2. Nonproductive cough: It should be suppressed.

Antitussives

They inhibit cough reflex by suppressing the cough centre in medulla. They are used for symptomatic treatment of dry, unproductive cough. Antitussives should be avoided in children younger than 1 year.

1. Codeine:

- (a) Has cough centre suppressant effect.
- (b) Causes mild CNS depression, hence drowsiness can occur.
- (c) Causes constipation by decreasing intestinal movements.
- (d) Should be avoided in children and asthmatics.

Codeine is administered orally, has mild analgesic effect and less addiction liability than morphine.

2. **Pholcodine:** Antitussive action is similar to codeine. It has no analgesic or addiction liability. It is administered orally and has a long duration of action.
3. **Noscapine:** It is an opium alkaloid and has potent antitussive effect. It is useful in spasmodic cough. It has no analgesic effect, does not cause constipation, addiction or CNS depression. The side effects are nausea and headache; bronchospasm can occur in asthmatics.
4. **Dextromethorphan:** It is a centrally acting antitussive agent. It has no analgesic property, does not cause constipation and addiction; mucociliary function in respiratory passages is not affected. It may cause sedation and hallucinations.
5. **Antihistamines:** Diphenhydramine, chlorpheniramine, promethazine, etc. are useful in cough due to their sedative, antiallergic and anticholinergic actions. They produce symptomatic relief in cold and cough associated with allergic conditions of respiratory tract.
6. **Prenoxdiazine:** It acts peripherally on stretch receptors on the airways.

Pharyngeal Demulcents

Syrups, lozenges, linctuses or liquorice may be used when cough arises due to irritation above the larynx. They increase salivation and produce protective soothing effect on the inflamed mucosa.

Syrup is a concentrated solution of sugar containing the drug to mask the bitter taste of the drug.

Lozenge, solid dosage form placed in the mouth and sucked; it dissolves slowly to liberate the active ingredient. It soothes the irritated mucosa of the throat, e.g. dyclonine (local anaesthetic) lozenge for sore throat.

Linctus, viscous liquid sipped slowly to allow it trickle down the throat; used for relief of cough, e.g. linctus codeine.

Expectorants (Mucokinetics)

They increase the volume of bronchial secretion and decrease viscosity of the sputum; hence, cough becomes less tiring and productive. They include iodides, chlorides, bicarbonates, acetates, volatile oils, etc.

Mucolytics

These agents break the thick tenacious sputum and lower the viscosity of sputum, so that sputum comes out easily with less effort.

Bromhexine. It is a semisynthetic agent used orally. It has potent mucolytic and mucokinetic effects.

Bromhexine liberates → lysosomal enzymes → digest the mucopolysaccharides → decreases viscosity of sputum → cough becomes less tiring and productive.

The side effects are rhinorrhoea and lacrimation.

Acetylcysteine and Carbocisteine. Acetylcysteine is a mucolytic used as an aerosol in the treatment of cough.

Acetylcysteine and carbocisteine → open disulphide bonds in mucoproteins of sputum → sputum becomes thin and less viscid → cough becomes less tiring and productive.

The side effects are nausea, vomiting and bronchospasm.

Carbocisteine is administered orally. It may cause gastric irritation, hence should be avoided in patients with peptic ulcer.

Drugs Used in the Treatment of Bronchial Asthma

PH1.32

In bronchial asthma, there is impairment of airflow due to contraction of bronchial smooth muscle (bronchospasm), swelling of bronchial mucosa (mucosal oedema) and increased bronchial mucus secretion. There is inflammation and hyperresponsiveness of airways.

Several factors may precipitate attacks of asthma in susceptible individuals. They include allergy, infection and psychological factors. The airway obstruction in asthma is mainly due to the release of mediators from sensitized mast cells in the lungs. They are histamine, 5-HT (serotonin), PGs, leukotrienes (LTC₄ and LTD₄), proteases, PAF, etc. Bronchial asthma may be either episodic or chronic.

Acute Asthma. It is characterized by episodes of dyspnoea associated with expiratory wheezing.

Chronic Asthma. There is continuous wheeze and breathlessness on exertion; cough and mucoid sputum with recurrent respiratory infection are common.

Status Asthmaticus (Acute Severe Asthma). When an attack of asthma is prolonged with severe intractable wheezing, it is known as acute severe asthma.

CLASSIFICATION OF ANTI-ASTHMATIC DRUGS

1. Bronchodilators

(a) Sympathomimetics

Selective β_2 -adrenergic agonists: Salbutamol and terbutaline (short acting); bambuterol, salmeterol and formoterol (long acting).

(b) Methylxanthines: Theophylline, aminophylline, etophylline, doxophylline.

(c) Anticholinergics: Ipratropium bromide, tiotropium bromide.

2. Leukotriene receptor antagonists: Zafirlukast, montelukast, zileuton.

3. Mast cell stabilizers: Sodium cromoglycate, ketotifen.

4. Glucocorticoids

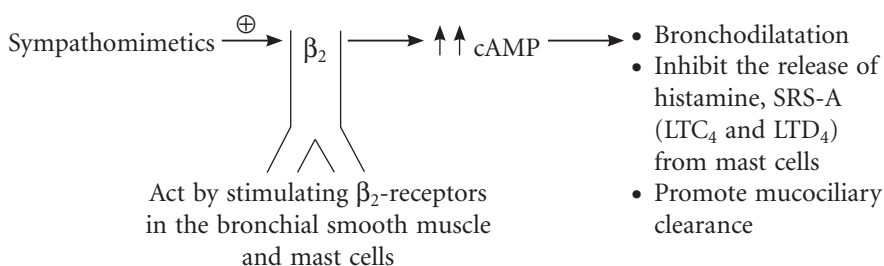
(a) **Inhaled glucocorticoids:** Beclomethasone, budesonide, fluticasone, ciclesonide.

(b) **Systemic glucocorticoids:** Hydrocortisone, prednisolone, methylprednisolone.

5. Anti-IgE monoclonal antibody: Omalizumab.

Sympathomimetics

Mechanism of Action



Adrenaline (Nonselective Sympathomimetic). It produces prompt and powerful bronchodilatation by acting through β₂-adrenergic receptors. It is useful in acute attack of asthma (not responding to other drugs) – 0.2–0.5 mL of 1:1000 solution given subcutaneously. Its use has declined because of its dangerous cardiac side effects.

Selective β₂-Adrenergic Agonists (Table 6.9). They are the first-line drugs for bronchial asthma. **For mechanism of action – see flowchart given above.**

They are well tolerated when inhaled. They may cause tremor, tachycardia, palpitation, hypokalaemia and rarely cardiac arrhythmias.

Bambuterol

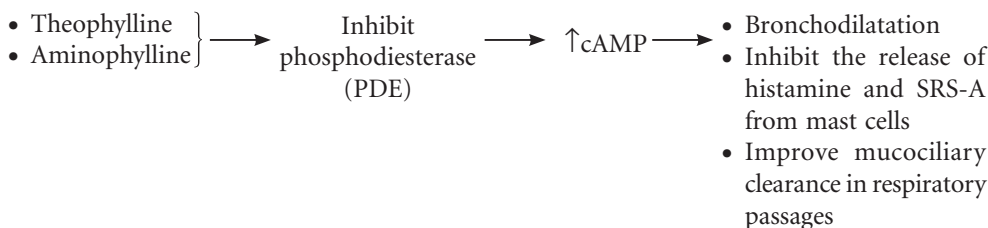
- Prodrug of terbutaline
- Is administered orally – once daily dose is used
- Has long duration of action

Table 6.9 ■ Selective β₂-agonists

Salbutamol and terbutaline	Salmeterol	Formoterol
<i>Selective β₂-agonists:</i> On inhalation, they have a rapid onset (within 1–5 minutes) and short duration of action; they are preferred for acute attack of asthma <i>Route and dose:</i> Inhalation, salbutamol 100–200 mcg every 6 hours, or as and when required through metered-dose inhaler (MDI) to terminate an acute attack; other routes of administration are oral, i.m. and i.v.	<i>Long-acting selective β₂-agonist:</i> It is preferred for moderate to severe, persistent asthma; it is not suitable for acute attack as it has a slow onset of action <i>Route and dose:</i> Inhalation, 50 mcg twice daily	<i>Long-acting selective β₂-agonist:</i> It has a rapid onset of action; it is preferred for moderate to severe persistent asthma due to its long duration of action <i>Route and dose:</i> Inhalation, 12–24 mcg twice daily

Methylxanthines. Use of methylxanthines in asthma has markedly diminished because of their narrow margin of safety and availability of better antiasthmatic drugs (selective β_2 -agonists, inhaled steroids and leukotriene antagonists).

Mechanism of Action of Methylxanthines



Methylxanthines inhibit phosphodiesterases (PDEs), thereby prevent degradation of cAMP and cGMP. This results in accumulation of intracellular cAMP and in some tissues, cGMP. Methylxanthines are competitive antagonists at adenosine receptors, which also results in bronchodilatation.

Pharmacokinetics. Methylxanthines are well absorbed after oral and parenteral administration; food delays the rate of absorption of theophylline. They are well distributed all over the body; they cross placental and blood–brain barrier. They get metabolized in liver and excreted in urine.

1. **Theophylline:** It is poorly water soluble, hence not suitable for injection. It is available for oral administration.
2. **Aminophylline:** It is water soluble but highly irritant. It can be administered orally or slow intravenously.
3. **Etophylline:** It is water soluble and can be given by oral, i.m. or i.v. routes.
4. **Doxophylline**
 - Methylxanthine derivative
 - Orally administered – once or twice daily dose is used
 - Less likely to cause GI and CNS side effects

Adverse Effects. They have a narrow margin of safety. They can cause tachycardia, palpitation, hypotension and sometimes sudden death due to cardiac arrhythmias (Fig. 6.6).

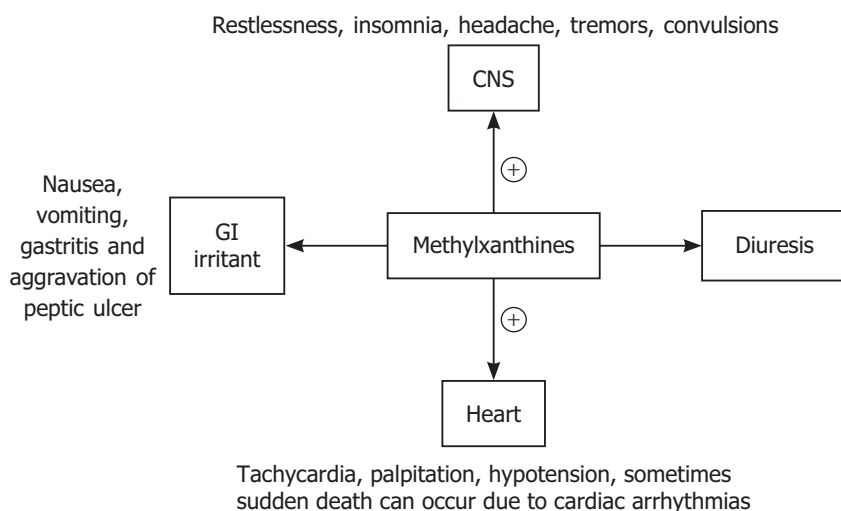
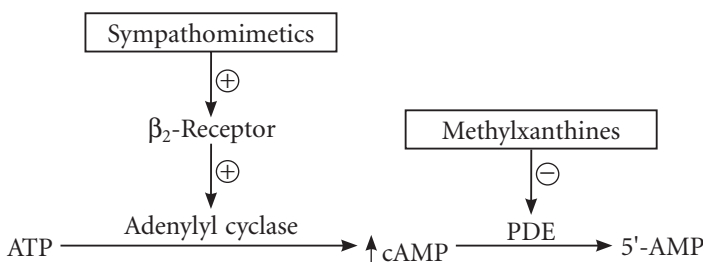


Fig. 6.6 Adverse effects of methylxanthines.

Drug Interactions**1. Sympathomimetics × methylxanthines**

Methylxanthines potentiate the effects of sympathomimetics:

- (a) Bronchodilatation (beneficial effect)
- (b) Cardiac stimulation (harmful effect)

2. **Phenytoin/rifampicin/phenobarbitone × theophylline:** They are enzyme inducers; hence, they accelerate the metabolism of theophylline and decrease its effect.
3. **Cimetidine/ciprofloxacin/erythromycin × theophylline:** They are enzyme inhibitors; hence, potentiate the effects of theophylline by interfering with its metabolism.

Uses of Methylxanthines

1. Bronchial asthma and COPD: Theophylline is used as an additional drug in moderate or severe persistent bronchial asthma.
2. Apnoea in premature infants: Aminophylline/cafeine is used intravenously to reduce the duration of apnoea episodes. Caffeine is safer than aminophylline.

Anticholinergics. Ipratropium bromide and tiotropium bromide are atropine substitutes. They selectively block the effects of acetylcholine in the bronchial smooth muscle and cause bronchodilatation. They do not affect mucociliary clearance. They have a slow onset of action and are less effective than sympathomimetic drugs in bronchial asthma. These anticholinergics are the preferred bronchodilators in COPD and can also be used in bronchial asthma. They are administered by inhalational route, and act primarily on larger airways. Tiotropium is longer acting and more efficacious than ipratropium.

Combined use of ipratropium with β_2 -adrenergic agonists produces greater and more prolonged bronchodilatation, hence used in acute severe asthma.

Leukotriene-Receptor Antagonists

These drugs competitively block the effects of cysteinyl leukotrienes (LTC_4 and LTD_4) on bronchial smooth muscle.



Thus, they produce bronchodilatation, suppress bronchial inflammation and decrease hyperreactivity. They are well absorbed after oral administration, highly bound to plasma proteins and metabolized extensively in the liver. They are effective for prophylactic treatment of mild asthma and moderate persistent asthma (in combination with other drugs). They are well tolerated, produce few adverse effects – headache, skin rashes and rarely eosinophilia.

Zileuton

- Inhibits 5-lipoxygenase and is administered orally
- Hepatotoxicity restricts its use

Mast Cell Stabilizers

Sodium cromoglycate (cromolyn sodium) and ketotifen are mast cell stabilizers. They are not bronchodilators. They inhibit the release of various mediators – histamine, LTs, PGs, PAF, etc. by stabilizing mast cell membrane (Fig. 6.7). They also reduce bronchial hyperreactivity to some extent but the AG:AB reaction is not affected. Onset of action is slow.

Sodium cromoglycate is not effective orally as it is poorly absorbed from the gut. In bronchial asthma, sodium cromoglycate is given by inhalation.

Uses

1. Allergic asthma: As a prophylactic agent to prevent bronchospasm induced by allergens and irritants.
2. It can also be used in allergic conjunctivitis, allergic rhinitis, allergic dermatitis, etc. by topical route as a prophylactic agent.

Adverse Effects. Systemic side effects are rare; it may cause symptoms of local irritation – cough, bronchospasm, headache, nasal congestion, etc.

Ketotifen. Mechanism of action is similar to sodium cromoglycate, has additional H_1 -blocking effect. It is orally effective but has a slow onset of action.

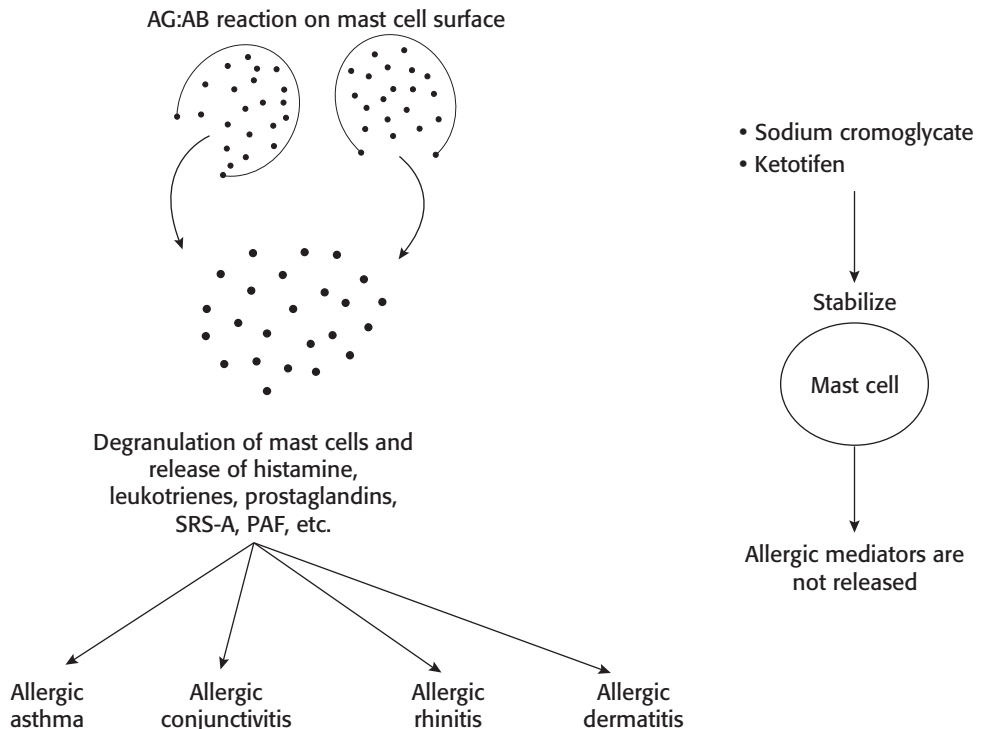


Fig. 6.7 Mechanism of action of mast cell stabilizers.

Glucocorticoids

1. **Systemic:** Hydrocortisone, prednisolone, methylprednisolone and others.
2. **Inhalational:** Beclomethasone, budesonide, fluticasone and ciclesonide.

Glucocorticoids induce synthesis of 'lipocortin', which inhibits phospholipase A₂ and thereby prevent the formation of various mediators such as PGs, TXA₂ and SRS-A. Glucocorticoids have antiallergic, anti-inflammatory and immunosuppressant effects. They:

1. Suppress inflammatory response to AG:AB reaction.
2. Decrease mucosal oedema.
3. Reduce bronchial hyperreactivity.

Glucocorticoids do not have direct bronchodilating effect but they potentiate the effects of β_2 -adrenergic agonists. They also prevent development of tolerance to β_2 -adrenergic agonists.

Inhaled glucocorticoids such as beclomethasone, budesonide, fluticasone and ciclesonide are used as prophylactic agents in bronchial asthma. Inhaled glucocorticoids are used in patients with persistent asthma who require inhaled β_2 -agonists frequently. Ciclesonide is a prodrug, gets activated by esterases in bronchial epithelium. They are well tolerated. Systemic side effects are minimal with these agents. The common side effects are hoarseness of voice, dysphonia and oropharyngeal candidiasis. These can be reduced by using a spacer, rinsing the mouth after each dose; oral thrush can be treated effectively by topical antifungal agent, nystatin or hamycin.

Combination of long-acting beta-agonist (LABA) with steroid is available, e.g. fluticasone + salmeterol; budesonide + formoterol. They have synergistic action; used in bronchial asthma and COPD. They are used in moderate and severe persistent asthma.

Systemic glucocorticoids are used in acute severe asthma and chronic severe asthma. Long-term use of systemic steroids produce severe side effects such as gastric irritation, Na⁺ and water retention, hypertension, muscle weakness, osteoporosis and HPA axis suppression.

Anti-IgE Monoclonal Antibody: Omalizumab

Omalizumab prevents the binding of IgE to mast cell, thus prevents mast cell degranulation. It has no effect on IgE already bound to mast cells. It is administered parenterally. It is used in moderate to severe asthma and allergic disorders such as nasal allergy and food allergy. It is approved for use in patients older than 12 years. It causes local side effects such as redness, stinging, itching and induration.

Inhalational Devices. They are

- *Pressurized metered-dose inhaler* (pMDI) – It is a handheld device which can be used alone or with spacer. It has a pressurized container (canister) with drug along with a propellant (hydrofluoroalkane, HFA) and other substances as solution or suspension. A specific amount of drug is delivered as a fine aerosol into the airways. The small particles reach the smaller airways whereas large ones are deposited in the oral cavity (minimized by using spacer). Proper coordination is required between use of device and breathing (difficult for children and elderly). Patient has to be trained on correct use of device.
- *Dry powder inhalers* – Spinhaler and Rotahaler. A capsule (rotacap) containing the drug in fine powder form is placed in the Rotahaler.
- *Nebulizers* – useful in acute severe asthma, COPD and for delivering drug in young children and elderly. The drug is delivered in the form of a mist which can easily reach the airways. They are expensive but do not require coordination unlike pMDI.

Antiasthmatic agents available for inhalation are β_2 -adrenergic agonists (salbutamol, terbutaline, salmeterol and formoterol), anticholinergics (ipratropium bromide and tiotropium bromide), mast cell stabilizers (sodium cromoglycate) and glucocorticoids (fluticasone, beclomethasone, budesonide, etc.).

Treatment of Acute Severe Asthma (Status Asthmaticus)

1. Humidified oxygen inhalation.
2. Nebulized β_2 -adrenergic agonist (salbutamol 5 mg/terbutaline 10 mg) + anticholinergic agent (ipratropium bromide 0.5 mg).
3. Systemic glucocorticoids: Intravenous hydrocortisone 200 mg i.v. stat followed by i.v. hydrocortisone 100 mg q6h or oral prednisolone 30–60 mg/day depending on the patient's condition.
4. Inj salbutamol 0.4 mg i.m.
5. Intravenous fluids to correct dehydration.
6. Potassium supplements: To correct hypokalaemia produced by repeated doses of salbutamol/terbutaline.
7. Sodium bicarbonate to treat acidosis.
8. Antibiotics to treat infection.

Drugs to be avoided in Patients with Bronchial Asthma

1. NSAIDs like aspirin, ibuprofen and diclofenac (paracetamol can be used).
2. β -Adrenergic blockers.
3. Cholinergic agents.

Drugs Used in the Treatment of Gastrointestinal Diseases

Emetics and Antiemetics

PH1.34

Nausea and vomiting are protective reflexes that help to remove toxic substances from the gastrointestinal tract (GIT). They are symptoms of altered function but are not diseases. Nausea denotes the feeling of impending vomiting, whereas vomiting refers to forceful expulsion of the contents of stomach and upper intestinal tract through mouth. Retching is the laboured rhythmic respiratory activity that usually precedes vomiting.

MECHANISM OF VOMITING

The act of vomiting is controlled by vomiting centre in the medulla. Stimuli are relayed to this centre from peripheral areas, i.e. gastric mucosa and other parts of GIT. Sensory stimuli also arise within the central nervous system (CNS) itself (i.e. cerebral cortex and vestibular apparatus) – the impulses are transmitted to vomiting centre (Fig. 7.1).

The lack of blood–brain barrier (BBB) at the chemoreceptor trigger zone (CTZ) allows it to be directly stimulated by blood-borne drugs and toxic substances. Nausea and vomiting may be the symptoms of pregnancy, serious organic disturbances of almost any of the viscera or may be produced by infection, drugs, radiation, painful stimuli, motion sickness, metabolic and emotional disturbances. The main neurotransmitters involved in the control of vomiting are acetylcholine (ACh), histamine, 5-hydroxytryptamine (5-HT) and dopamine.

EMETICS

The drugs that cause vomiting are called emetics, e.g. mustard, common salt, ipecac and apomorphine. They cause emesis either by stimulation of CTZ or gastric irritation or both. Mustard and common salt are commonly used household emetics. Syrup ipecac is a safer emetic than apomorphine. Emetics are indicated in certain cases of poisoning.

Contraindications for the use of emetics:

1. Unconscious patients because of risk of aspiration.
2. Corrosive and caustic poisoning – further damage to oesophageal lining occurs.
3. Poisoning due to CNS stimulants because of risk of precipitation of seizures.
4. Kerosene poisoning as aspiration may occur.

ANTIEMETICS

The drugs that are used to prevent or control vomiting are called antiemetics (Table 7.1).

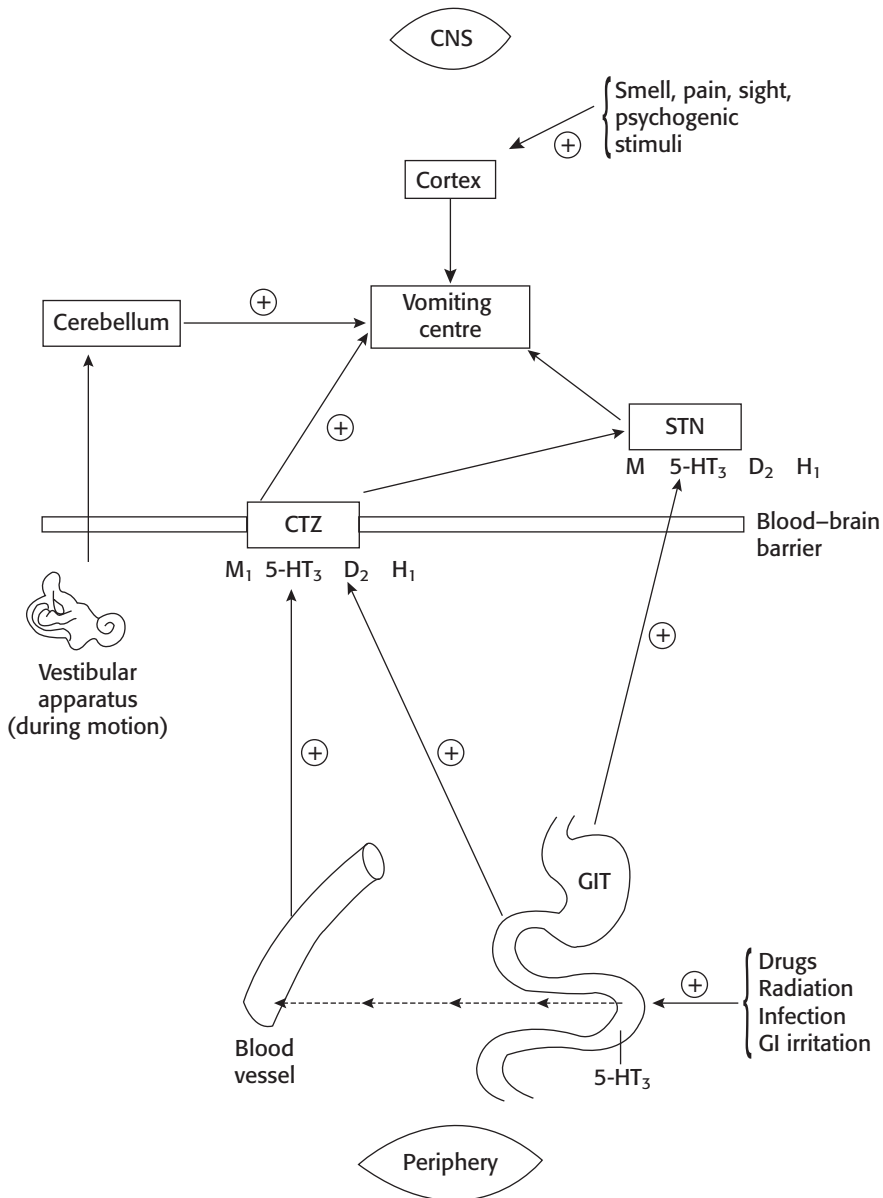


Fig. 7.1 Central and visceral structures involved in emesis. CTZ, chemoreceptor trigger zone; STN, solitary tract nucleus. (Source: Adapted from Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 12e.)

Classification

1. **$5-HT_3$ -receptor antagonists:** Ondansetron, granisetron, dolasetron, palonosetron, ramosetron.
2. **Prokinetic agents:** Metoclopramide, domperidone, levosulpiride.
3. **Antihistamines (H_1 -blockers):** Dimenhydrinate, diphenhydramine, cyclizine, meclizine, hydroxyzine, promethazine, doxylamine.
4. **Anticholinergics:** Scopolamine (hyoscine), dicyclomine.
5. **Neuroleptics:** Chlorpromazine, fluphenazine, prochlorperazine, haloperidol.

Table 7.1 ■ **Antiemetics with their uses and side effects**

Drugs	Uses	Important side effects
1. 5-HT ₃ receptor antagonists	Cancer chemotherapy-induced vomiting, radiation sickness and postoperative vomiting	Headache, dizziness and diarrhoea
2. Prokinetic drugs • Metoclopramide • Domperidone	• Drug-induced, disease-induced, postoperative, cancer chemotherapy-induced vomiting and radiation sickness • Preferred antiemetic in children and levodopa-induced vomiting	• Drowsiness, dizziness, diarrhoea, acute dystonias and other extrapyramidal symptoms (EPS) • Dryness of mouth, diarrhoea and headache
3. Antihistamines	Motion sickness, morning sickness, Meniere disease, drug induced, postoperative, radiation sickness and cancer chemotherapy-induced vomiting	Drowsiness and dryness of mouth
4. Anticholinergics (scopolamine)	Motion sickness	Sedation, dryness of mouth, blurred vision and urinary retention
5. Neuroleptics	Drug-induced, disease-induced, postoperative, cancer chemotherapy-induced and radiation-induced vomiting	EPS, sedation, dystonic reactions and orthostatic hypotension
6. Neurokinin (NK ₁)-receptor antagonist	Cancer chemotherapy-induced vomiting	Dizziness, diarrhoea and fatigue
7. Dronabinol	Vomiting due to cytotoxic drugs and radiation sickness	Sedation, dysphoria, hallucinations and drug dependence
8. Glucocorticoids (adjuvant antiemetics)	Adjuvant antiemetic along with ondansetron or metoclopramide in cancer chemotherapy-induced vomiting	Metabolic disturbances
9. Benzodiazepines (adjuvant antiemetics)	Psychogenic and anticipatory vomiting	Sedation and drowsiness

6. Neurokinin (NK₁)-receptor antagonists: Aprepitant, fosaprepitant.

7. Cannabinoids: Dronabinol.

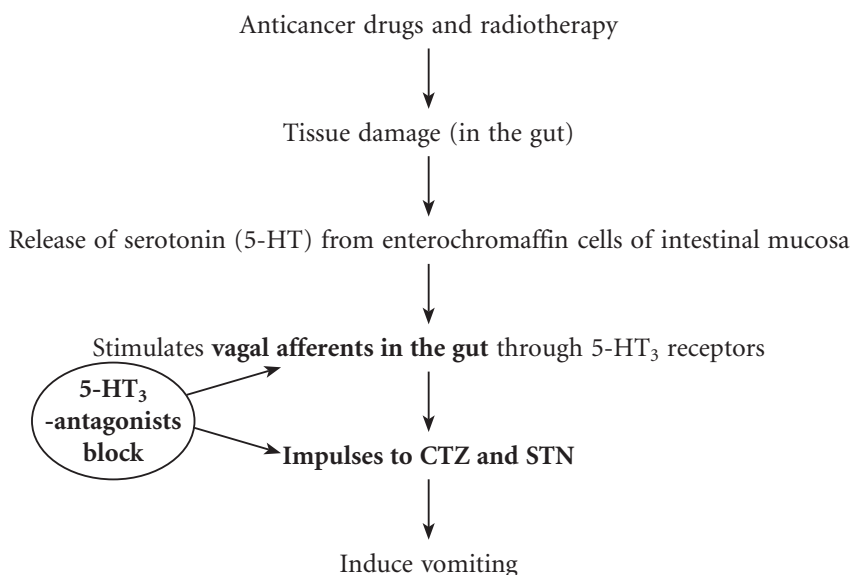
8. Adjuvant antiemetics

(a) *Glucocorticoids:* Betamethasone, dexamethasone, methylprednisolone.

(b) *Benzodiazepines:* Lorazepam, alprazolam.

5-HT₃-Receptor Antagonists. Ondansetron is the prototype drug. Other drugs are granisetron, dolasetron, palonosetron and ramosetron. Their antiemetic effect is mainly due to

blockade of 5-HT₃-receptors on vagal afferents in the gut (peripheral action). In addition, they also block 5-HT₃-receptors in the CTZ and solitary tract nucleus (central action).



Pharmacokinetics. 5-HT₃ antagonists are well absorbed after oral administration. The metabolites are excreted in urine and faeces. These agents are also available for intravenous administration. Ondansetron can also be administered intramuscularly. Granisetron is more potent and longer acting than ondansetron. Transdermal patch of granisetron is available for prevention of cancer chemotherapy-induced vomiting. Palonosetron has the longest duration of action among (half-life is 40 hours) the 5-HT₃ antagonists.

Uses

1. 5-HT₃ antagonists are the most effective agents for prevention and treatment of chemotherapy-induced nausea and vomiting (CINV). They are effective for prevention and control of acute phase vomiting following chemotherapy. Palonosetron is superior to ondansetron in preventing delayed emesis following chemotherapy. Combination with dexamethasone/diazepam/aprepitant enhances the antiemetic efficacy.
2. They are also effective in hyperemesis of pregnancy, postoperative, postradiation and drug-induced vomiting but they are ineffective against motion sickness.
3. Ramosetron can be used in irritable bowel syndrome.

Adverse Effects. 5-HT₃ antagonists are well tolerated. They may cause headache, dizziness and diarrhoea.

Prokinetic Drugs. Drugs that promote coordinated movement of GIT and hasten gastric emptying are called prokinetic drugs. They include metoclopramide, domperidone, mosapride, itopride, cisapride and levosulpiride. Of these, metoclopramide and domperidone are used as antiemetics.

Metoclopramide. Metoclopramide is a dopamine (D₂)-receptor antagonist. It has two important actions – central and peripheral.

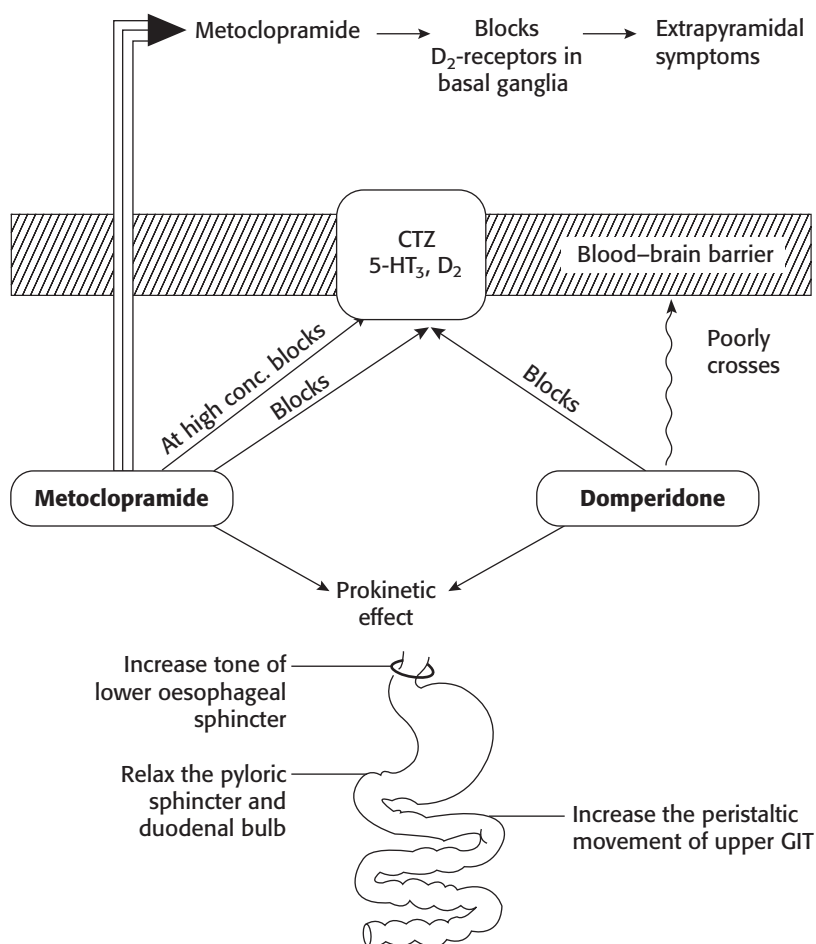
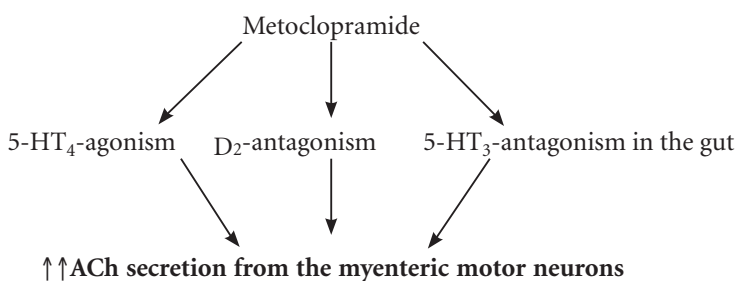


Fig. 7.2 Effects of metoclopramide and domperidone.

Central Actions. The antiemetic effect of metoclopramide is mainly due to blockade of D_2 -receptors in CTZ. At high concentration, it also blocks $5-HT_3$ -receptors in CTZ (Fig. 7.2).

Prokinetic Effect on Upper GIT



Metoclopramide enhances release of ACh from myenteric neurons. This effect is due to D_2 -antagonism and $5-HT_4$ -agonism in the GI tract. Thus, peripherally, it has prokinetic effect on upper GIT (Fig. 7.2) and enhances the rate of gastric and duodenal emptying.

The effects of metoclopramide on upper GI tract:

1. Increase in tone of lower oesophageal sphincter (LES).
2. Increase in tone and amplitude of antral contractions.
3. Relaxation of pyloric sphincter.
4. Increase in peristalsis of small intestine.

Thus, it promotes forward movement of contents in the upper GIT. It does not have significant effect on motility of colon.

Pharmacokinetics. Metoclopramide is rapidly absorbed after oral administration. It can also be administered by i.m. or i.v. routes. Onset of action is within half an hour after oral dose; a few minutes after parenteral administration. It has a short half-life of 4 hours; poorly bound to plasma proteins; crosses blood–brain barrier. The drug is partly metabolized and excreted in urine.

Uses

1. As an antiemetic: Metoclopramide is effective for prevention and treatment of:
 - (a) Disease-associated vomiting.
 - (b) Drug-induced vomiting (not used to control levodopa-induced vomiting).
 - (c) Postoperative vomiting.
 - (d) Cancer chemotherapy-induced vomiting. It is used in combination with 5-HT₃ antagonists/dexamethasone/promethazine/diazepam.
 - (e) Vomiting due to radiation sickness.

It is less effective against motion sickness.

2. Gastroesophageal reflux disease (GERD): Metoclopramide produces symptomatic relief in patients with reflux oesophagitis by increasing the tone of LES. By prokinetic effect, it also reduces the volume of gastroduodenal contents that reflux into oesophagus. It is less effective than proton-pump inhibitors (PPIs) and H₂-blockers.
3. To alleviate symptoms associated with gastric stasis in patients with diabetes, postoperative or idiopathic gastroparesis: Gastric stasis is characterized by upper abdominal discomfort, distension, bloating, nausea, vomiting, etc. By prokinetic effect, it controls the above symptoms.
4. To stimulate gastric emptying before general anaesthesia in emergency surgeries.
5. Metoclopramide has been used in the treatment of intractable hiccups.

Adverse Effects. They are drowsiness, dizziness and diarrhoea. Acute dystonias (spasm of muscles of face, tongue, neck and back) can occur. Other extrapyramidal symptoms (EPS: tremor, rigidity, etc.) are due to blockade of D₂-receptors in basal ganglia (drug-induced parkinsonism). Acute dystonias can be treated with centrally acting anticholinergics (e.g. benzhexol and bengtropine) or antihistamines with anticholinergic action (e.g. promethazine and diphenhydramine).

Long-term use may lead to gynaecomastia, galactorrhoea and menstrual irregularities due to blockade of inhibitory effect of dopamine on prolactin release.

Drug Interactions. Metoclopramide and levodopa: Metoclopramide crosses BBB, blocks D₂-receptors in the basal ganglia, thus interfering with the anti-parkinsonian effect of levodopa. Hence, it is not used to treat levodopa-induced vomiting.

Metoclopramide accelerates the absorption of diazepam but reduces digoxin absorption by its prokinetic effect.

Domperidone. It is a butyrophenone derivative (related to haloperidol) and has effects almost similar to metoclopramide. Its antiemetic and prokinetic effects are due

to blockade of D₂-receptors (Fig. 7.2). It is less potent and less efficacious than metoclopramide. It poorly crosses BBB; hence, extrapyramidal side effects are rare. Atropine blocks the prokinetic effect of metoclopramide but not that of domperidone. It is usually administered orally, but its oral bioavailability is low because of extensive first-pass metabolism; metabolized in liver and metabolites are excreted in urine. Domperidone is a preferred antiemetic in children, as it rarely produces EPS. It counteracts vomiting induced by levodopa or bromocriptine without affecting their anti-parkinsonian effect as it poorly crosses BBB. Hence, it is preferred over metoclopramide to treat vomiting induced by these drugs. It increases prolactin levels. The important side effects are dryness of mouth, diarrhoea, headache, skin rashes, galactorrhoea and menstrual irregularities.

Other prokinetic agents

Cisapride, prokinetic agent, was banned because of its dangerous side effect – ventricular fibrillation (torsades de pointes).

Mosapride

- The prokinetic effect is due to 5-HT₄-agonism; also has weak 5-HT₃ antagonistic effect
- Does not cause EPS, hyperprolactinaemia (no D₂-blocking action)
- May be useful in dyspepsia, diabetic gastroparesis, GERD
- Side effects are dizziness, diarrhoea, headache, etc.; QT prolongation has been reported

Itopride

- Prokinetic effect is due to D₂-antagonism and anticholinesterase activity
- Drug interactions are rare and does not cause EPS

Cinitapride

- It blocks 5-HT₂ and D₂-receptors in the gut. It is useful in GERD.

Levosulpiride

- It blocks D₂-receptors – has prokinetic and antiemetic effects. It is useful in irritable bowel syndrome.

Anticholinergics. Scopolamine (hyoscine) is the drug of choice to prevent motion (travel) sickness. It blocks afferent impulses from vestibular apparatus to the vomiting centre by its anticholinergic action. Its sedative effect also contributes to its antiemetic effect. Scopolamine is administered orally, intramuscularly or as transdermal patch (see Chap. 2, p. 67).

Antihistamines (H₁-Blockers). H₁-blockers are mainly useful for the prevention of motion sickness. They are also effective in morning sickness, postoperative and other types of vomiting (Table 7.1). Dimenhydrinate, diphenhydramine, doxylamine, promethazine, cinnarizine, cyclizine and meclizine are some of the H₁-blockers that have antiemetic properties. Their antiemetic effect is due to sedative, H₁ blockade and central anticholinergic actions. Cyclizine and meclizine have less sedative effect. Meclizine has a long duration of action (24 hours).

Neuroleptics. They are potent antiemetics. Their antiemetic effect is due to blockade of D₂-receptors in the CTZ. In addition, they have anticholinergic and antihistaminic actions. Among these, prochlorperazine is commonly used as an antiemetic. They are effective in the treatment of vomiting due to drugs, uraemia and systemic infections. Prochlorperazine, in low doses, may be used in hyperemesis gravidarum. They are also useful for the treatment of chemotherapy and radiation-induced vomiting. They are less

effective in motion sickness. The common side effects are sedation, muscle dystonia and other EPS, dryness of mouth, hypotension, etc.

Neurokinin (NK₁)-Receptor Antagonists. Aprepitant (orally) and fosaprepitant (infused intravenously) are neurokinin-receptor antagonists. They block action of substance P in CTZ and NTS. They are highly effective in prevention of delayed emesis following moderately or highly emetogenic chemotherapy and increase the efficacy of standard antiemetic regimens (e.g. 5-HT₃ antagonist + dexamethasone). They are well tolerated; flatulence can occur.

Cannabinoids

Dronabinol. It is either obtained from marijuana plant or synthesized and is used to prevent cancer chemotherapy-induced vomiting not responding to other antiemetics. It is effective orally. It produces serious side effects such as sedation, central sympathomimetic effects (tachycardia, palpitations and hypotension), hallucinations, disorientation and drug dependence – hence kept as a reserve antiemetic.

Adjuvant Antiemetics

Glucocorticoids. Glucocorticoids, such as dexamethasone, betamethasone and methylprednisolone are used as adjuvant antiemetics. These agents are commonly used in combination with ondansetron or metoclopramide in the treatment of anticancer drug-induced acute and delayed vomiting. The beneficial effect of steroids is due to their anti-inflammatory property.

Benzodiazepines. Lorazepam, diazepam and alprazolam are used to control psychogenic and anticipatory vomiting. The beneficial effect is mainly due to their sedative, amnesic and antianxiety effects.

Antidiarrhoeal Agents

PH1.34

Generally, the term ‘diarrhoea’ denotes passage of unusually loose or watery stools at least three times or more in a 24-hour period (WHO). Based on the pattern of onset, there are two types of diarrhoea, i.e. acute and chronic. In most of the cases, acute diarrhoeas are caused by infectious agents. In acute diarrhoea, irrespective of the aetiology, emphasis is given to prevent dehydration, which is responsible for most of the mortalities. Diarrhoea is called chronic when it persists for more than 2 weeks. In chronic diarrhoea, finding out the cause is important for effective management.

MANAGEMENT OF DIARRHOEA

1. Oral and parenteral rehydration
2. Antimotility agents: *Opioids*: codeine, loperamide, diphenoxylate
3. Antisecretory agents: Racecadotril, octreotide.
4. Probiotics
5. Antimicrobial agents

Oral Rehydration Solution (ORS). In acute diarrhoea, it is important to maintain water and electrolyte balance with proper fluid replacement (rehydration). Oral rehydration seems to be the simplest, safest and least expensive method of choice for acute diarrhoea. WHO-ORS contains sodium chloride 2.6 g, potassium chloride 1.5 g, sodium citrate 2.9 g

and glucose 13.5 g. It has to be dissolved in 1 L of water. This provides sodium 75 mM, potassium 20 mM, chloride 65 mM, citrate 10 mM and glucose 75 mM. The total osmolarity is 245 mOsm/L. Amount of sodium and glucose is lower than older preparations; this promotes better absorption of water from the solution. Sodium and potassium are administered to replace the losses. Sodium is transported along with glucose by sodium-glucose cotransporter in the ileum. Citrate, a base, corrects acidosis. ORS decreases stool volume and vomiting. It is also effective in cholera. ORS is also useful in heat stroke and maintenance of hydration in burn patients. In case of severe diarrhoea with dehydration, intravenous fluids are indicated.

WHO recommends the use of zinc supplement (10–14 days) with ORS in acute diarrhoea in children. It decreases intestinal secretions, promotes regeneration of intestinal epithelium and reduces duration and severity of diarrhoea.

Antimotility and Antisecretory Agents

Codeine. It is a natural opium alkaloid. It decreases GI motility and produces constipation. It has abuse potential.

Diphenoxylate. It is related to pethidine. In high doses, it has abuse liability, hence is usually available in combination with a small dose of atropine to discourage abuse or overdose. The side effects are constipation, paralytic ileus and drug addiction. This drug has been banned in many countries.

Loperamide. It is an opiate analogue and has more potent antidiarrhoeal effect than morphine. By interacting with μ -opioid receptors in the gut, loperamide reduces GI motility and increases the anal sphincter tone. It decreases secretion induced by cholera toxin and some toxins of *Escherichia coli*. It is orally effective and has a rapid onset of action. It poorly penetrates BBB and has no abuse potential. The usual dose of loperamide is 4 mg stat and then 2 mg after each loose stool, but the maximum dose should not exceed 16 mg in 24 hours. It has been used in both acute and chronic diarrhoeas. It can also be used in travellers' diarrhoea. The toxic effects are skin rashes, headache and paralytic ileus. It should not be used in children younger than 4 years.

Antimotility drugs produce only symptomatic relief in diarrhoea and should be avoided in acute infectious diarrhoeas, as it can lead to penetration of organisms into bloodstream. These drugs also increase intraluminal pressure; hence, they should be avoided in inflammatory bowel disease (IBD).

Clonidine. It has an antisecretory as well as antimotility effect. It has been used to control diarrhoea due to opioid withdrawal and in diabetes patients with autonomic neuropathy. The side effects are depression and hypotension.

Octreotide. It is an analogue of somatostatin which is useful in secretory diarrhoea due to hormone-secreting tumours of the GIT and pancreas. It inhibits secretion of 5-HT, vasoactive intestinal peptide (VIP), gastrin, insulin, etc. It is administered either intravenously or subcutaneously. It can be used to treat diarrhoea in patients with AIDS.

Racecadotril. Racecadotril (prodrug) $\Rightarrow$ active metabolite $\Rightarrow$ enkephalinase inhibitor $\Rightarrow$ inhibits degradation of enkephalins (μ/δ agonists) in intestinal mucosa $\Rightarrow$ increases the concentration of enkephalins in intestinal mucosa $\Rightarrow$ decrease in intestinal secretion. It is used in acute secretory diarrhoeas. It can be used in children. Side effects are nausea, vomiting and drowsiness.

Probiotics

They consist of either bacteria or yeast like *Lactobacillus*, *Bifidobacterium* and *Saccharomyces boulardii*. They may produce beneficial effect by competing with pathogens in the gut.

Table 7.2 ■ List of commonly used chemotherapeutic agents for specific treatment of infectious diarrhoea

Organism	Preferred drug with route and dose	Alternative drugs
1. <i>Shigella</i> species	Ciprofloxacin 500 mg b.d. × 5 days	Ofloxacin, ampicillin and cotrimoxazole
2. <i>Salmonella</i>	Ciprofloxacin 500 mg b.d. × 10 days	Ceftriaxone, cefoperazone, ofloxacin and levofloxacin
3. <i>Campylobacter jejuni</i>	Ciprofloxacin 500 mg b.d. × 5 days	Erythromycin and doxycycline
4. <i>Vibrio cholerae</i>	Doxycycline 100 mg b.d. × 5 days	Ciprofloxacin
5. <i>Escherichia coli</i>	Ciprofloxacin 500 mg b.d. × 5 days	Cotrimoxazole and rifaximin
6. <i>Clostridium difficile</i>	Metronidazole 800 mg t.d.s. × 10 days	Vancomycin
7. <i>Entamoeba histolytica</i>	Metronidazole 400 mg t.d.s. + Diloxanide furoate 500 mg t.d.s. × 7 days	Tinidazole, secnidazole and ornidazole
8. <i>Giardia lamblia</i>	Metronidazole 200 mg t.d.s. × 5 days	Tinidazole, paromomycin and nitazoxanide

Antimicrobials

Irrational use of antimicrobials should be avoided. They are indicated in acute bloody diarrhoea. They are also useful in cholera, pseudomembranous enterocolitis and amoebic dysentery. A list of antimicrobials is provided in Table 7.2.

Pharmacotherapy of Inflammatory Bowel Disease PH1.34

IBD includes Crohn disease and ulcerative colitis, which are characterized by diarrhoea, bleeding, abdominal discomfort, anaemia and weight loss.

COMMONLY USED DRUGS

- 1. Aminosalicylates: Sulphasalazine, mesalamine, olsalazine, balsalazide.
- 2. Glucocorticoids: Prednisolone, methylprednisolone, hydrocortisone, budesonide.
- 3. Immunomodulators: Azathioprine, 6-mercaptopurine (6-MP), methotrexate, cyclosporine.
- 4. Biological response modifiers: Infliximab.
- 5. Antibiotics: Metronidazole, ciprofloxacin, clarithromycin.
- 6. Others: Probiotics.

Aminosalicylates (Fig. 7.3)

Sulphasalazine. It is a prodrug and is composed of sulphapyridine and 5-aminosalicylic acid (5-ASA). On oral administration, sulphasalazine reaches the colon, where it is

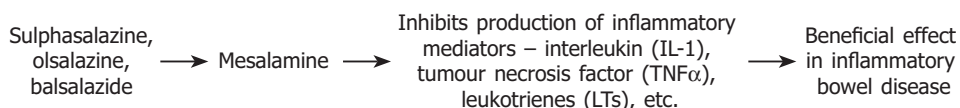


Fig. 7.3 Aminosalicylates and their mechanism of action.

broken down by colonic bacteria to 5-ASA and sulphapyridine. The released 5-ASA acts locally by inhibiting the production of inflammatory mediators. Sulphapyridine gets absorbed and causes side effects like nausea, vomiting and headache. Allergic side effects are skin rashes, fever, hepatitis, pancreatitis, pneumonitis, etc. To avoid the side effects of sulphapyridine, several 5-ASA compounds have been developed which can be directly targeted to the colon.

Mesalamine, Olsalazine and Balsalazide. *Mesalamine (mesalazine)* is 5-ASA. Mesalamine is well absorbed in the upper GIT; therefore, it has to be given as special formulations (delayed release capsules or pH-dependent tablets). It can be administered as suppository or enema.

Olsalazine is composed of two molecules of 5-ASA with an azo linkage. It is poorly absorbed after oral administration. In the colon, it is cleaved into two molecules of 5-ASA by colonic bacteria.

Balsalazide is split into 5-ASA and a metabolite in the colon.

Mesalamine, olsalazine and balsalazide have a lower incidence of side effects than sulphasalazine. They may cause headache and skin rashes. Diarrhoea is common with olsalazine.

5-ASA agents are mainly effective for mild to moderate ulcerative colitis.

Glucocorticoids

Glucocorticoids are used for the short-term treatment of moderate to severe IBD. Various glucocorticoids used in IBD are prednisolone (oral), methylprednisolone (oral, parenteral), hydrocortisone (enema, suppository) and budesonide (oral). Prolonged use of glucocorticoids can lead to hypothalamic–pituitary–adrenal axis suppression and other side effects like osteoporosis, peptic ulcer, infections and hyperglycaemia.

Antibiotics

Metronidazole, ciprofloxacin and clarithromycin are used as adjuncts in patients with active Crohn disease.

Immunosuppressants

Azathioprine, 6-mercaptopurine, methotrexate and cyclosporine are used in severe disease or in patients with steroid-dependent/steroid unresponsive IBD.

Biological Response Modifiers

Infliximab, adalimumab (TNF- α inhibitors) and certolizumab can be used in severe cases of Crohn disease and refractory ulcerative colitis. The main disadvantages of biologics are their cost and increased susceptibility to infections.

Probiotics

Probiotics (e.g. *Lactobacillus*, *Bacteroides*, etc.) are used to restore the intestinal flora; useful as adjunct therapy in patients with severe IBD.

Laxatives (Purgatives, Cathartics)

PH1.34

Laxatives are drugs that facilitate evacuation of formed stools from the bowel. Purgatives cause evacuation of watery stools. The terms laxatives, purgatives and cathartics are often used interchangeably.

CLASSIFICATION (ACCORDING TO MECHANISM OF ACTION)

1. Bulk laxatives

- *Dietary fibre* – Bran, methylcellulose, ispaghula (isabgol)

2. Stimulant or irritant laxatives

- Bisacodyl, sodium picosulphate, senna, cascara sagrada, lubiprostone, prucalopride

3. Osmotic laxatives

- Magnesium sulphate, magnesium hydroxide, sodium phosphate, sodium sulphate, lactulose, lactitol, polyethylene glycol

4. Stool softeners (emollient laxatives)

- Docusates, liquid paraffin

Bulk-Forming Laxatives

They are indigestible, hydrophilic substances like bran, methylcellulose, agar and ispaghula, which absorb water, swell up and increase the bulk of stools. They cause mechanical distension, so stimulate peristalsis and promote defaecation. It takes 1–3 days for the evacuation of formed stools. Ispaghula is obtained from the seed of *Plantago ovata*. Large amount of water should be taken with bulk purgatives to avoid intestinal obstruction. Dietary fibres like pectin-bind bile acids increase their excretion in faeces and lower plasma LDL. Fibre diet should be encouraged in patients with irritable bowel syndrome, but should be avoided in those with megacolon or megarectum. The side effects include abdominal discomfort and flatus.

Stool Softeners (Emollient laxatives)

Docusates. Common docusate salts are dioctyl sodium sulphosuccinate (DOSS) and dioctyl calcium sulphosuccinate. They are anionic surfactants. They lower the surface tension of stool, thereby cause accumulation of fluid and fatty substance, thus softening the stools. These agents act within 1–3 days. They are administered orally or as a retention enema. Docusates increase the absorption of liquid paraffin, hence should not be given together.

Liquid Paraffin (Note the 'Ls'). Liquid paraffin is a mineral oil and is administered orally. It softens stools. It also has a Lubricant effect which helps in smooth defaecation. It is useful in patients with cardiac disease because it prevents straining during defaecation.

Adverse Effects of Liquid Paraffin

1. Lipid pneumonia may occur due to entry of drug into lungs; hence, liquid paraffin should not be given at bed time and in lying down position.
2. Long-term use may cause malabsorption of vitamins A, D, E and K (fat-soluble vitamins).
3. Leakage of faecal matter through anal sphincter may lead to soiling of clothes.

Stimulant (Irritant) Laxatives

These agents have direct action on enteric neurons and GI mucosa. They increase prostaglandin (PG) and cyclic adenosine monophosphate (cAMP) levels, but inhibit Na^+ , K^+ -ATPase activity in the intestinal mucosa. This causes an increased secretion of water and electrolytes by the mucosa thus stimulating peristalsis. They cause evacuation of semifluid stools. Chronic use of stimulant laxatives may cause atonic colon. Large doses may cause loss of fluid and electrolytes. They are contraindicated in pregnancy as they cause reflex stimulation of uterus.

Bisacodyl. The major site of action is colon. It is available as an enteric-coated oral tablet and also as a rectal suppository. It is poorly absorbed after oral administration and undergoes activation by esterases in the bowel. Hence, the effect is seen only after 6–8 hours of oral administration. Therefore, it is usually given at bed time. Rectal suppositories act more rapidly within an hour by irritation of rectal mucosa. Bisacodyl is used in constipation and to empty the bowel before endoscopy, surgery and radiological investigations. The side effects are local irritation and inflammation.

Sodium Picosulphate. It is a stimulant purgative given orally at bed time. It can be used to evacuate the bowel before surgery or colonoscopy.

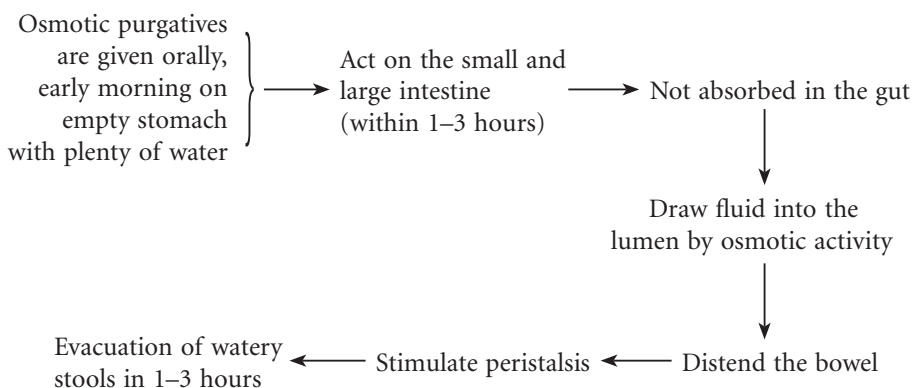
Prucalopride. Prucalopride, a prokinetic drug, is a 5-HT₄ agonist. It is useful in chronic constipation not responding to laxatives. It increases colonic motility.

Lubiprostone. Lubiprostone, a PG analogue, is useful in chronic constipation and irritable bowel syndrome. It increases intestinal secretion.

Anthraquinone Derivatives. The popular anthracene purgatives are senna and cascara. They take 6–8 hours to act, hence are usually administered at bed time to produce their effect in the morning. They are poorly absorbed in the small intestine. The unabsorbed portion reaches the colon, where it is reduced by bacteria to anthrol that acts locally and induces purgation. They should not be prescribed to lactating mothers, as they are secreted in milk. The side effects are skin rashes, black pigmentation of the colonic mucosa and discolouration of urine. Prolonged use can cause colonic atony.

Osmotic Laxatives

They are salts of magnesium, sodium or potassium. Those having magnesium or phosphate are known as saline laxatives.



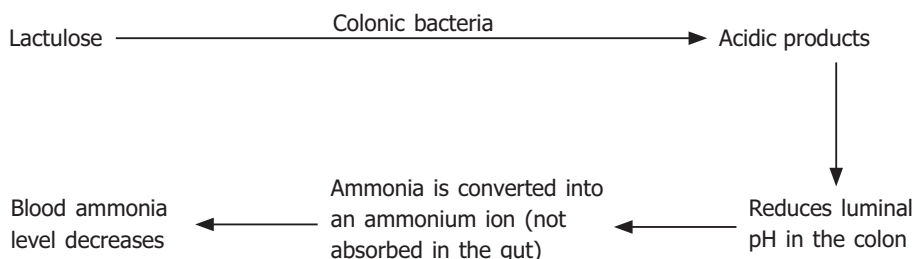


Fig. 7.4 Action of lactulose in hepatic coma.

In addition, magnesium salts cause release of cholecystokinin. To mask the bitter taste, they are often administered with fruit juice. The important osmotic laxatives are magnesium sulphate (Epsom salt), magnesium hydroxide (milk of magnesia), sodium phosphate, lactulose, etc. They should be avoided in young children and patients with renal failure, as they may cause CNS or cardiac depression.

Sodium phosphate is commonly used orally for colon preparation before surgery or colonoscopy. It can also be used as an enema. Sodium salts should be avoided in cardiac patients.

Lactulose. Lactulose is a disaccharide of fructose and galactose. Lactulose is available as liquid and powder. On oral administration, it is not absorbed through GI mucosa. Colonic bacteria convert it into acidic products, which exert osmotic effect – draw fluid into the lumen and distend it, thus useful in constipation. It produces soft to loose stools. It can be used to treat constipation in children and pregnant women. Lactulose is used in hepatic coma to reduce blood ammonia levels (Fig. 7.4). The side effects include abdominal discomfort and flatulence.

Lactitol. Its actions are similar to lactulose. It is useful in constipation and hepatic encephalopathy.

Polyethylene Glycol. It is an osmotic laxative which is used to evacuate the bowel prior to surgical, radiological and endoscopic procedures. It is available as powder and solution. The powder should be mixed with water or fruit juice.

USES OF LAXATIVES WITH PREFERRED PREPARATIONS

1. Acute functional constipation (atonic or spastic) – bulk laxatives.
2. To prevent straining during defaecation in patients with cardiovascular disease, eye surgery, hernia, etc. – docusates or bulk laxatives.
3. In patients with hepatic coma to reduce the blood ammonia level – lactulose.
4. Preoperatively in bowel surgery, colonoscopy and abdominal X-ray – osmotic laxatives or bisacodyl.
5. Following anthelmintics (e.g. for *Taenia solium*) – saline laxatives are used to expel the worm segments.
6. In drug poisoning to wash out the poisonous material from the gut – saline laxatives.
7. To treat constipation in children and pregnant women – lactulose.

Treatment of opioid-induced constipation

Laxatives are the preferred drugs. If patient does not respond to laxatives, opioid antagonists like methylnaltrexone and naloxegol can be used. Methylnaltrexone (s.c.),

naloxegol (oral) are peripherally acting μ -opioid receptor antagonists. They are devoid of central effects; used to treat opioid-induced constipation in cancer patients. Adverse effects are nausea, vomiting and diarrhoea.

Pharmacotherapy of Peptic Ulcer and Gastroesophageal Reflux Disease

PH1.34

Physiology of gastric secretion

The stomach secretes roughly about 2–3 litres of gastric juice per day. The chief or peptic cells secrete pepsinogen, which is converted to pepsin by gastric acid. Parietal or oxyntic cells secrete acid and intrinsic factor (IF). Superficial epithelial cells secrete alkaline mucus and bicarbonate ions.

Regulation of gastric acid secretion

The secretion of gastric acid by parietal cells is regulated by ACh, histamine, gastrin and prostaglandin E_2 (PGE_2). Binding of histamine, ACh and gastrin to their specific receptors on the parietal cell results in increased secretion of gastric acid. In contrast, the binding of PGE_2 to its receptor decreases gastric acid secretion. There are various phases of gastric acid secretion – basal, cephalic and hormonal. A membrane-bound proton pump H^+ , K^+ -ATPase plays an important role in the final step of gastric acid secretion.

Damage to the mucosa and deeper tissue exposed to acid and pepsin is known as peptic ulcer. The exact cause of peptic ulcer is not clear. In most of the cases, peptic ulcers are caused by *Helicobacter pylori* infection or the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

CLASSIFICATION OF DRUGS USED IN PEPTIC ULCER

Drugs used in peptic ulcer are classified as follows (Fig. 7.5):

1. Drugs that inhibit gastric acid secretion

- PPIs*: Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole.
- H_2 -receptor antagonists (H_2 -blockers)*: Cimetidine, ranitidine, famotidine, roxatidine, nizatidine.

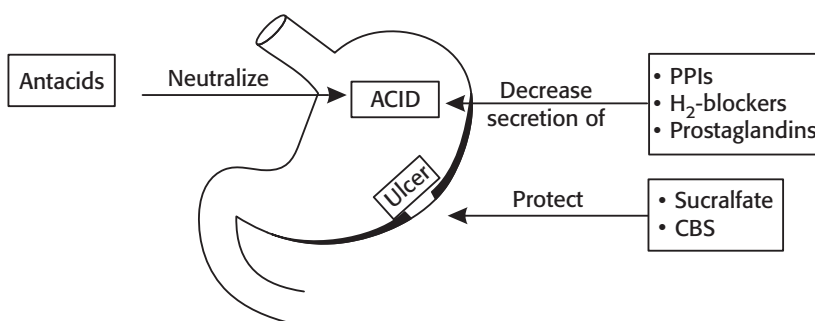


Fig. 7.5 Drugs used in peptic ulcer. PPIs, proton-pump inhibitors; CBS, colloidal bismuth subcitrate.

- (c) *Antimuscarinic agents (anticholinergic agents)*: Pirenzepine, telenzepine.
- (d) *Prostaglandin analogues*: Misoprostol.
- 2. Ulcer protectives**
Sucralfate, colloidal bismuth subcitrate (CBS).
- 3. Drugs that neutralize gastric acid (antacids)**
 - (a) *Nonsystemic antacids*: Magnesium hydroxide, magnesium trisilicate, aluminium hydroxide, calcium carbonate.
 - (b) *Systemic antacids*: Sodium bicarbonate, sodium citrate.
- 4. Anti-*H. pylori* agents**
Amoxicillin, tetracycline, clarithromycin, metronidazole, tinidazole, bismuth subsalicylate, H_2 -antagonists, PPIs.

Drugs That Inhibit Gastric Acid Secretion

Proton-Pump Inhibitors (PPIs). Proton pump (H^+ , K^+ -ATPase) is a membrane-bound enzyme that plays an important role in the final step of gastric acid secretion (basal and stimulated; Fig. 7.6). Omeprazole is the prototype drug. The other PPIs are lansoprazole, pantoprazole and rabeprazole. PPIs (prodrugs) $\rightarrow$ absorbed in small intestine $\rightarrow$ blood $\rightarrow$ diffuse into parietal cells $\rightarrow$ canaliculi of the cell (acidic pH) $\rightarrow$ converted to sulphenamide (active, charged form). The activated form (sulphenamide) binds covalently with SH group of the proton pump and irreversibly inactivates it. PPIs are the most powerful inhibitors of gastric acid secretion. They inhibit both fasting and stimulated acid secretion. As PPIs act in the final step of acid secretion, they are effective in inhibiting acid production following any stimulation. PPIs are administered orally about 30 minutes before food because food stimulates secretion of acid (in the canaliculi of parietal cell), which is necessary for activation of PPIs. Food decreases absorption of PPIs. Though the half-life of PPIs is short (~ 1.5 hours), acid secretion is suppressed for up to 24 hours as they cause irreversible inhibition of proton pumps. In the commonly used doses, PPIs suppress acid production by about 80%–98%. PPIs are available as enteric coated form or as powder containing sodium bicarbonate to prevent their activation by acid in the stomach. Esomeprazole, pantoprazole and lansoprazole have higher oral bioavailability than omeprazole. Ilaprazole is more potent than omeprazole. Parenteral (i.v.) formulations are available for esomeprazole, lansoprazole, pantoprazole

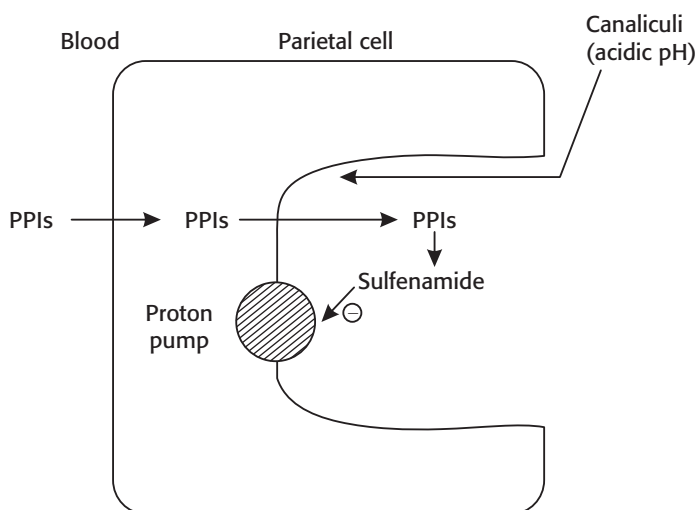


Fig. 7.6 Mechanism of action of proton-pump inhibitors.

and rabeprazole. They are highly bound to plasma proteins; extensively metabolized in liver and metabolites are excreted in urine.

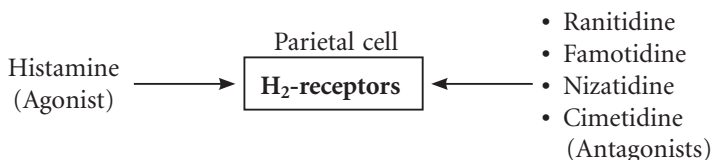
Therapeutic Uses

1. **Peptic ulcer:** PPIs are the most powerful acid suppressive agents. They inhibit all phases of gastric acid secretion. PPIs are superior to H_2 -blockers as their onset of action is rapid and cause faster ulcer healing. The standard dose of omeprazole is 20 mg, lansoprazole 30 mg and pantoprazole 40 mg once daily. *Duodenal ulcers* require 4 weeks' therapy and *gastric ulcers* require 6–8 weeks' therapy for healing. In *acute bleeding ulcers*, intravenous PPIs are preferred. By suppressing acid secretion, they promote healing of ulcer.
H. pylori-associated ulcers: Combination therapy of two or three antimicrobials and a PPI is the most effective regimen for these ulcers.
Stress ulcers (Curling ulcer): Prophylactic use of intravenous PPIs reduce the incidence of stress ulcers in critically ill patients.
NSAID-induced ulcers: PPIs are more effective than H_2 -blockers for prevention and treatment of NSAID-induced ulcers.
2. PPIs can be used preoperatively to reduce the risk of aspiration pneumonia.
3. **Zollinger–Ellison (Z–E) syndrome:** Z–E syndrome is characterized by hypergastrinaemia with multiple peptic ulcers. PPIs are the preferred agents for Z–E syndrome. Higher doses of PPIs are needed for healing of ulcers. Surgery is the definitive treatment. In inoperable cases, prolonged therapy with PPIs has been recommended.
4. **Gastroesophageal reflux disease:** In GERD, the goal of therapy is to produce symptom relief, heal erosive oesophagitis and prevent complications. PPIs are the preferred agents for the treatment of GERD and are usually given once daily. They are more effective than H_2 -blockers. Patients with erosive oesophagitis or peptic ulcer with stricture need prolonged maintenance therapy with PPIs.

Adverse Effects. PPIs are generally well tolerated. The side effects are headache, nausea, diarrhoea and abdominal pain. Skin rashes and arthralgia can rarely occur. Long-term use of PPIs can decrease vitamin B_{12} absorption, increase the risk of infections (e.g. hospital-acquired pneumonia) and osteoporosis. Chronic use also results in hypergastrinaemia which may predispose to gastric tumours. Gynaecomastia and erectile dysfunction with omeprazole therapy have been reported.

Drug interactions. Omeprazole can inhibit the metabolism of drugs like phenytoin, warfarin and diazepam. PPIs decrease the bioavailability of itraconazole, iron salts, etc. Drug interactions are minimal with pantoprazole.

H_2 -Receptor Antagonists (H_2 -Blockers)



Mechanism of Action. H_2 -receptor antagonists competitively block H_2 -receptors on parietal cell and inhibit gastric acid production. They suppress all phases (basal, cephalic and gastric) of acid secretion. They are mainly effective in suppressing nocturnal acid secretion. H_2 -blockers also reduce acid secretion stimulated by ACh, gastrin, food, etc.

They are less potent than PPIs – 24-hour acid secretion is suppressed by 60%–70%. Cimetidine is the prototype drug and was the first H₂-blocker developed. It is seldom used now because of its adverse effects (Table 7.3).

H₂-blockers are usually administered orally and are well absorbed; metabolized in liver and the metabolites are excreted in urine. Cimetidine, ranitidine and famotidine are also available for intravenous administration.

- *Nizatidine*: All the features are similar to ranitidine but it has higher bioavailability (almost 100%).
- *Famotidine*: Most of the features are similar to ranitidine. It is more potent and longer acting than ranitidine. It has no antiandrogenic effect. Drug interactions are negligible.
- *Lafutidine*: It is an H₂-receptor blocker and decreases acid secretion. It increases mucosal blood flow and mucin synthesis. Nitric oxide production is increased.

Therapeutic Uses

1. **Peptic ulcer**: H₂-blockers are one of the commonly used drugs in peptic ulcer. H₂-blockers produce symptomatic relief within days and ulcer healing within weeks. The duration of treatment for duodenal ulcer is 4–6 weeks. Gastric ulcer requires prolonged therapy for 6–8 weeks. But, PPIs are more frequently used because they have higher efficacy and are well tolerated.
 - *H. pylori*–associated ulcers: H₂-blockers can be used along with antimicrobial agents to treat *H. pylori* infection.
 - *Stress ulcers* are commonly seen in critically ill patients with severe medical or surgical illness. They may be associated with upper gastrointestinal bleeding. Intravenous H₂-blockers are used to prevent and treat stress-related ulcer and bleeding.
 - *NSAID-induced ulcers*: H₂-blockers can be used for healing of NSAID-induced ulcers but they are less effective than PPIs.

Table 7.3 ■ Comparison of cimetidine and ranitidine

Cimetidine	Ranitidine
1. H ₂ -blocker (competitive blocker)	H ₂ -blocker (competitive blocker)
2. Less potent	More potent
3. Has shorter duration of action (6–8 hours)	Has longer duration of action (24 hours)
4. Cimetidine is an enzyme inhibitor, hence increases the plasma concentration of many co-administered drugs, such as phenytoin, digoxin, theophylline, warfarin and propranolol	Has less affinity for hepatic cytochrome P450 enzymes, hence drug interactions are rare
5. Increases plasma prolactin level; can cause menstrual irregularities and galactorrhoea in women; gynaecomastia, oligospermia and impotence in men	Has no antiandrogenic effect; does not increase prolactin secretion
6. Crosses BBB and produces CNS side effects like confusion, headache and hallucinations	Poorly crosses BBB, CNS side effects are rare

2. **Gastroesophageal reflux disease:** In GERD, H₂-blockers are effective and produce symptomatic relief. PPIs are more effective than H₂-blockers.
3. **Zollinger–Ellison syndrome:** In Z–E syndrome, surgery is the definitive therapy. PPIs or H₂-blockers are used to control the hypersecretion of acid. PPIs are the preferred agents in Z–E syndrome.
4. **H₂-blockers are used preoperatively** to reduce the risk of aspiration pneumonia.

Anticholinergic Agents. Pirenzepine and telenzepine, selective M₁-receptor blockers, inhibit acid secretion. They are not commonly used because of their low efficacy and anticholinergic side effects.

Prostaglandin Analogues. Misoprostol, a synthetic PG analogue (PGE₁), is effective orally for prevention and treatment of NSAID-induced gastric and duodenal ulcers. PGs inhibit gastric acid secretion, increase mucus and bicarbonate secretion; they also increase mucosal blood flow (cytoprotective effect). The common side effects are diarrhoea and abdominal cramps. Misoprostol is contraindicated in pregnancy, as it may cause uterine contractions. Because of its adverse effects and need for frequent dosing, it is rarely used.

Ulcer Protectives

Sucralfate. It is a complex of aluminium hydroxide and sulphated sucrose. In the acidic environment of stomach (pH < 4), sucralfate undergoes polymerization to form a sticky polymer that adheres to the ulcer base and protects it. It also precipitates proteins at the ulcer base – forms a barrier against acid–pepsin. It stimulates the release of PGs and epidermal growth factor locally, thus produces cytoprotective effect. It also increases mucus and bicarbonate secretion – enhances mucosal defence and repair.

Sucralfate is given orally on an empty stomach at least 1 hour before meals. It reduces the absorption of drugs, such as digoxin, tetracyclines, ketoconazole and fluoroquinolones. Since it requires pH < 4 for activation, concurrent administration of antacids, H₂-blockers or PPIs should be avoided. Constipation is a common side effect. Nausea may occur. Aluminium toxicity can occur in patients with renal failure.

After the introduction of PPIs, sucralfate is seldom used in peptic ulcer. Sucralfate is effective for prevention of bleeding from stress ulcers and to reduce the risk of aspiration pneumonia. It is also useful in GERD with oesophagitis, as it is a mucosal protector. Other uses are oral mucositis, radiation proctitis, rectal ulcer, burns, bed sores, etc.

Bismuth-Containing Preparations. Bismuth subsalicylate and CBS are the most commonly used oral bismuth preparations. Their mode of action is not clear. They probably:

1. Precipitate proteins and protect ulcer base.
2. Stimulate the secretion of PGE₂, mucus and bicarbonate.
3. Have antimicrobial effect against *H. pylori*.

They are one of the components in certain anti-*H. pylori* regimens. The side effects are blackening of the tongue and stools.

Drugs that Neutralize Gastric Acid (Antacids)

Antacids are weak bases that neutralize gastric acid and raise the gastric pH. They do not affect acid production. Acid neutralizing capacity reflects the potency of an antacid.

An Ideal Antacid

1. should be insoluble and capable of neutralizing acid.
2. should not liberate CO₂.

3. should be nonabsorbable.
4. should not disturb the acid–base balance of the body.

Types of Antacids

1. **Nonsystemic:** Magnesium hydroxide, magnesium trisilicate, aluminium hydroxide gel and calcium carbonate.
2. **Systemic:** Sodium bicarbonate and sodium citrate.

Nonsystemic Antacids. Magnesium hydroxide, magnesium trisilicate, aluminium hydroxide, calcium carbonate, etc. form respective chloride salts in stomach. When this reaches the intestine, the chloride salt reacts with bicarbonate, so HCO_3^- is not available for absorption; hence, there is no systemic alkalosis.

Combination of antacids produces various beneficial effects. They are as follows:

1. Aluminium salts cause constipation and magnesium salts cause diarrhoea, so combination of these two can counteract the adverse effects of each other.
 2. Magnesium hydroxide has a rapid onset of action, but aluminium hydroxide acts slowly – the combined product produces rapid and sustained effect.
 3. Dose of individual antacid is reduced; hence, systemic toxicity is minimized.
- Calcium may be absorbed from its salts resulting in hypercalcaemia and hypercalciuria.

Systemic Antacids

Sodium bicarbonate (NaHCO_3). It rapidly neutralizes gastric acid, but the duration of action is short. The disadvantages of NaHCO_3 are that (i) it is highly water soluble and rapidly absorbed from the gut; (ii) it releases CO_2 that can cause abdominal distension and belching; (iii) it may cause metabolic alkalosis; and (iv) it produces rebound acidity.

Sodium bicarbonate is also used to alkalinize urine and to treat acidosis. It should be avoided in patients with hypertension and congestive cardiac failure (CCF), as it causes sodium retention.

Formulations. Antacids are available as suspension, tablet and powder. Tablet should be chewed and swallowed for better effect. Suspensions have better neutralizing capacity than other formulations.

Drug Interactions. All antacids increase the pH of stomach and form insoluble and nonabsorbable complexes with many drugs – iron, tetracyclines, fluoroquinolones, ketoconazole, etc.; thus, antacids reduce the absorption of these drugs. There should be a gap of 2 hours between administration of these drugs and antacids.

Antifoaming Agents

Methylpolysiloxane (simethicone and dimethicone): They are antifoaming agents, usually present in some antacid preparations. They decrease foaming and relieve flatulence. **Oxethazaine:** It is a topical anaesthetic and is used to anaesthetize gastric mucosa. It produces symptomatic relief in gastritis and GERD. It is available in combination with antacids.

Sodium alginate: It forms froth on the contents in the stomach – prevents effects of gastroesophageal reflux.

Anti-*H. pylori* Agents

H. pylori, Gram-negative, rod-shaped bacterium, is associated with gastritis, duodenal ulcer, gastric ulcer and gastric carcinoma (Fig. 7.7).

The mechanism by which *H. pylori* causes mucosal inflammation and damage is not clear. The ammonia produced by urease activity may directly damage the cells.

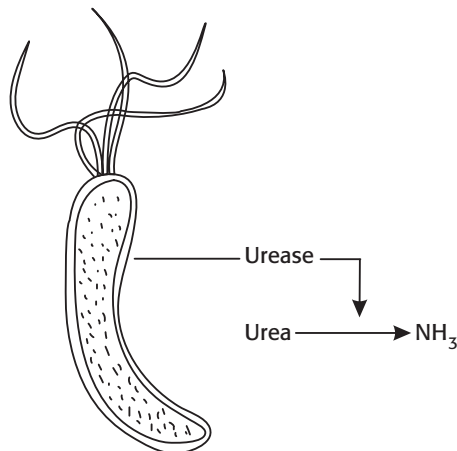


Fig. 7.7 *Helicobacter pylori* (*H. pylori*).

Many regimens are available for the eradication of *H. pylori*. Combination therapy (triple/quadruple) is always recommended. The objectives of combination therapy are as follows:

1. To prevent or delay the development of resistant organism.
2. To prevent relapse.
3. To promote rapid ulcer healing.
4. To eradicate *H. pylori* infection.

The duration of treatment could be 1 week or 2 weeks, of which 14-day therapy is more effective.

The antimicrobials used in *H. pylori* infection are amoxicillin, tetracycline, clarithromycin, metronidazole and tinidazole. Resistance develops rapidly to metronidazole and clarithromycin but not to amoxicillin. Amoxicillin should be avoided in patients with history of penicillin allergy. Other anti-*H. pylori* drugs are PPIs, H₂-blockers and CBS. Some of the recommended regimens are listed below:

Triple Therapy × 14 Days (2 Weeks)

- Lansoprazole 30 mg b.d. +
- Clarithromycin 500 mg b.d. +
- Amoxicillin 1 g b.d.

Quadruple Therapy × 14 Days (2 Weeks)

- Omeprazole 20 mg b.d. +
- CBS 120 mg q.i.d. +
- Tetracycline 500 mg q.i.d. +
- Metronidazole 400 mg t.i.d.

After completion of the above-recommended regimen, PPI should be continued for 6 more weeks to enhance ulcer healing.

DRUGS USEFUL IN GASTROESOPHAGEAL REFLUX DISEASE

PH1.34

1. PPIs and H₂-receptor blockers: They decrease acid secretion → pH of gastric contents rise → relief of symptoms and healing of esophageal lesions. PPIs are more effective than H₂-blockers. They do not affect LES tone.

2. Antacids are used occasionally in GERD. They are rapid acting.
3. Prokinetic drugs, e.g. metoclopramide and mosapride increase tone of LES, enhance gastric emptying but do not affect acid secretion.

DRUGS FOR DISSOLVING GALLSTONES.**PH1.34**

Ursodiol decreases biliary secretion of cholesterol and helps to dissolve cholesterol stones. It is administered orally. A functional gall bladder is required. Elevation of liver enzymes may occur. It is used in those patients with gallstones in whom surgery cannot be done.

Drugs Affecting Coagulation and Blood Formation

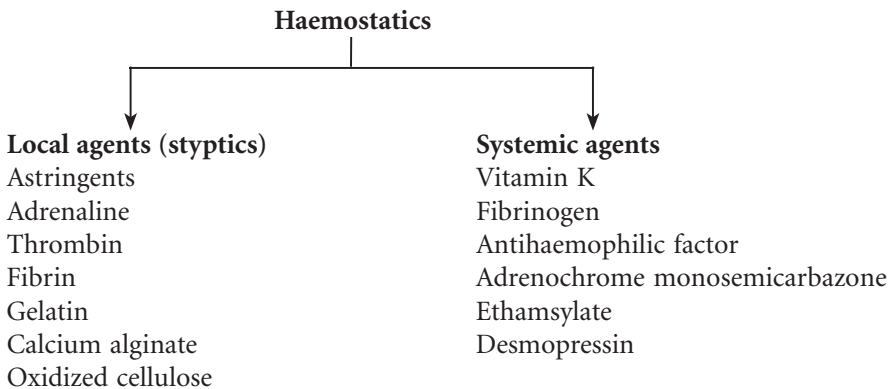
Drugs Affecting Coagulation and Bleeding

PH1.25

HAEMOSTATIC AGENTS

They arrest bleeding either by vasoconstriction or by promoting coagulation of blood.

Classification



Local Haemostatics (Styptics). These drugs are commonly used locally to control bleeding from capillaries and minute vessels, e.g. bleeding following tooth extraction, abrasions, epistaxis, etc.

Astringents. They precipitate proteins locally in the bleeding site and control capillary oozing, e.g. solution of ferric chloride, tannic acid, etc. They are useful in bleeding gums.

Adrenaline. It causes vasoconstriction (α_1) and arrests bleeding. A cotton pad soaked in 0.1% adrenaline solution is applied on the bleeding site to control capillary oozing, e.g. epistaxis, bleeding after tooth extraction, etc. Adrenaline should be avoided in patients with hypertension, congestive heart failure, arrhythmias, ischaemic heart disease and uncontrolled hyperthyroidism as it may precipitate myocardial infarction (MI) or aggravate the existing condition.

Thrombin. It is a freeze-dried powder derived from bovine or human plasma. It is used topically to control bleeding from capillaries. It can cause hypersensitivity reactions. Thrombin should not be injected.

Fibrin. It consists of fibrinogen, factor XIII, thrombin, Ca^{2+} and other clotting components. It is used to control bleeding during surgical procedures or as a spray on bleeding surface.

Gelatin. It is an absorbable haemostatic and is available as a sponge or film. It produces haemostasis by providing a physical meshwork on which clotting can occur.

Calcium Alginate. It is obtained from sea weeds. It is an absorbable haemostatic and is used to promote wound healing.

Oxidized Cellulose. It is an absorbable haemostatic. It should be applied dry so that it swells up and helps in the formation of clot. It is used to control bleeding from capillaries and arterioles where ligation is not possible. It may cause tissue necrosis, nerve damage or vascular stenosis.

Haemocoagulase. Haemocoagulase enzyme complex is isolated from the venom of *Bothrops atrox* (viper). It has a powerful haemostatic effect. It promotes coagulation by converting fibrinogen to fibrin. It can also shorten bleeding and clotting time, thereby reducing blood loss. It is available for topical, intravenous (i.v.), intramuscular (i.m.) and subcutaneous (s.c.) administration.

Systemic Agents

Vitamin K. Vitamin K, a fat-soluble vitamin, is required for the synthesis of clotting factors II, VII, IX and X. Vitamin K exists in different forms: vitamin K₁ (phytonadione, fat soluble) is from plant and animal source, vitamin K₂ (menaquinone) is produced by intestinal bacteria, whereas vitamin K₃ (menadione – fat soluble; salts are water soluble) is a synthetic form.

Dietary Source. Vitamin K is found in spinach, cabbage, cauliflower and tomatoes. It is also present in butter, meat, milk, liver and pears. The average daily intake for an adult is estimated to be 70–140 mcg/day.

Pharmacokinetics. Vitamin K₁ and menadione require the presence of bile for their absorption. Vitamin K is transported along with low-density lipoprotein (LDL) and is stored mainly in liver. Its metabolites are excreted in bile and urine.

Actions. Vitamin K acts as a cofactor for γ -carboxylation of glutamic acid residues of clotting factors II, VII, IX, X (which allows them to bind calcium and membrane phospholipids during the process of coagulation) and osteocalcin (bone protein which is important for bone development).

Deficiency. Vitamin K deficiency may occur due to inadequate absorption (lack of bile salts), loss of vitamin (chronic diarrhoea) and administration of broad-spectrum antibiotics (suppression of bacterial flora). In vitamin K deficiency, there is an increased tendency to bleed – epistaxis, haematuria, gastrointestinal bleeding and postoperative bleeding.

Adverse Effects. Oral vitamin K is safe. Intravenous injection may cause flushing, sweating, dyspnoea, cyanosis, collapse and anaphylactoid reactions. Menadione may cause haemolysis, hyperbilirubinaemia and kernicterus in newborn.

Preparations

Phytonadione (vitamin K₁): It is available for oral, s.c., i.m. and i.v. administration.

Menadione sodium diphosphate (vitamin K₃): It is a water-soluble preparation and is available for i.v., i.m. and oral administration. Menadione and its water-soluble salts have low efficacy and are toxic, hence they are not commonly used.

Uses. For prevention and treatment of bleeding associated with vitamin K deficiency:

1. In obstructive jaundice with haemorrhagic symptoms, parenteral vitamin K₁ is preferred. It is also administered to treat vitamin K deficiency resulting from prolonged antimicrobial therapy.
2. Vitamin K₁ (1 mg phytonadione, i.m.) is given routinely to all neonates to prevent bleeding, as the intestinal flora, which is necessary for the synthesis of vitamin K, is not developed.
3. To control bleeding due to oral anticoagulant therapy, phytonadione is used (see p. 291).
4. Vitamin K₁ is used in salicylate poisoning with haemorrhagic complications.

Antihæmophilic Factor. It contains coagulation factor VIII with von Willebrand's factor. It is administered as i.v. infusion to control bleeding episodes in hæmophiliacs. Adverse effects include fever with chills, headache and skin rashes.

Adrenochrome Monosemicarbazone. It is available for oral and parenteral administration. It is used to control capillary oozing following tooth extraction, epistaxis, haematuria, etc.

Ethamsylate. It is a haemostatic available for oral and i.v. administration. It corrects abnormal platelet adhesion and maintains stability of the capillary wall. It is used to prevent and control bleeding from small blood vessels, e.g. menorrhagia, bleeding following tooth extraction. It may cause skin rashes, hypotension and headache.

Desmopressin. It is a synthetic analogue of vasopressin. It is administered as an i.v. infusion to control mild to moderate bleeding in haemophilia A and von Willebrand's disease.

Fibrinogen. It is obtained from human plasma. It is used to control bleeding associated with hypofibrinogenaemia and is infused intravenously.

ANTICOAGULANTS

Anticoagulants are drugs that prevent or reduce coagulability of blood.

Classification

1. Used in vitro:
 - a. Heparin
 - b. Sodium citrate: Used in blood banks to store blood
 - c. Sodium oxalate
 - d. Sodium edetate
 } Used as anticoagulant in the laboratory
2. Used in vivo:
 - a. **Parenteral anticoagulants**
 - 1) *Indirect thrombin inhibitors*:
 - Heparin (UFH – unfractionated heparin)
 - Low-molecular-weight heparins (LMWHs): Enoxaparin, dalteparin, ardeparin, reviparin
 - Synthetic: Fondaparinux
 - 2) *Direct thrombin inhibitors*: Bivalirudin, argatroban, desirudin
 - b. **Oral anticoagulants**
 - 1) *Coumarin derivatives*: Warfarin, dicumarol, acenocoumarol
 - 2) *Indandione derivative*: Phenindione
 - 3) *Direct thrombin inhibitor*: Dabigatran
 - 4) *Factor Xa inhibitor*: Rivaroxaban, apixaban, edoxaban

PARENTERAL ANTICOAGULANTS

Indirect Thrombin Inhibitors

Heparin (Unfractionated Heparin; Table 8.1). Heparin, the strongest organic acid in the body, was discovered by a medical student, McLean. It was later isolated and identified by Howell as a sulphated mucopolysaccharide. It is strongly electronegative. Commercially, heparin is obtained from *ox* lung and *pig* intestinal mucosa.

Mechanism of Action (Fig. 8.1). Heparin binds to plasma antithrombin III (AT III) and activates it. For binding to AT III, five saccharides (pentasaccharide) of heparin is essential. The heparin–antithrombin III complex enhances the rate of inactivation of activated clotting factors Xa, IIa, IXa, XIa, XIIa and XIIIa. To accelerate IIa (thrombin) inactivation, heparin must bind to AT III as well as thrombin. This requires a long length of heparin (18 saccharides). For inactivation of factor Xa, binding of heparin (pentasaccharides) to AT III only is required.

At low concentration, heparin selectively inhibits the conversion of prothrombin to thrombin. Heparin thus prevents further thrombus formation. Heparin, in high doses,

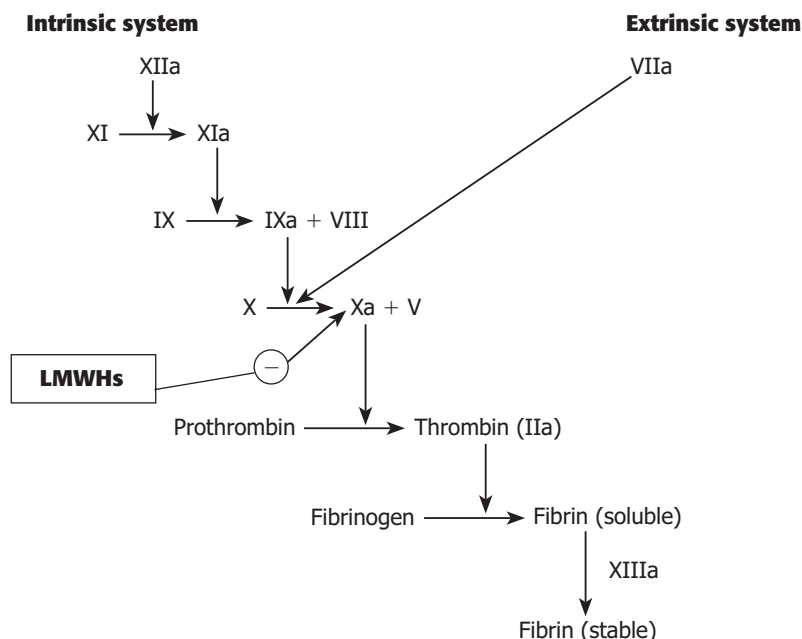


Fig. 8.1 The coagulation cascade. Heparin inactivates factors XIIa, XIa, IXa, Xa, IIa and XIIIa through antithrombin. Low-molecular-weight heparins (LMWHs) inhibit Xa through antithrombin.

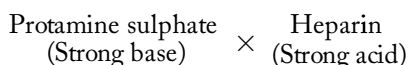
has antiplatelet action and prolongs the bleeding time. It releases lipoprotein lipase which hydrolyses triglycerides, resulting in clearing of lipaemic plasma.

Pharmacokinetics. Heparin is not absorbed after oral administration because of its high negative charge and large molecular size. Therefore, it must be given parenterally – intravenously or subcutaneously. On i.v. administration, the anticoagulant effect starts immediately, whereas through s.c. route, it takes 1–2 hours. Heparin is highly protein bound. It does not cross blood–brain barrier or placental barrier and is safe for use during pregnancy. It is rapidly inactivated in liver by heparinase and the metabolites are excreted in urine.

Mode of Administration. Heparin is usually administered by i.v. infusion (for treatment) or s.c. route (if it cannot be given as i.v. infusion or when given in low dose for prophylaxis). Intramuscular administration may cause haematomas, hence should not be used. During heparin therapy, activated partial thromboplastin time (aPTT) monitoring is necessary and it should be maintained at 1.5–2.5 times the control.

Adverse Effects and Contraindications

- 1. Bleeding:** The main side effect is bleeding. Overdosage may cause serious and fatal haemorrhage. Bleeding can occur in urinary (haematuria is generally the earliest sign) and gastrointestinal tract or anywhere in the body. Hence, heparin therapy requires aPTT monitoring. No antagonist is required in cases of mild bleeding, as effect of heparin disappears within hours of stoppage of therapy. If life-threatening haemorrhage occurs, it can be controlled rapidly by slow i.v. infusion of protamine sulphate (heparin antagonist). It is a strongly basic protein, and hence rapidly neutralizes the anticoagulant effect of heparin.



Protamine sulphate is a specific heparin antagonist, which is obtained from fish sperm. One milligram of protamine sulphate approximately neutralizes 100 units of heparin (chemical antagonism). Protamine sulphate itself may cause bleeding as it has weak anticoagulant effect. Hence, the maximum dose must not exceed 50 mg.

2. **Heparin-induced thrombocytopenia (HIT):** Heparin rarely causes thrombocytopenia. It is due to the formation of antibodies against platelet factor–heparin complex leading to a decrease in platelet count. Thrombotic complications can occur. The incidence is higher with UFH than with LMWHs. Heparin should be discontinued. LMWHs cannot be used in such patients.
3. **Hypersensitivity reactions** can occur rarely. They are skin rashes, urticaria, fever, etc.
4. **Osteoporosis:** Dose-dependent osteoporosis with spontaneous fractures may occur during long-term therapy.
5. **Reversible alopecia** has been reported.
6. Abnormalities in liver function test can occur.

Heparin is contraindicated in haemophiliacs, patients with HIT, severe hypertension, intracranial haemorrhage, bacterial endocarditis, active tuberculosis, peptic ulcer, threatened abortion, cirrhosis, etc.

Low-Molecular-Weight Heparins. Enoxaparin, dalteparin, tinzaparin, ardeparin, reviparin, etc. are LMWHs and are obtained from standard heparin by fractionation. LMWHs produce anticoagulant effect mainly by inactivation of factor Xa through antithrombin. As they are not of sufficient length to bind to both thrombin and antithrombin simultaneously, they have little effect on thrombin inhibition. Hence, LMWH has less effect on aPTT as compared to UFH. LMWH therapy usually does not require aPTT monitoring but patients with chronic renal failure may need monitoring by measuring factor Xa activity since they are excreted through kidney. The effects of LMWHs are not completely reversed by protamine sulphate. LMWHs are given subcutaneously. The following are the advantages of LMWHs:

1. They have a higher s.c. bioavailability as compared to UFH.
2. They have a longer $t_{1/2}$; can be administered once a day.
3. They do not routinely require aPTT monitoring.
4. There is a lower incidence of thrombocytopenia and osteoporosis as compared to UFH.

(Uses, adverse effects and contraindications are same as other anticoagulants.)

Fondaparinux. It is a synthetic parenteral anticoagulant. It binds to antithrombin and selectively inactivates factor Xa without any effect on thrombin. Fondaparinux is administered subcutaneously. It is useful in pulmonary embolism and deep vein thrombosis (DVT). It has a long $t_{1/2}$ of 17 hours and good subcutaneous bioavailability; incidence of thrombocytopenia and osteoporosis is lower with fondaparinux. It does not require routine laboratory monitoring. Its effects are not reversed by protamine sulphate. Fondaparinux should not be administered in patients with renal failure.

Parenteral Direct Thrombin Inhibitors. They bind directly to thrombin and inactivate it. They do not bind to AT III.

Lepirudin, obtained by recombinant DNA technology, inhibits thrombin irreversibly.

Argatroban and **Bivalirudin** are synthetic, reversible direct thrombin inhibitors with rapid onset of action. They are short acting and administered as i.v. infusion. They are used as anticoagulants in patients who are at risk of HIT. Adverse effect is bleeding.

Argatroban affects INR (international normalized ratio). It is secreted in bile and can be used in patients with renal failure.

ORAL ANTICOAGULANTS (Table 8.1)

Among oral anticoagulants, coumarin derivatives (warfarin and acenocoumarol) are commonly used. Oral anticoagulants act only in vivo. They are vitamin K antagonists.

Mechanism of Action. (Fig. 8.2). Clotting factors II, VII, IX and X are synthesized in liver as inactive proteins. These factors are rich in glutamic acid residues and are carboxylated in liver where vitamin K acts as a cofactor. Carboxylation of glutamic acid residues is necessary for clotting factors to bind calcium and membrane phospholipids in coagulation pathway. Vitamin K is converted to inactive epoxide form by oxidation and is regenerated to its active form by vitamin K epoxide reductase (VKOR) enzyme. Warfarin is a coumarin derivative and has a structure similar to that of vitamin K. It competitively inhibits epoxide reductase, prevents regeneration of active form of vitamin K resulting in inhibition of synthesis of factors II, VII, IX and X. The onset and duration of anticoagulant effect of warfarin depends on the half-lives (in hours) of clotting factors, which are as follows: VII (6), IX (24), X (36) and II (50). There is always a delay in the onset of anticoagulant effect because the levels of clotting factors already present in plasma decline slowly over a period of 1–3 days.

Pharmacokinetics. Warfarin is almost completely absorbed after oral administration. It is highly bound to plasma proteins, freely crosses placental barrier, is metabolized in liver and the inactive metabolites are excreted in urine and stool. It has a long half-life of about 40 hours and the duration of action is 3–6 days.

Acenocoumarol. It has a rapid onset but shorter duration of action than warfarin.

Table 8.1 ■ Differences between heparin (parenteral anticoagulant) and warfarin (oral anticoagulant)

Heparin	Warfarin
1. Naturally occurring anticoagulant: animal source – ox lung, pig intestine	Synthetic anticoagulant
2. Active in vivo and in vitro	Active only in vivo
3. Administered parenterally (i.v., s.c.)	Administered orally
4. Acts by activating antithrombin III and inactivates Xa, IIa, IXa, XIa, XIIa and XIIIa	It inhibits synthesis of vitamin K-dependent clotting factors II, VII, IX and X
5. Has a rapid onset, but short duration of action (3–6 hours)	Has a delayed onset, but long duration of action (3–6 days)
6. Therapy is monitored by measuring aPTT	Therapy is monitored by measuring INR
7. Overdosage is treated with protamine sulphate (antagonist)	Overdosage is treated with fresh frozen plasma and vitamin K ₁
8. Does not cross the placental barrier and is safe during pregnancy	Crosses placental barrier and has teratogenic potential
9. Heparin is used mainly to initiate therapy	For maintenance therapy
10. Expensive	Not expensive

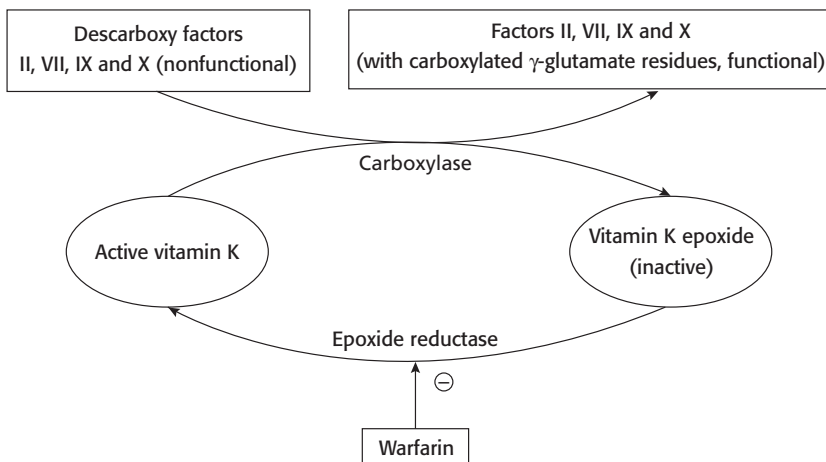


Fig. 8.2 The role of vitamin K in clotting and mechanism of action of warfarin.

Adverse Effects

1. **Bleeding:** Bleeding is the most important and common side effect of warfarin. Bleeding can occur anywhere – skin, pulmonary, gastrointestinal and urinary tract, etc. Oral anti-coagulant therapy is monitored by measuring international normalized ratio (INR).

$$\text{INR} = \left\{ \frac{\text{PT}_{\text{pt}}}{\text{PT}_{\text{ref}}} \right\}^{\text{ISI}}$$

PT_{pt} = Prothrombin time of patient;

PT_{ref} = Prothrombin time of reference sample; ISI = International sensitivity index.

Measurement of prothrombin time measured has been standardized internationally by each laboratory calibrating its own thromboplastin against the standard one.

If bleeding is mild, few doses of warfarin can be skipped till INR returns to desired range. If bleeding is severe, warfarin has to be stopped. Bleeding can be controlled by oral or parenteral vitamin K_1 (depending on severity). About 6–24 hours is required for the synthesis of clotting factors. Fresh frozen plasma should be given in severe bleeding for immediate replacement of clotting factors.

2. **Teratogenic effect:** Warfarin is contraindicated during pregnancy as it may cause nasal hypoplasia, CNS abnormalities, fetal haemorrhage, abortion or intrauterine death.
3. **Skin necrosis:** It is a rare complication that occurs within the first week of therapy. The skin lesions are commonly seen on breast, buttocks, abdomen and thighs.
4. **Other rare side effects:** These include diarrhoea, alopecia, urticaria, dermatitis, abdominal cramps and anorexia.

Drug Interactions

1. **Warfarin $\times$ cholestyramine:** Cholestyramine is a bile acid-binding resin. It binds to and reduces the absorption of warfarin from the gut, thus decreases the bioavailability of warfarin and its anticoagulant effect.
2. **Oral anticoagulants $\times$ barbiturates/carbamazepine/rifampicin:** They are enzyme inducers, increase metabolic clearance of oral anticoagulants and decrease the anticoagulant effect.
3. **Warfarin $\times$ oral contraceptives:** The levels of clotting factors increase leading to decreased anticoagulant effect.

4. *Warfarin* × *phenytoin/sulphonamides*: Warfarin is highly protein bound. These drugs displace warfarin from plasma protein binding site, increase the free plasma concentration of warfarin, which can result in bleeding (enhanced anticoagulant effect).
5. *Warfarin* × *erythromycin/metronidazole*: They decrease metabolic clearance of warfarin and increase the anticoagulant effect.
6. *Warfarin* × *tetracyclines*: Tetracyclines suppress the bacterial flora and decrease vitamin K production, hence potentiate warfarin effect.
7. *Warfarin* × *cefoperazone/ceftriaxone*: Severe bleeding can occur due to hypoprothrombinaemia.
8. *Warfarin* × *aspirin and other NSAIDs*: NSAIDs have an antiplatelet effect and displace warfarin from the plasma protein binding site, thus potentiate warfarin effect.

Factors Affecting Warfarin Action

- Liver disease and hyperthyroidism result in decreased levels of clotting factors – enhance anticoagulant effect of warfarin.
- Excessive intake of vitamin K and hereditary warfarin resistance decrease anticoagulant effect of warfarin.

Contraindications. The contraindications for warfarin are similar to heparin. In addition, warfarin is contraindicated in pregnancy.

Oral Direct Thrombin Inhibitor

Dabigatran Etexilate. It is a prodrug that is converted to dabigatran. It causes reversible inhibition of thrombin. Its anticoagulant effect is reversed by i.v. idarucizumab.

Factor Xa Inhibitors

Rivaroxaban and Apixaban. They are orally effective direct inhibitors of factor Xa.

Use. Dabigatran, rivaroxaban and apixaban are approved for prevention and treatment of venous thromboembolism (VTE). Advantages over warfarin include faster onset and shorter duration of action, lower incidence of bleeding, less drug interactions and no requirement for laboratory monitoring

Adverse effects. Bleeding can occur but risk is low

Therapeutic Uses of Anticoagulants

The main aim of anticoagulant therapy is to prevent formation of intravascular thrombus or further extension of the already formed clot. They do not break the clot or thrombus once it is formed. An oral anticoagulant, warfarin, is used for maintenance therapy but is usually started simultaneously as it has a delayed onset of action.

1. **Venous thromboembolism (VTE):** Venous thrombi are mainly formed of fibrin network with a long tail that can easily detach and result in embolization of pulmonary arteries. Anticoagulants are used for the treatment and prevention of thromboembolism. Treatment is initiated with parenteral anticoagulants, e.g. LMWH/UFH/fondaparinux (because of their rapid action). LMWH/fondaparinux are preferred over UFH as they are administered subcutaneously, have better bioavailability, are longer acting and usually do not require laboratory monitoring. For patients with VTE and coexisting severe renal disease, UFH is preferred. It is also indicated in patients who require anticoagulation but have a high risk of bleeding (postsurgery) due to its short lasting effect and reversibility with protamine. Warfarin is also started simultaneously with parenteral anticoagulant.

LMWH/fondaparinux/UFH is continued for about 4–5 days till effect of warfarin is obtained. Dabigatran, rivaroxaban and apixaban can be used for prophylaxis of deep vein thrombosis (DVT) and pulmonary thromboembolism following orthopaedic surgery like knee and hip replacement.

- 2. Atrial fibrillation:** Oral anticoagulants, e.g. warfarin, dabigatran, rivaroxaban and apixaban are used to reduce the risk of systemic embolization and stroke in patients with atrial fibrillation.
- 3. Myocardial infarction (MI):** Antiplatelets are the primary agents used in MI. In patients undergoing stenting, a short course of parenteral anticoagulants is administered.
- 4. Anticoagulants,** e.g. vitamin K antagonists (along with low-dose aspirin) are useful in patients with prosthetic valves to prevent thrombosis.

Summary of mechanism of action of anticoagulants

Anticoagulant	Mechanism of action	Clotting factors affected
Heparin (parenteral)	Activates AT III and forms heparin–AT III complex	Inactivates factors IIa, IXa, Xa, XIa, XIIa, XIIIa
LMWH (parenteral)	LMWH–AT III complex	Inactivates factor Xa
Fondaparinux (parenteral)	Fondaparinux–AT III complex	Inactivates factor Xa
Bivalirudin, argatroban (parenteral)	Direct inhibitors of thrombin	Thrombin
Dabigatran (oral)	Direct inhibitor of thrombin	Thrombin
Rivaroxaban, apixaban (oral)	Direct inhibition of Xa	Xa
Warfarin (oral)	Inhibits vitamin K epoxide reductase	Inhibits synthesis of clotting factors II, VII, IX, X

AT III, antithrombin III; LMWH, low-molecular-weight heparin.

FIBRINOLYTICS (THROMBOLYTICS)

PH1.25

In response to stimuli (injury, stasis), tissue plasminogen activator (t-PA) is released from vascular endothelium. It binds to fibrin-bound plasminogen and converts it to plasmin which degrades fibrin. Fibrinolytics are drugs that lyse thrombi rapidly by promoting conversion of plasminogen to plasmin. Plasmin degrades fibrin and rapidly dissolves the blood clot (Fig. 8.3).

Streptokinase, urokinase, alteplase, reteplase and tenecteplase are plasminogen activators (Table 8.2). Reteplase and tenecteplase are obtained from DNA recombinant technology. They have longer plasma half-life than alteplase. Tenecteplase requires only a single i.v. bolus injection and is more specific for fibrin-bound plasminogen.

Uses of Fibrinolytics

- 1. Acute MI:** The main aim of fibrinolytic therapy is to restore coronary artery patency. They are used as alternatives when reperfusion with PCI cannot be done. These drugs dissolve the clot by promoting the conversion of plasminogen to plasmin. They should be administered as early as possible once diagnosis is made. Early administration will help to decrease infarct size, improve left ventricular function and decrease mortality. Thrombolytic therapy is most effective if they are administered within 1 hour of onset of symptoms. As time

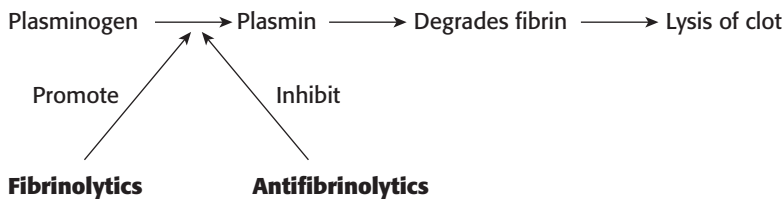


Fig. 8.3 Mechanism of action of fibrinolytics and antifibrinolytics.

Table 8.2 ■ Pharmacological properties of fibrinolytics

Streptokinase	Urokinase	Alteplase (rtPA)
1. It is a protein derived from β -haemolytic streptococci	It is an enzyme obtained from human fetal kidney cell culture	It is derived from recombinant DNA technology
2. It binds with plasminogen to form a complex that activates plasminogen to plasmin; both circulating and fibrin-bound plasminogen are activated	It directly activates plasminogen to plasmin	It has more effect on plasminogen that is bound to fibrin than circulating plasminogen
3. Streptokinase is • antigenic • pyrogenic • destroyed by circulating antistreptococcal antibodies, hence not suitable for repeated use • less expensive	Urokinase is • nonantigenic • nonpyrogenic	Alteplase is • nonantigenic • not destroyed by antibodies • rapid acting, • short half-life, so heparin has to be administered along with it to prevent rethrombosis • expensive
4. Administered by i.v. infusion	Administered initially as i.v. bolus, followed by i.v. infusion	Administered initially as i.v. bolus, followed by i.v. infusion
5. Adverse effects: Bleeding, hypotension, allergic reactions like fever, chills, skin rashes and rarely anaphylactoid reaction	Bleeding can occur; hypotension and allergic reactions are rare	Lower risk of bleeding and allergic reactions

between onset of symptoms to administration of fibrinolytics increases, benefit of therapy declines.

- 2. **DVT:** Thrombolytic therapy helps to provide symptom relief, improve limb perfusion and prevent pulmonary embolism.
- 3. **Pulmonary embolism:** Fibrinolytics are used to lyse the clot – improve pulmonary perfusion and right ventricular function.

Contraindications. These include recent trauma, recent surgery, recent abortion, recent stroke, severe hypertension, severe diabetes, severe liver damage, peptic ulcer and bleeding disorders.

ANTIFIBRINOLYTICS

Antifibrinolytics block the conversion of plasminogen to plasmin and inhibit the fibrinolytic activity (Fig. 8.3).

Epsilon-Amino Caproic Acid (EACA). It is administered orally or intravenously. It is used mainly to control bleeding due to overdose of fibrinolytics. Thrombosis can occur.

Tranexamic Acid. It is more potent than EACA. It is available for oral, i.v. and topical administration. It is used to control excessive bleeding due to fibrinolytic overdose, following dental extraction in haemophiliacs, menorrhagia, etc. Its side effects are nausea, vomiting, diarrhoea, headache, etc.

Antiplatelet Drugs (Fig. 8.4)

PH1.25

Drugs that inhibit platelet aggregation are called antiplatelet drugs.

Classification

1. **Thromboxane (TXA₂) synthesis inhibitor:** Low-dose aspirin.
2. **Phosphodiesterase inhibitor:** Dipyridamole.
3. **Purinergic (P2Y₁₂) receptor antagonists:** Ticlopidine, clopidogrel, prasugrel, cangrelor, ticagrelor.
4. **Glycoprotein (GP) II_b/III_a receptor antagonists:** Abciximab, eptifibatide, tirofiban.

TXA₂ Synthesis Inhibitor. Low-dose aspirin (50–325 mg/day) irreversibly acetylates platelet COX-1 and reduces the production of TXA₂. Since platelets cannot synthesize new enzymes, the antiplatelet effect lasts for the lifetime of the platelets, i.e. 7–10 days. In higher doses, aspirin inhibits both TXA₂ and PGI₂, hence antiplatelet efficacy is reduced. Common adverse effects are gastric irritation and bleeding.

Phosphodiesterase Inhibitor. Dipyridamole is a vasodilator. It inhibits phosphodiesterase and increases the concentration of cyclic adenosine monophosphate (cAMP) levels which inhibits platelet aggregation. It is occasionally used in combination with warfarin during postoperative period in patients with prosthetic heart valves.

P2Y₁₂ Receptor Antagonists. Adenosine diphosphate (ADP) released from platelets promotes their aggregation (Fig. 8.4)

Ticlopidine, clopidogrel and prasugrel are prodrugs and structurally related. They inhibit ADP-mediated platelet aggregation by irreversibly blocking purinergic (P2Y₁₂) receptors on the platelets. The antiplatelet effect persists even after discontinuation of the drugs. They produce synergistic effect when combined with aspirin or GP II_b/III_a antagonists. They are administered orally. Prasugrel has a faster onset of action and better antiplatelet effect than ticlopidine and clopidogrel. Bleeding is an important adverse effect; risk is more with prasugrel. The other adverse effect of ticlopidine and clopidogrel is diarrhoea. Neutropenia and thrombocytopenia are serious adverse effects of ticlopidine but rare with clopidogrel.

Ticagrelor inhibits ADP-mediated platelet aggregation by reversibly blocking platelet P2Y₁₂ receptors. It is rapid acting and more potent. It is administered orally. Nausea, dyspnoea, arrhythmias and bleeding are some of its adverse effects.

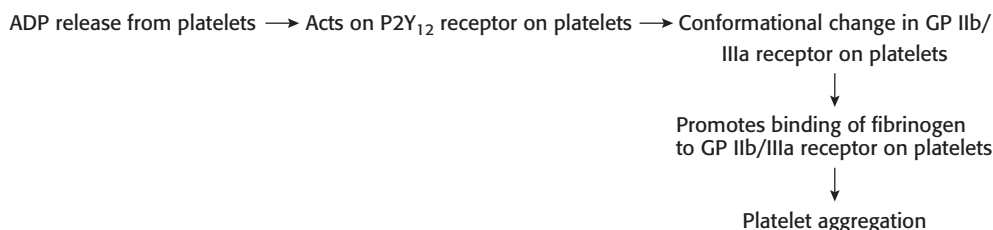


Fig. 8.4 Mechanism of platelet aggregation by adenosine diphosphate (ADP). P2Y₁₂, purinergic receptor; GP, glycoprotein. (Source: Adapted from Alfred Gilman Sr. and Louis S. Goodman: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12th edition, p. 868, Fig. 30-8, McGraw Hill, 2018.)

Glycoprotein IIb/IIIa Receptor Antagonists. Activation of GP II_b/III_a receptors on platelets favours binding of fibrinogen to these receptors resulting in platelet aggregation (Fig. 8.4) **Abciximab, eptifibatide and tirofiban** block GP II_b/III_a receptors on platelet surface to inhibit final step of platelet aggregation. Abciximab is a monoclonal antibody that binds to GP II_b/III_a receptor. Eptifibatide is a synthetic drug, which is more specific for GP II_b/III_a receptor. Tirofiban is a nonpeptide GP II_b/III_a receptor antagonist. They are useful as adjunctive therapy in high risk patients with acute coronary syndrome undergoing PCI. The main side effects of these drugs are bleeding and thrombocytopenia.

Thrombin Receptor Antagonist.

Vorapaxar blocks protease-activated receptor 1 (PAR-1) on the surface of platelets, thus produces antiplatelet effect. It is used as an adjunct with aspirin/clopidogrel in patients with MI and peripheral vascular disease. Bleeding is the main side effect.

Uses of Antiplatelet Agents

- 1. Acute coronary syndrome:** It includes acute MI and unstable angina. Dual antiplatelet therapy is used – incidence of MI, stroke and mortality is reduced. It decreases occurrence of reocclusion and reduces risk of stent thrombosis. Aspirin in combination with other antiplatelet is used. Patients with unstable angina/NSTEMI should receive low-dose aspirin with P2Y₁₂ blocker (ticagrelor/prasugrel/clopidogrel). In patients with STEMI, the antiplatelet to be used in addition to aspirin depends on reperfusion therapy – primary PCI or fibrinolytics. Aspirin with clopidogrel is used in patients with STEMI treated with fibrinolytics. Aspirin with ticagrelor/prasugrel is preferred in those patients undergoing primary PCI. If no reperfusion therapy is given, then ticagrelor is preferred. For patients at risk of recurrent ischaemic episodes, GP IIb/IIIa antagonist can be added to antiplatelet therapy.
- 2. Coronary artery disease:** Studies have shown that low-dose aspirin reduces the occurrence of subsequent MI, stroke and death in post-MI patients. Clopidogrel can be used as an alternative if aspirin cannot be used.
- 3. Prosthetic heart valves:** Valve thrombosis and thromboembolism are problems associated with prosthetic valves. Aspirin with warfarin reduces these risks. Dipyridamole may be used with warfarin to prevent thromboembolism in patients with prosthetic heart valves.
- 4. Transient ischaemic attack (TIA):** Early initiation of aspirin in patients with TIA reduces risk of recurrent attacks.
- 5. Peripheral artery disease:** Aspirin/clopidogrel may prevent thromboembolism.

Haematinics and Haematopoietic Growth Factors

PH1.35

Haematinics

Haematinics, such as iron, vitamin B₁₂, folic acid, etc. are essential for the formation of blood. They are used in the treatment of anaemia. In anaemia, there is decreased oxygen-carrying capacity of blood due to reduction in blood haemoglobin (Hb) level and number of circulating RBCs. Anaemia results from deficiency of nutrients (iron, vitamin B₁₂, folic acid), depression of bone marrow (due to cytotoxic drugs, radiation, etc.), blood loss (e.g. hookworm infestation, GI bleeding, etc.) and RBC destruction.

Iron. Iron is an essential element of the body. The important sources are liver, fish, dry fruits, jaggery, spinach, banana, meat, etc. Iron is a component of haemoglobin (Hb), myoglobin and a number of enzymes necessary for oxygen transfer (cytochrome, catalases, etc.). The total amount of iron in an adult male is about 4 g.

Pharmacokinetics. Dietary iron exists in ferric form, which is reduced to ferrous iron with the help of acid in the stomach (Fig. 8.5). Absorption of most of the iron takes place in the duodenum and upper jejunum. Iron absorption is regulated by a protein, apoferritin, in the intestinal mucosal cells. Ferrous iron is oxidized in mucosal cells to ferric iron and this combines with apoferritin to form ferritin. From ferritin, iron is very slowly released, so iron (as ferritin) will be in the mucosal cells for a long time.

The ferrous iron in plasma is oxidized again to ferric iron. This ferric iron gets bound to transferrin (transport protein). This is taken up by various tissues like reticulocytes in the bone marrow (Hb synthesis), reticuloendothelial cells in liver, spleen, etc. and stored. Small amount of iron is excreted from the body mainly by shedding of GI mucosal cells, desquamated skin, very little in the bile, sweat and least in urine.

Factors Affecting Iron Absorption. Iron absorption is enhanced by acidic pH of the stomach, ascorbic acid, cysteine, etc., which reduce the ferric iron to ferrous form. Iron

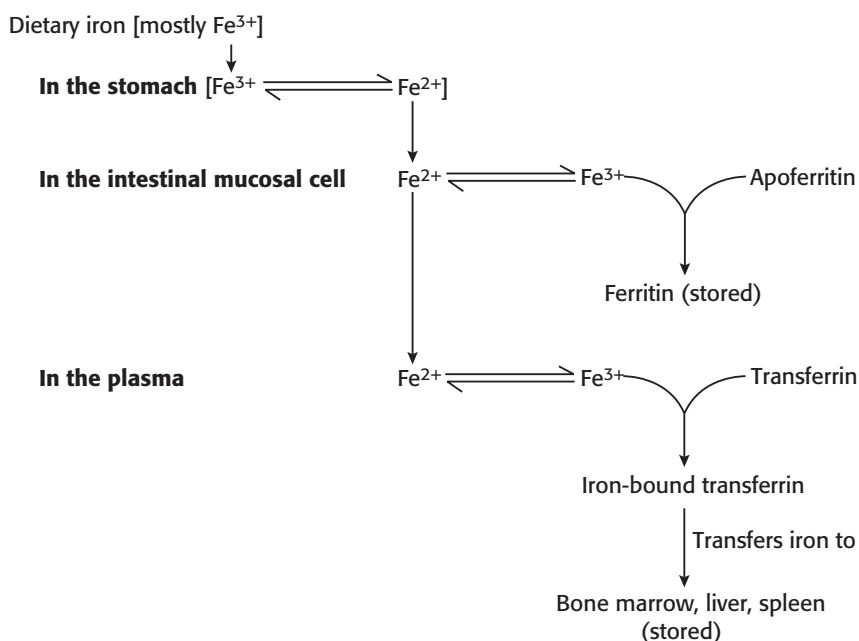


Fig. 8.5 Schematic representation of iron absorption and storage.

deficiency states also increase the absorption of iron. Iron absorption is inhibited by excess of phosphates, oxalates, phytates, etc. Milk, antacids and tetracyclines reduce iron absorption by forming insoluble complexes. Absorption of oral iron is more in empty stomach.

Preparations of Iron

Oral Preparations. Oral administration of iron is convenient for the patient. The amount of elemental iron in each compound is important. Various preparations are as follows:

1. *Ferrous sulphate* contains 20% (hydrated salt) and 32% (dried salt) elemental iron. It is the oldest and cheapest iron preparation.
2. *Ferrous fumarate* contains 33% elemental iron.
3. *Ferrous gluconate* contains 12% elemental iron.

Other oral preparations are *ferrous succinate*, *iron choline citrate*, *ferric ammonium citrate*, *colloidal ferric hydroxide* (50% elemental iron), *carbonyl iron* (highly purified metallic iron), etc.

Adverse effects of oral iron are nausea, vomiting, epigastric discomfort, dyspepsia, metallic taste, constipation or diarrhoea and staining of teeth (with liquid preparation).

Parenteral Preparations

1. **Iron sorbitol citric acid complex:** It is given intramuscularly, but never intravenously.
2. **Iron dextran:** It can be administered intravenously or intramuscularly.
3. Newer formulations like **ferrous sucrose, ferric carboxymaltose, iron isomaltoside and ferumoxytol** are administered intravenously. Hypersensitivity reactions are less frequent as compared to older formulations of parenteral iron.

Indications for Parenteral Iron Therapy

1. Intolerance to oral iron
2. Malabsorption of iron
3. Noncompliance to oral iron
4. Severe iron deficiency
5. Patients with renal disease receiving erythropoietin

The total dose of iron (including amount required to replenish the stores) is calculated using the formula

$$\text{Iron requirement (mg)} = 4.4 \times \text{body weight (kg)} \times \text{Hb deficit (g/dL)}$$

(Normal Hb: in men = 14–16 g%; women = 12–14 g%)

1. **Intramuscular therapy:** The preparations used are

- Iron dextran complex
- Iron sorbitol–citric acid complex

The recommended adult dose is 100 mg daily (2 mL) or on alternate days until the total required dose is administered or to a maximum of 2 g. To prevent staining of the skin, injections are given deep intramuscularly into the buttock using 'Z-track' technique (pull the skin and underlying subcutaneous tissue at the site of injection to one side before injecting the drug).

2. **Intravenous therapy:** The preparations used are

Iron dextran (low molecular weight): It can be administered as a total dose infusion. The total dose required is diluted in 500 mL of normal saline and infused slowly intravenously over 6–8 hours, after administering a test dose, under constant supervision. It can also be given intravenously slowly in small doses of 2 mL daily.

Ferrous sucrose: It is administered as multiple infusions. It is useful in patients with chronic kidney disease.

Ferric carboxymaltose: It is an iron hydroxide complex with iron bound to a carbohydrate. It is administered as i.v. infusion.

Iron isomaltoside: It consists of tightly bound iron. There is slow release of labile-free iron from this preparation. Since it is administered as single i.v. infusion, it is convenient for patients.

Ferumoxytol: It has superparamagnetic iron oxide nanoparticles coated with carbohydrate. It is indicated for use in anaemia of chronic kidney disease.

Adverse Effects. The i.m. injections are painful, may cause abscess and discolouration of the skin at the site of injection. The systemic side effects following administration by i.m./i.v. routes are headache, pyrexia, nausea, vomiting, arthralgia, lymphadenopathy, urticaria and circulatory collapse. Anaphylactoid reaction can occur. All patients should be monitored when receiving i.v. infusion of iron preparation. Facilities for resuscitation should be available. Hypersensitivity reactions are more frequent with older than newer formulations.

Therapeutic Uses of Iron

1. To treat iron-deficiency anaemia (microcytic hypochromic anaemia)

- a. During pregnancy
- b. Due to blood loss
- c. Due to nutritional iron deficiency
- d. Due to poor absorption of iron from the gut

Most of the patients can be treated with oral iron. For treatment of iron-deficiency anaemia, 200 mg of elemental iron is required per day. Ferrous sulphate is the most commonly used preparation 200 mg of ferrous sulphate (60 mg elemental iron) is given thrice daily after food (to minimize gastric irritation). There is a feeling of well-being within few days of therapy. Treatment should be continued till the Hb level returns to normal (usually 4–8 weeks), and later, iron should be continued for at least 3–6 months to replenish iron storage. The expected rise in Hb concentration after iron therapy is 0.7–1 g/dL/week. Initially, the rate of Hb increase is rapid but later it is slow. Response to parenteral iron is not faster than oral iron but iron stores are more quickly filled up.

- 2. Prophylaxis:** Prophylactic iron therapy is usually indicated during pregnancy and infancy. Iron is required prophylactically to meet the increased demand by the growing fetus and uterus and to combat loss during labour. For prophylaxis, 100 mg of elemental iron is administered daily starting from second trimester. Folic acid 0.5 mg/day is given from the first trimester to prevent neural tube defects. Treatment of megaloblastic anaemia with vitamin B₁₂/folic acid results in a brisk haematologic response. If iron stores are inadequate, increased demands of iron cannot be met. So, iron must be supplemented in such patients.

Acute Iron Poisoning. It is seen frequently in young children. The manifestations are nausea, vomiting, epigastric pain, bloody diarrhoea, dehydration, cyanosis, drowsiness, hyperventilation, metabolic acidosis, convulsions, coma and death.

Treatment

1. General measures
2. Specific therapy

General Measures. Supportive measures: Airway, breathing, circulation, fluid and electrolyte balance should be maintained.

Vomiting can be induced to remove iron from the stomach. Gastric lavage with sodium bicarbonate precipitates iron and reduces its absorption. Diazepam i.v. slowly to control convulsions.

Specific Therapy. Desferrioxamine (deferioxamine), a potent iron chelating agent, is administered by i.v. infusion or intramuscularly depending on the severity of poisoning. It binds with iron in the blood and facilitates its excretion. Deferiprone, an oral iron chelator, is less effective than desferrioxamine in acute poisoning. Calcium edetate is also useful in iron poisoning.

Maturation Factors

Maturation factors are vitamin B₁₂ and folic acid. Both vitamin B₁₂ and folate are essential for DNA synthesis. The deficiency of one or both results in defective DNA synthesis and megaloblastic anaemia.

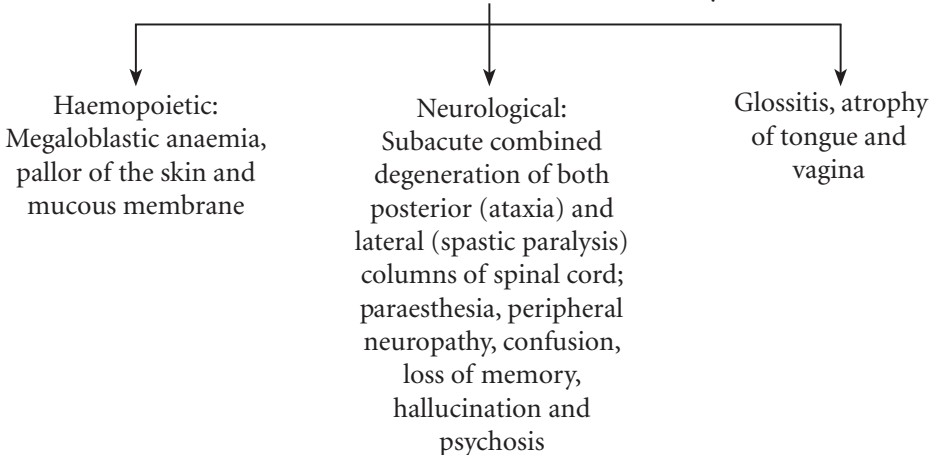
Vitamin B₁₂. Vitamin B₁₂ is a cobalt-containing compound which is synthesized by the colonic bacteria and is present in the food of animal origin, such as meat, liver, egg, fish, etc. Vitamin B₁₂ is essential for normal haemopoiesis and maintenance of normal myelin.

Functions. Vitamin B₁₂ acts as a coenzyme in certain metabolic pathways. Methylcobalamin (methyl B₁₂) and deoxyadenosylcobalamin (DAB₁₂) are the coenzyme forms of vitamin B₁₂. Methylcobalamin is necessary for the conversion of homocysteine to methionine, whereas for the conversion of methylmalonyl CoA to succinyl CoA, DAB₁₂ is required.

Pharmacokinetics. The ingested vitamin B₁₂ complexes with intrinsic factor (IF) in the stomach, which is secreted by gastric parietal cells. The vitamin B₁₂-IF complex reaches terminal ileum, where it binds to specific receptors and vitamin B₁₂ gets absorbed into blood. In blood, vitamin B₁₂ is bound to transcobalamin-II and is transported to various cells of the body. Excess vitamin B₁₂ is transported to liver for storage. Vitamin B₁₂ is excreted in bile and undergoes enterohepatic cycling.

Deficiency of vitamin B₁₂ can be due to pernicious anaemia, malabsorption, fish tapeworm infestation, increased demand and rarely, inadequate intake.

Manifestations of vitamin B₁₂ deficiency



Preparations. Cyanocobalamin (oral, i.m. or s.c.), hydroxocobalamin (i.m.) and methylcobalamin (oral). Vitamin B₁₂ is available for oral and parenteral administration (never intravenously because of risk of anaphylaxis). The choice of a route depends on

the cause of deficiency. As hydroxocobalamin is more plasma protein bound, it produces a sustained effect. But, in some patients antibodies may be formed against protein–vitamin B₁₂ complex resulting in a decrease in its levels.

Uses. Pernicious anaemia: It is due to autoimmune destruction of the gastric parietal cells that synthesize IF. Vitamin B₁₂ is administered lifelong. Response is seen within 24–48 hours of start of treatment. There is a sense of well-being, appetite improves. Reticulocytes increase after 2 days; increase in Hb levels occurs later. Neurological signs present for few months will disappear but those of long duration may not subside. Administration of folic acid alone in vitamin B₁₂ deficiency may correct the megaloblastic anaemia but will aggravate or precipitate neurological abnormalities. This is due to utilization of small quantities of vitamin B₁₂ present in the body for haemopoiesis.

Other uses. Prophylactic therapy with vitamin B₁₂ is indicated in patients at high risk of developing deficiency, e.g. patients who have undergone gastrectomy.

Oral methylcobalamin has been used in the treatment of diabetic and other neuropathies. In tobacco amblyopia, weekly injection of hydroxocobalamin is administered as it binds to cyanide.

Folic Acid. Folic acid is a combination of glutamic acid, para-aminobenzoic acid and pteridine nucleus. It is abundantly found in fresh green leafy vegetables, liver, yeast, kidney, fruits, etc. Much of it is destroyed by cooking. Minimum daily requirement of an adult is 50–100 mcg. The requirement of folic acid increases during pregnancy and lactation, i.e. 500–800 mcg/day.

Pharmacokinetics. Most of the dietary folic acid is found as polyglutamates, but these are not absorbed unless they are cleaved to monoglutamate by the action of intestinal enzyme folate conjugase. It is readily absorbed in the proximal part of the jejunum. In the mucosa of the jejunum, it is reduced to tetrahydrofolate and then gets methylated. In blood, it is transported to various tissues as methyl tetrahydrofolate (MTHF). Constant supply of MTHF is maintained by food intake and enterohepatic cycling. Folate is stored mainly in liver. The stores are exhausted in about 3–4 months, hence the manifestations of folate deficiency appear in about 3–4 months.

Folic acid itself is inactive. Its active form, tetrahydrofolate, is essential for the biosynthesis of amino acids, purines, pyrimidines, choline, DNA and therefore in cell division.

Causes of Folate Deficiency

1. Dietary deficiency: most common.
2. Decreased absorption (malabsorption, tropical sprue).
3. Diminished storage (hepatic disease, vitamin C deficiency).
4. Drug induced (phenytoin, antifolates, e.g. methotrexate, trimethoprim, pyrimethamine).
5. Increased demand (pregnancy, lactation, haemolytic anaemias).

Manifestations of Folate Deficiency

1. Megaloblastic anaemia – microscopically the blood picture is similar in both folate and vitamin B₁₂ deficiency.
2. Glossitis, diarrhoea, general weakness and weight loss.

Preparations. Folic acid is available for oral (tablet and liquid) and parenteral administration (combination with other vitamins or iron).

Folinic acid (calcium leucovorin) is used in the treatment of methotrexate toxicity and as an adjuvant in methanol poisoning.

Uses

- 1. **Megaloblastic anaemias** due to nutritional folate deficiency, increased demand (pregnancy and lactation), pernicious anaemia (along with vitamin B₁₂) and antiepileptic therapy (e.g. phenytoin).
Folic acid is given orally in a dose of 1–5 mg daily and continued for about 3–4 months. Administration of folic acid alone in vitamin B₁₂ deficiency may correct the megaloblastic anaemia but will aggravate or precipitate neurological abnormalities. This results from use of small quantities of vitamin B₁₂ present in the body for haemopoiesis.
- 2. **Prophylactic therapy:** During pregnancy, routine prophylactic folic acid 0.5 mg/day is given from the first trimester to prevent neural tube defects.
- 3. **Methotrexate toxicity:** Folinic acid, active form of folic acid, is used to antagonize methotrexate toxicity.
- 4. To increase the anticancer effect of 5-fluorouracil, folinic acid is coadministered with it.

Adverse Effects. Oral folic acid is safe, but injections may rarely cause hypersensitivity reactions.

Haematopoietic Growth Factors

They stimulate growth and differentiation of blood cells. They include erythropoietin, myeloid and thrombopoietic growth factors (Table 8.3). They are usually administered parenterally.

Erythropoietin. Erythropoietin is produced by peritubular interstitial cells of the kidney in response to hypoxia. Erythropoietin stimulates erythropoiesis by acting on the erythropoietic stem cells in bone marrow.

Commercially, erythropoietin is produced by recombinant DNA technology. It is administered by i.v. or s.c. route. The preparations available are epoetin alfa and darbepoetin alfa.

Uses. Erythropoietin is used in anaemia associated with renal failure, anticancer drugs, zidovudine-induced anaemia in HIV patients, etc.

Adverse Effects. These include rise in blood pressure, haematocrit and thromboembolic complications. Rarely, allergic reactions also may occur. Flu-like symptoms, nausea, vomiting and tachycardia can occur with epoetin

Table 8.3 ■ Functions and uses of myeloid and thrombopoietic growth factors PH1.35

Drug	Function	Uses
Myeloid growth factors, e.g. human granulocyte colony stimulating factor (G-CSF): <i>filgrastim</i> ; human granulocyte macrophage colony stimulating factor (GM-CSF): <i>sargramostim</i>	Stimulate proliferation and differentiation of WBCs	Patients whose WBCs are suppressed by anticancer or antiretroviral drugs
Thrombopoietic growth factors, e.g. interleukin-11 (<i>oprelvekin</i>) and recombinant <i>thrombopoietin</i>	Stimulate production of platelets	To treat cancer chemotherapy-induced thrombocytopenia

Endocrine Pharmacology

Introduction

Hormone is a substance produced by specialized cells in specific glands and transported to a distance where it acts on target tissues.

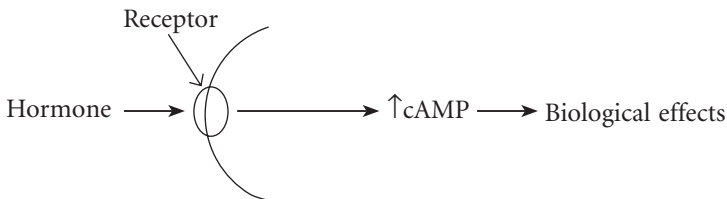
Types of Hormones

1. **Peptides:** Hypothalamic regulatory hormones, pituitary hormones, insulin, glucagon, parathyroid hormones.
2. **Steroids:** Adrenocortical hormones, sex steroids.
3. **Catecholamines:** Adrenaline, noradrenaline.
4. **Others:** Thyroxine (T_4), triiodothyronine (T_3).

Site and Mode of Action of Hormones. They act on their specific receptors situated:

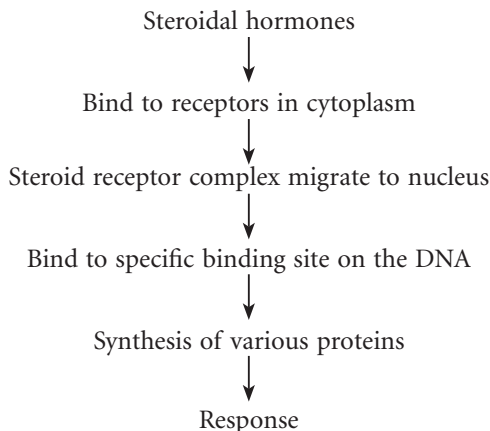
1. On the cell membrane:

- (a) Some hormones bind with the cell membrane receptors and increase cAMP concentration, e.g. catecholamines, most of the peptide hormones.

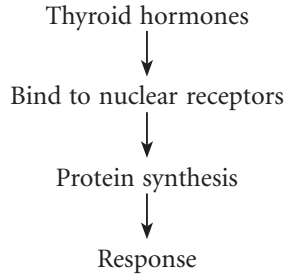


- (b) Some hormones cause inhibition of cAMP production by binding to cell membrane receptors, e.g. somatostatin.

2. In the cytoplasm:



3. In the nucleus:



Hypothalamic and Pituitary Hormones

PH1.37

HYPOTHALAMIC REGULATORY HORMONES

Hypothalamus produces releasing and inhibitory hormones that control pituitary secretion (Fig. 9.1). **Hypothalamus** controls the secretion of anterior pituitary through portal circulation that carries the releasing and inhibitory hormones. Posterior pituitary is the direct extension of hypothalamus.

ANTERIOR PITUITARY HORMONES

1. Growth hormone (GH)
2. Prolactin (PRL)
3. Gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH])
4. Adrenocorticotrophic hormone (ACTH)
5. Thyrotropin- or thyroid-stimulating hormone (TSH)
6. Melanocyte-stimulating hormone (MSH)

Growth Hormone–Releasing Hormone (GHRH). It stimulates anterior pituitary to synthesize and release growth hormone. It is used rarely for testing growth hormone responsiveness.

Growth Hormone. It is a peptide hormone released by anterior pituitary. Its secretion is regulated by hypothalamic hormones.

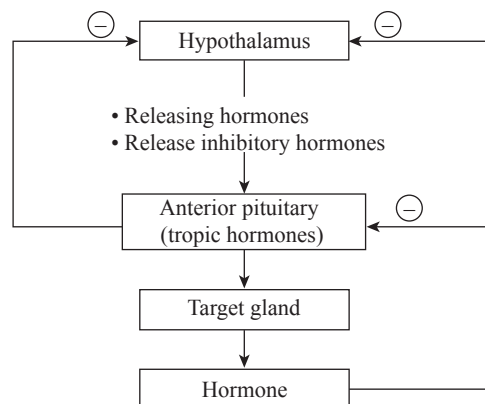


Fig. 9.1 Regulation of anterior pituitary hormone synthesis and release. ⊖, Inhibition.

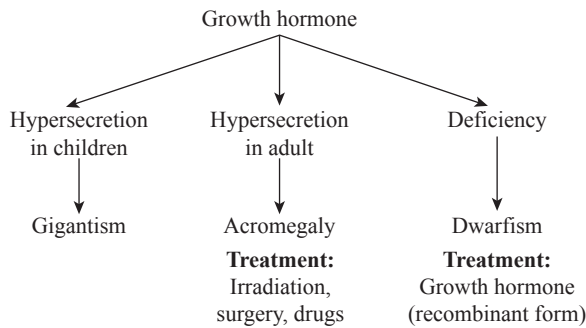


Fig. 9.2 Clinical disorders of growth hormone.

Functions of Growth Hormone. It has growth-promoting effect; produces anabolic effect on muscle. It maintains positive nitrogen balance; promotes utilization of fat.

Clinical Disorders of Growth Hormone (Fig. 9.2)

Uses. Recombinant human GH (somatropin and somatrem) is available for parenteral administration. It is used to treat

- Growth hormone deficiency in children and adults. Following early initiation of treatment with GH in children, stature can be almost normal. In adults, body fat is reduced.
- AIDS-related wasting.

Mecasermin is a recombinant human IGF-1 (insulin-like growth factor 1). It is administered parenterally to promote growth in children with IGF deficiency not responding to GH. The adverse effects are hypoglycaemia (can be avoided by giving the drug after food) and lipodystrophy.

Somatostatin. It is a peptide hormone secreted by pancreas and parts of the central nervous system (CNS) in addition to hypothalamus. Somatostatin inhibits release of growth hormone, glucagon, insulin and gastrin. Other actions include constriction of hepatic, splanchnic and renal blood vessels. It has a very short half-life (1–3 minutes). Hence, its **synthetic analogue octreotide** is preferred for therapeutic use.

Octreotide. It is more potent and longer acting than somatostatin. Unlike somatostatin, it mainly inhibits growth hormone secretion. It can be administered subcutaneously and intravenously.

Uses of Octreotide

1. Acromegaly.
 2. Symptomatic treatment of various hormone-secreting tumours, e.g. carcinoid syndrome.
 3. Diarrhoea associated with diabetes.
 4. Acute control of bleeding from oesophageal varices. It constricts hepatic blood vessels and decreases variceal bleeding.
- The common side effects of octreotide are nausea, diarrhoea and abdominal cramps.

Lanreotide. It is a somatostatin analogue with a long duration of action.

Drugs Used to Treat Acromegaly

1. **Somatostatin analogues:** Octreotide is used to treat acromegaly when surgery and irradiation are contraindicated. It acts by inhibiting synthesis and release of growth hormone. Lanreotide can also be used.
2. **Dopamine-receptor agonists:** Dopamine agonists like bromocriptine and cabergoline stimulate the secretion of GH in normal subjects but paradoxically decrease GH secretion in patients with acromegaly. Hence, they can be used to treat acromegaly when patients are unwilling to take regular injection.
3. **Pegvisomant** (GH-receptor antagonist): It is used subcutaneously to treat acromegaly in patients not responding to somatostatin analogues.

Thyrotropin-Releasing Hormone. Thyrotropin-releasing hormone (TRH) is now rarely used to diagnose thyroid disorders as very sensitive assays for thyrotropin and thyroid hormones are now available.

Corticotropin-Releasing Hormone. Corticotropin-releasing hormone (CRH) stimulates release of ACTH from anterior pituitary. CRH is used only for diagnosis of hypercorticism to distinguish between Cushing disease and ectopic ACTH secretion.

Gonadotropin-Releasing Hormone. Pulsatile gonadotropin-releasing hormone (GnRH) secretion stimulates gonadotroph cells in the anterior pituitary to synthesize and release LH and FSH. Sustained nonpulsatile administration of GnRH or its analogues can be used for initial stimulation and later suppression of gonadal hormone secretion.

Gonadotropins (Gns)

Follicle-Stimulating Hormone. The functions of FSH are

In females	–	development of ovarian follicles
	–	ovarian steroidogenesis
In males	–	regulation of spermatogenesis
	–	conversion of testosterone to oestrogen in Sertoli cells.

Preparations of FSH

- Urofollitropin – obtained from urine of postmenopausal women
- Follitropin alfa and follitropin beta – recombinant forms of FSH

Luteinizing Hormone. The functions of LH are

In females	–	ovarian steroidogenesis
	–	ovulation
In males	–	testosterone production by Leydig cells

Preparations of LH. Lutropin, recombinant form of LH, is available for use.

Human Chorionic Gonadotropin. It is secreted by placenta – helps to maintain corpus luteum of pregnancy. It exerts its actions through LH receptors. Human chorionic gonadotropin (hCG) purified from urine and a recombinant form of hCG are available for use.

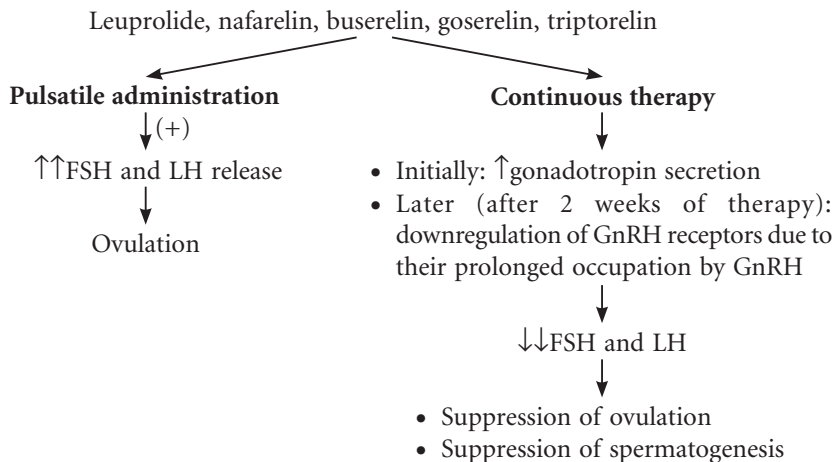
Uses of FSH, LH and hCG

- For controlled ovarian hyperstimulation in assisted reproduction technology.
- Stimulation of spermatogenesis in hypogonadal infertile males.

Adverse Effects of FSH, LH and hCG. Ovarian hyperstimulation syndrome and multiple pregnancy in females; gynaecomastia in males.

Gonadorelin. It is a synthetic human GnRH. Pulsatile administration stimulates the release of FSH and LH → increased release of oestrogen and progesterone. It has a short duration of action; is administered i.v. or s.c.; useful to test function of pituitary – gonadal axis.

GnRH Analogues (Superactive GnRH Agonists). For example:



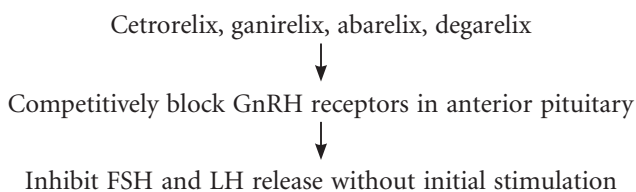
GnRH analogues are commonly administered subcutaneously. Nafarelin is available as nasal spray.

Uses of GnRH Analogues

- Prostatic carcinoma
- Precocious puberty
- Breast cancer in premenopausal women
- Uterine fibroid, endometriosis
- Polycystic ovarian disease
- Controlled ovarian hyperstimulation in assisted reproduction

Adverse Effects. Hot flushes, loss of libido and vaginal dryness can occur.

GnRH Antagonists. For example:



- Males: Decrease testosterone level; useful in advanced prostate cancer
- Females: To suppress LH surge during controlled ovarian hyperstimulation

Advantages of GnRH antagonists over GnRH agonists include quick onset of action and lower risk of ovarian hyperstimulation syndrome.

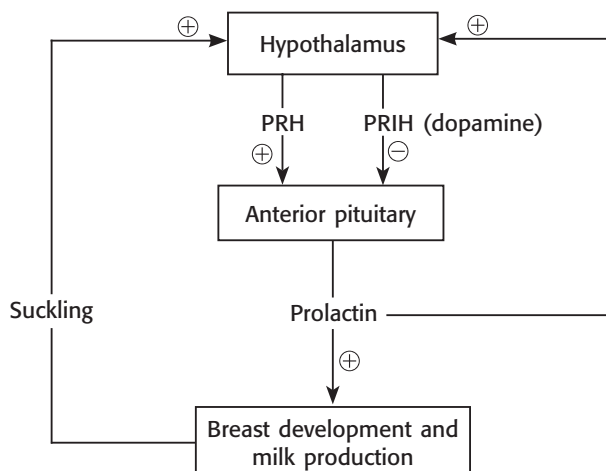


Fig. 9.3 Regulation of prolactin secretion. PRH, prolactin-releasing hormone; PRIH, prolactin-release inhibitory hormone.

Prolactin. Prolactin is a peptide hormone secreted by anterior pituitary. It is also known as mammotropin or lactogenic hormone.

Control of prolactin secretion is mainly inhibitory unlike other anterior pituitary hormones (Fig. 9.3). Dopamine, secreted by hypothalamus, inhibits prolactin secretion. Thus, dopamine agonists (bromocriptine, cabergoline) inhibit prolactin secretion whereas dopamine antagonists (e.g. chlorpromazine, haloperidol, metoclopramide) cause increase in prolactin levels.

Hyperprolactinaemia. This is a relatively common condition resulting from hypothalamic or pituitary disorders. The common causes are prolactin-secreting pituitary adenomas and dopamine antagonists. For prolactin-secreting tumours, treatment options are surgery, irradiation and drugs. Postoperatively, most of the patients require treatment with dopamine-receptor agonists. These drugs decrease both prolactin secretion and size of adenoma.

Dopamine-Receptor Agonists. Bromocriptine is the prototype of ergot-derived dopamine agonist. Other ergot derivatives used to treat hyperprolactinaemia are *pergolide* and *cabergoline*.

Bromocriptine. It is a semisynthetic ergot derivative acting as a potent dopamine agonist (mainly at D₂-receptors). As dopamine is a neurotransmitter at different sites in the brain, it produces various motor, behavioural and endocrine effects.

Pharmacological Actions

1. Endocrine:

- Dopamine (prolactin release-inhibiting hormone, PRIH) is the main factor controlling prolactin secretion. Bromocriptine, a dopamine agonist, effectively reduces the secretion of prolactin.
- Bromocriptine increases GH level in normal individuals, but in patients with acromegaly, it acts paradoxically to reduce GH levels.

2. It relieves symptoms of parkinsonism that results from dopamine deficiency in nigrostriatal pathway.
3. Nausea and vomiting may occur with bromocriptine due to stimulation of dopamine receptors in chemoreceptor trigger zone (CTZ).
4. It may cause hypotension due to α -adrenergic blockade.

Pharmacokinetics. Bromocriptine is partly absorbed after oral administration, undergoes first-pass metabolism extensively and metabolites are excreted in bile.

Uses. It is useful in hyperprolactinaemia, acromegaly, parkinsonism and restless leg syndrome.

Adverse Effects

1. Gastrointestinal tract (GIT): Nausea, vomiting and constipation
2. Cardiovascular system (CVS): Postural hypotension – due to α -adrenergic blockade
3. CNS: Hallucinations, confusion and psychosis

Cabergoline. It is more potent and longer acting than bromocriptine. It is the preferred drug for hyperprolactinaemia. It is also useful in acromegaly.

Thyroid and Antithyroid Drugs

PH1.36

The hormones secreted by the thyroid gland are thyroxine (T_4), triiodothyronine (T_3) and calcitonin. The thyroid follicular cells have specialized mechanism for synthesis of thyroid hormones. This is regulated by TSH secreted by anterior pituitary, which, in turn, is inhibited by free thyroid hormone levels (Fig. 9.4). The 'C' cells of thyroid secrete calcitonin which is a functionally distinct hormone regulating calcium metabolism.

The deficiency of thyroid hormones in children results in cretinism characterized by mental retardation and other features of hypothyroidism (Table 9.1); in adults, it results in myxoedema. Hypersecretion of these hormones also has effects on various organ systems resulting in 'thyrotoxicosis'.

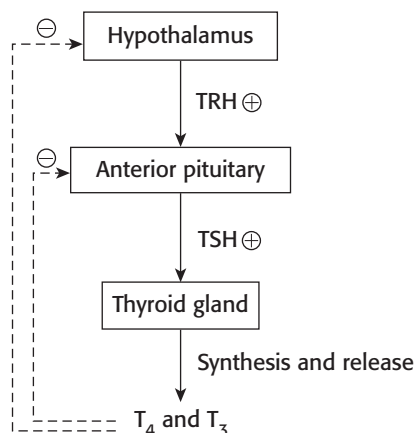


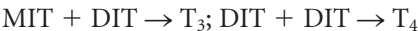
Fig. 9.4 Control of thyroid hormone synthesis and release. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; ⊕, stimulation; ⊖, inhibition.

Table 9.1 ■ Features of hyperthyroidism and hypothyroidism

System	Hyperthyroidism (thyrotoxicosis)	Hypothyroidism (myxoedema)
1. Metabolic • Lipid • Carbohydrate • Protein	Increased basal metabolic rate (BMR) Decreased cholesterol and triglycerides Increased glycogenolysis and gluconeogenesis → hyperglycaemia Negative nitrogen balance and wasting	Decreased BMR Hypercholesterolaemia Hypertriglyceridaemia Hypoglycaemia in severe myxoedema Positive nitrogen balance and weight gain due to accumulation of mucoproteins
2. Cardiovascular system	Increased heart rate, stroke volume, cardiac output with decreased peripheral vascular resistance, high-output cardiac failure, arrhythmias, angina	Decreased heart rate, stroke volume and cardiac output, low-output cardiac failure, pericardial effusion
3. CNS	Nervousness, anxiety	Lethargy and mental retardation in cretinism
4. Musculoskeletal system	Weakness, muscle fatigue, increased deep tendon reflexes, hypercalcaemia, osteoporosis	Stiffness and muscle fatigue
5. Gastrointestinal tract	Increased appetite, diarrhoea	Decreased appetite, constipation, ascites
6. Haematopoietic system	Anaemia due to increased RBC turnover, usually normochromic	Anaemia due to decreased RBC production – may be normochromic, hyperchromic or hypochromic
7. Reproductive system	Menstrual irregularities, decreased fertility	Menorrhagia, infertility, decreased libido, impotence, oligospermia
8. Eyes and face	Lid retraction, periorbital oedema, exophthalmos	Puffy face, large tongue
9. Skin and appendages	Warm moist skin; heat intolerance; fine, thin hair	Pale, dry skin, intolerance to cold, brittle hair and nail

SYNTHESIS OF THYROID HORMONES

- 1. Iodide trapping:** Active transport of iodide ions (I^-) into follicular cells of thyroid gland is known as iodide trapping and takes place by a basement membrane protein called sodium/iodide symporter.
- 2. Oxidation and iodination:** The iodide ion is oxidized to iodine by peroxidase enzyme. Iodine combines with tyrosine residues of thyroglobulin molecule and forms monoiodotyrosine (MIT) and diiodotyrosine (DIT).
- 3. Coupling:** This is the final step in the synthesis of thyroid hormones and is catalysed by thyroid peroxidase. Two molecules of DIT couple to form thyroxine (T_4) and one molecule of MIT with one molecule of DIT forms triiodothyronine (T_3).

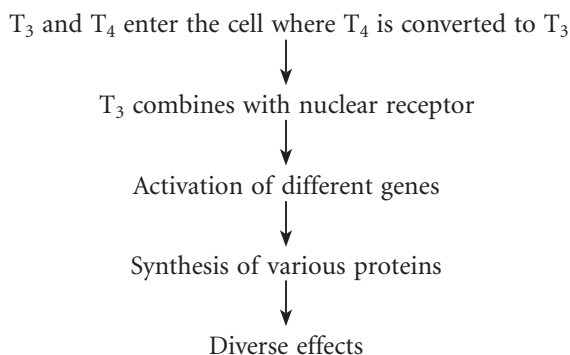


4. **Hormone release:** Release of thyroid hormones takes place under the control of TSH. The process involves endocytosis and proteolysis of iodinated thyroglobulin and results in release of T_4 , T_3 , MIT and DIT.
5. **Peripheral conversion of T_4 to T_3 :** Most of the hormone released from thyroid is T_4 , which is less potent than T_3 . Conversion of T_4 to T_3 occurs mainly in liver and kidney. Peripheral conversion of T_4 to T_3 is inhibited by propylthiouracil, iopanoic acid, propranolol and glucocorticoids.

Differences between T_3 and T_4

T_3 (Triiodothyronine)	T_4 (Thyroxine)
Formed by $DIT + MIT = T_3$	Formed by $DIT + DIT = T_4$
Relatively rapid onset of action	Slower onset of action
Short duration of action (half-life: 1 day)	Long duration of action (half-life: 7 days)
More potent than T_4	Less potent
Useful to treat myxoedema coma	Used to treat myxoedema coma and for regular treatment of myxoedema

Mechanism of Action. Mechanism of action of thyroid hormones is similar to that of steroid hormones. Thyroxine needs to be converted into T_3 inside the cell for binding to nuclear receptor.



Preparations

1. Levothyroxine sodium (T_4): tablets and parenteral preparation (i.v.)
2. Liothyronine (T_3 , triiodothyronine): oral tablets, parenteral preparation (not commonly available)
3. Combination of T_4 and T_3 (4:1): tablets

Therapeutic Uses. Replacement therapy in hypothyroid states

1. **Cretinism and myxoedema:** For cretinism, treatment of newborn should be started as early as possible after birth to ensure normal growth and cognitive development. Replacement in elderly and patients with coronary artery disease should be started with low dose of levothyroxine sodium such as 12.5–25 mcg daily and slowly increased to prevent precipitation of ischaemia and myocardial infarction. In young adults with hypothyroidism, full replacement doses of levothyroxine sodium can be administered (50–100 mcg daily as a single dose orally in the morning on an empty stomach). The goal of therapy is to relieve symptoms and restore serum TSH to normal levels; treatment is for lifetime.

2. **Myxoedema coma:** This is a medical emergency and usually common in long-standing untreated myxoedema cases. It is usually precipitated by infection or other forms of stress.

Diagnosis

- Clinical features: Hypothermia, bradycardia, pleural effusion, pericardial effusion with coma.
- History of previous thyroid surgery or replacement therapy with poor compliance.
- Estimation of plasma levels of T_3 , T_4 and TSH.
- Treatment should be started based on clinical features without waiting for confirmation.

Treatment

- (a) Levothyroxine, intravenously (i.v.)
- (b) Intravenous hydrocortisone
- (c) Correction of hypothermia by warming the patient
- (d) Correction of electrolyte imbalance, e.g. hyponatraemia
- (e) Ventilatory support may be required
- (f) Antibiotics, if infection is the precipitating cause
3. Benign thyroid nodule – some cases, therapy with T_4 suppresses TSH levels.
4. Thyroid carcinoma – thyroid hormone suppression therapy is used in papillary carcinoma of thyroid to suppress TSH and prevent its stimulation of growth of tumour.

ANTITHYROID DRUGS (Fig. 9.5)

These drugs reduce the level of thyroid hormones by reducing thyroid hormone synthesis or release or both. These drugs play an important role in the management of hyperthyroidism caused by both benign and malignant conditions of thyroid gland.

Classification

1. Thyroid hormone **synthesis inhibitors** (thioamide derivatives): Propylthiouracil, methimazole, carbimazole
2. Inhibitors of **iodide trapping** (anion inhibitors): Thiocyanates, perchlorates
3. Hormone **release inhibitors**: Iodine, organic iodide, iodides of Na^+ and K^+
4. Thyroid **tissue destroying** agent: Radioactive iodine (^{131}I)
5. Others: Propranolol, atenolol, diltiazem, dexamethasone

Thioamides (Thiourea Derivatives)

Propylthiouracil, methimazole and carbimazole are thioamides used to treat hyperthyroidism. Important features of propylthiouracil and carbimazole are given on p. 313.

Mechanism of Action of Thioamides (Fig. 9.5). Thioamides act by inhibiting

1. Thyroid peroxidase enzyme, which converts iodide to iodine
2. Iodination of tyrosine residues in thyroglobulin
3. Coupling of iodotyrosines (MIT and DIT)

Propylthiouracil also inhibits the peripheral deiodination of T_4 to T_3 . Other thioamides do not have this action.

Pharmacokinetics. Thioamides are well absorbed orally. Propylthiouracil is most rapidly absorbed. Carbimazole is converted to methimazole after absorption. They are widely distributed but get accumulated in thyroid gland. Propylthiouracil has a short half-life and needs to be given every 6–8 hours. They are excreted in urine. They cross placental barrier and can cause fetal hypothyroidism. Both propylthiouracil and carbimazole/methimazole

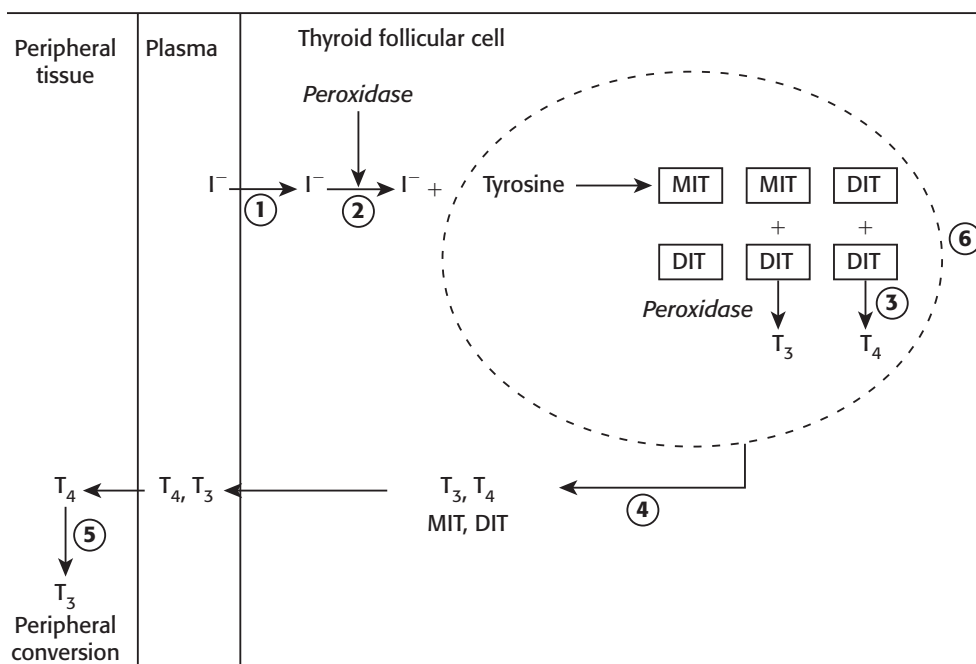


Fig. 9.5 Synthesis, storage and secretion of thyroid hormones and drugs affecting them.

Site 1: Thiocyanates, perchlorates, excess iodides

Sites 2 and 3: Iodides, thioamides

Site 4: Iodides

Site 5: Propylthiouracil, propranolol, iopanoic acid, ipodate, glucocorticoids

Site 6: Radioactive iodine (destruction of thyroid tissue)

are safe for use in pregnancy. Propylthiouracil is preferred to carbimazole/methimazole for treatment of hyperthyroidism during first trimester of pregnancy.

Adverse Effects. Skin rashes are most common. The other side effects are joint pain, fever, hepatitis, nephritis, etc. A dangerous but rare adverse effect is agranulocytosis, which usually occurs during first few weeks or months of therapy but may occur later also. This may develop rapidly, so regular blood counts may not be helpful. The drugs should be stopped at the first sign of agranulocytosis, i.e. sore throat and/or fever. Hepatotoxicity can occur with propylthiouracil. Hypothyroidism may occur but it is reversible.

Important features of Propylthiouracil and Carbimazole

Propylthiouracil	Carbimazole
Less potent	More potent
Highly bound to plasma proteins	Less protein bound
Has short duration of action (4–8 hours)	Has longer duration of action (12–24 hours)
Inhibits peripheral conversion of T ₄ to T ₃	Negligible action
No active metabolite	Gets converted to methimazole which is active
Passage across placenta is low	Passage across placenta is low
Levels in breast milk are low	Levels in breast milk are low

Uses

1. For long-term treatment of hyperthyroidism due to Graves disease/toxic nodular goitre where surgery is not indicated or not feasible and radioactive iodine is contraindicated. Carbimazole/methimazole is preferred for long-term treatment as it is long acting and is not hepatotoxic.
2. Preoperatively in thyrotoxic patients before subtotal thyroidectomy – carbimazole is used to achieve euthyroidism.
3. Along with radioactive iodine: Radioactive iodine has a slow onset of action. Hence, carbimazole is also administered for initial control of hyperthyroidism in those patients treated with radioactive iodine.
4. For treatment of thyrotoxic crisis, propylthiouracil is used along with iodide and propranolol.

Anion Inhibitors

Thiocyanates, perchlorates and other anions block uptake of iodide by thyroid, but are highly toxic and have unpredictable effects. For these reasons, they are not used clinically.

Iodine and Iodides

Iodides are the oldest agents used to treat hyperthyroidism. They are the most rapid acting antithyroid drugs. They have a paradoxical effect on thyroid hormone synthesis when given in therapeutic doses. Although the exact mechanism of action is not completely explained, high concentration of iodide appears to inhibit almost all steps in the synthesis of thyroid hormones. But the major mechanism is inhibition of hormone release (thyroid constipation). High level of intracellular iodide rapidly inhibits iodination of tyrosine residues and hormone synthesis (Wolff–Chaikoff effect) which is transient; later, thyroid escape occurs.

Preparations and Uses

1. **Lugol's iodine** (5% iodine in 10% solution of KI).

2. **Iodate sodium and iopanoic acid**

The above preparations of iodine (1 and 2) are used orally preoperatively before thyroidectomy and in thyroid storm. They render the gland firm, less vascular and decrease its size, which makes surgery convenient with less bleeding and complications.

3. **As an expectorant:** Potassium iodide (KI) acts as a mucolytic agent that enhances expectoration.
4. **As an antiseptic:** Tincture of iodine (iodine in alcohol).
5. **Prophylaxis of endemic goitre:** Iodized salt is used.

Adverse Effects. Allergic reactions: Angioedema, laryngeal oedema, arthralgia, fever, eosinophilia and lymphadenopathy may occur acutely (type III hypersensitivity).

Chronic overdose with iodide results in iodism. The symptoms are headache, sneezing and irritation of eyes with swelling of eyelids; sometimes pulmonary oedema can occur. These resolve after few days of stopping iodine.

Hypothyroidism may also occur.

Use of iodides during pregnancy may cause fetal goitre.

Radioactive Iodine

Therapeutically used radioactive iodine is ^{131}I (half-life: 8 days). Sodium iodide ^{123}I (half-life: 13 hours) is used for diagnostic scan.

It gets concentrated in the same way as stable iodine in thyroid and emits γ -rays and β -particles. The β -particles cause destruction of follicular cells leading to fibrosis and correction of hyperthyroid state.

Preparation. ^{131}I is used orally as solution or capsule. The dose is expressed in microcurie.

Uses and Contraindications. Radioactive iodine is used for treatment of hyperthyroidism due to toxic nodular goitre/Graves disease specially in elderly and patients with coexisting cardiac disease. It is also useful in hyperthyroidism due to adenoma or carcinoma when surgery is not feasible or contraindicated. It is contraindicated in pregnancy, children and nursing mothers.

Advantages

1. Treatment is simple; does not require hospitalization – can be done in outpatient department
2. Low cost
3. No risk of surgery and scar
4. Permanently cures hyperthyroidism

Disadvantages. It is slow acting and causes local soreness in the neck. Incidence of hypothyroidism is high. It is not suitable for pregnant women, children and young patients.

β -Adrenoceptor Blockers (β -Blockers)

Propranolol, atenolol and metoprolol can be used. They produce dramatic improvement in symptoms of thyrotoxicosis like tachycardia, palpitation and tremors. Propranolol also has an inhibitory effect on peripheral conversion of T_4 to T_3 .

Uses

1. To control symptoms of thyrotoxicosis initially till antithyroid drugs act
2. In thyrotoxic crisis
3. Preoperatively before thyroid surgery

Thyrotoxic Crisis (Thyroid Storm)

This is a manifestation of severe hypermetabolic state due to very high levels of circulating thyroid hormones. Besides the usual features of hyperthyroidism, this is characterized by hyperpyrexia, cardiac arrhythmias (e.g. atrial fibrillation), nausea, vomiting, diarrhoea and mental confusion. It is usually precipitated by infection, trauma, surgery (thyroid or nonthyroid), diabetic ketoacidosis, myocardial infarction, etc.

Treatment

1. Hospitalization.
2. Supportive care: Cooling blankets, hydration, sedation and antibiotics to treat infection.
3. Propranolol, 1–2 mg i.v. slowly every 4 hours; then, oral propranolol 40–80 mg every 6 hours. It controls palpitations, tremors, tachycardia and inhibits peripheral conversion of T_4 to T_3 .
4. Propylthiouracil is administered via nasogastric tube.
5. Sodium ipodate, 0.5 g orally, is administered orally. It inhibits release of thyroid hormones and peripheral conversion of T_4 to T_3 .
6. Diltiazem can be used if propranolol is contraindicated.
7. Intravenous hydrocortisone 100 mg i.v. every 8 hours – inhibits peripheral conversion of T_4 to T_3 ; also corrects adrenal insufficiency, if present.

Sex Hormones and Their Antagonists

PH1.37

ANDROGENS

Testosterone is the main androgen in men. It is synthesized by Leydig cells (interstitial cells) of the testes under the influence of interstitial cell-stimulating hormone, ICSH (LH) of anterior pituitary. FSH is responsible for spermatogenesis (Fig. 9.6).

Classification

1. **Natural androgens:** Testosterone, dihydrotestosterone, dehydroepiandrosterone, androstenedione.
2. **Synthetic androgens**
 - Methyltestosterone, fluoxymesterone – given orally; slowly metabolized; longer acting than testosterone.
 - Esters of testosterone in the form of cypionate (i.m.), propionate (i.m.), enanthate (i.m.) and undecanoate (oral, i.m.) are slowly absorbed from site of administration.

Actions of Testosterone (Natural Androgen). Testosterone has both androgenic and anabolic actions. Testosterone and dihydrotestosterone are responsible for the development of male secondary sexual characteristics, maturation of reproductive organs (androgenic action), increase in mass and strength of skeletal muscle (anabolic action) and erythropoiesis.

Pharmacokinetics. Testosterone is extensively metabolized in liver after oral administration and is, therefore, given by intramuscular (i.m.) route.

Adverse Effects

1. In females, androgens cause virilization leading to hirsutism, menstrual irregularities, breast atrophy, acne and deepening of voice.

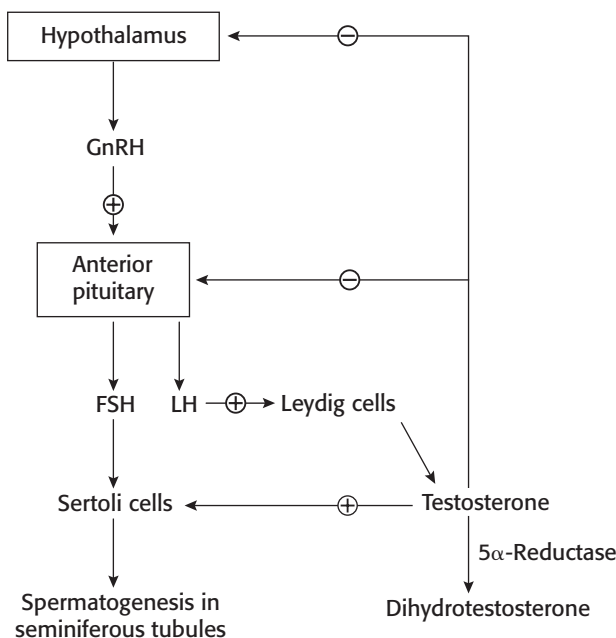


Fig. 9.6 Androgen synthesis and regulation. Testosterone (but not dihydrotestosterone) mediates negative feedback inhibition. GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

2. In children, impairment of growth due to premature closure of epiphyses.
3. Sodium and water retention leading to oedema.
4. Cholestatic jaundice mainly with methyltestosterone.

Therapeutic Uses

1. Androgens are mainly used in replacement therapy in males with hypogonadism due to testicular failure, hypopituitarism, etc. Transdermal/parenteral preparations of testosterone or dihydrotestosterone are commonly used – maintains serum testosterone levels within normal range.
2. In HIV patients with low testosterone levels, administration of testosterone increases muscle mass and strength.
3. Osteoporosis in elderly males.

Precautions and Contraindications

1. Pregnancy: Androgens should not be used during pregnancy because of fear of virilization of female fetus.
2. Carcinoma of prostate and breast cancer in men.
3. Renal and cardiac diseases.

Anabolic Steroids (Synthetic Androgens)

Anabolic steroids promote protein synthesis and increase muscle mass, resulting in weight gain. They are synthetic androgens with greater anabolic and lesser androgenic activity. Testosterone has potent anabolic effect, but it cannot be used because of its strong androgenic effect. The ratio, anabolic to androgenic activity with testosterone, is

1. Some of the commonly used anabolic steroids are Nandrolone phenylpropionate (i.m.), Nandrolone decanoate (i.m.), Oxandrolone (oral), Stanozolol (oral), Ethylestrenol (oral), Methandienone (oral, i.m.).

Mnemonic. NOSE.

Uses

1. In chronic illness, to improve appetite and feeling of well-being.
2. During recovery from prolonged illness, surgery, burns, trauma or chronic debilitating diseases.
3. In senile osteoporosis, though they are not the drugs of choice.

Adverse Effects and Contraindications. Adverse effects and contraindications are the same as androgens. Anabolic steroids are often misused by athletes to increase muscle strength and athletic performance, hence are included in ‘dope test’.

Danazol

- Weak androgenic, glucocorticoid and progestational activities
- Suppresses FSH and LH surge; inhibits gonadal function
- Useful orally in endometriosis and fibrocystic breast disease
- Hot flushes, amenorrhoea, hirsutism and muscle cramps may occur
- Other adverse effects are GI side effects and hepatotoxicity
- Contraindicated in pregnancy

ANTIANDROGENS

1. *Physiological antagonist:* Oestrogens.
2. *Testosterone synthesis inhibitors:* Ketoconazole, spironolactone.

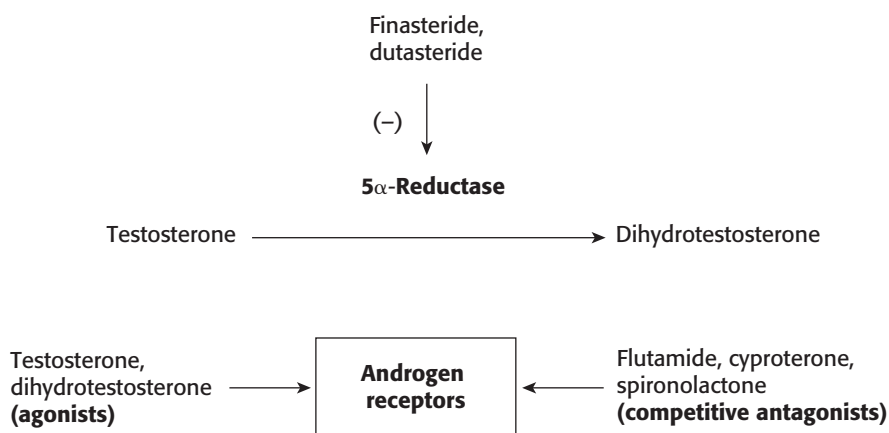


Fig. 9.7 Mechanism of action of antiandrogens. ⊖, inhibition.

3. *Androgen-receptor antagonists*: Flutamide, bicalutamide, cyproterone, spironolactone.
4. *5α-reductase inhibitors*: Finasteride, dutasteride.

The mechanism of action of antiandrogens is shown in [Fig. 9.7](#).

- **Oestrogens** decrease androgen levels by inhibiting gonadotrophin secretion.
- **Ketoconazole** is an antifungal agent that inhibits adrenal and gonadal steroid synthesis.
- **Spironolactone** is an aldosterone antagonist that inhibits testosterone synthesis; it is also a competitive blocker of androgen receptors. The side effects are hyperkalaemia, gynaecomastia and menstrual irregularities.
- **Cyproterone acetate and flutamide** competitively block androgen receptors. They block the action of androgens on the target cell. These drugs are used to treat carcinoma of prostate, hirsutism in females and acne in both sexes. Adverse effects are impotence, hot flushes, gynaecomastia, hepatic damage, decreased spermatogenesis and gastrointestinal (GI) side effects such as nausea, vomiting and diarrhoea. **Bicalutamide** (oral) is more potent, longer acting and better tolerated than flutamide.
- **Finasteride and dutasteride** block the conversion of testosterone to dihydrotestosterone by inhibiting 5α-reductase enzyme. **Dutasteride** is slow acting but has long duration of action. Given orally, they decrease serum and prostatic dihydrotestosterone levels. Dihydrotestosterone is more active and is responsible for most of the actions of androgens in many tissues. These drugs decrease the size of prostate and improve urinary flow rate. They are less effective when compared to surgery and α₁-blockers in the treatment of BPH. Combined use of finasteride and α₁-adrenergic blockers results in better effect. Prolonged treatment is necessary to sustain benefit. Stoppage of the drug results in regrowth of the prostate. They are also useful in male pattern baldness. The side effects of finasteride are impotence, skin rashes, itching and decreased libido.

Oestrogens

Oestrogens are naturally occurring sex hormones produced by ovary, adrenal gland and placenta.

1. **Natural oestrogens**: Oestradiol (the most potent and main oestrogen secreted by the ovary); oestrone and oestriol (formed in the liver from oestradiol)

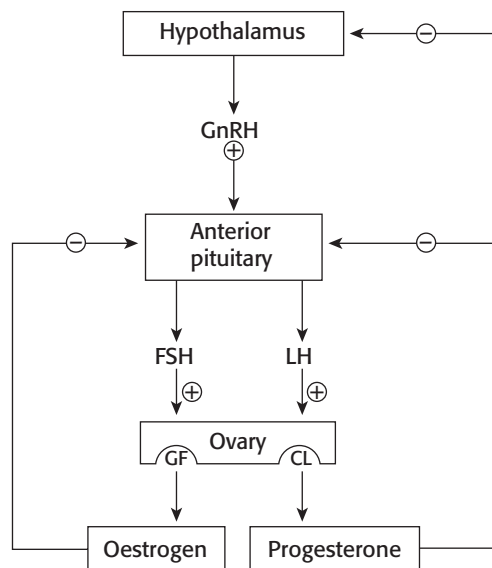


Fig. 9.8 Synthesis and regulation of female sex hormones. GF, Graafian follicle; CL, corpus luteum; GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; $\ominus$, inhibition; $\oplus$, stimulation.

2. Synthetic oestrogens

(a) *Steroidal*: Ethinyl oestradiol, mestranol, tibolone

(b) *Nonsteroidal*: Diethylstilbestrol, dienestrol

Oestrogen has negative feedback control primarily on the anterior pituitary. Progesterone has negative feedback control on both hypothalamus and anterior pituitary (Fig. 9.8).

Mechanism of Action (Fig. 9.9)

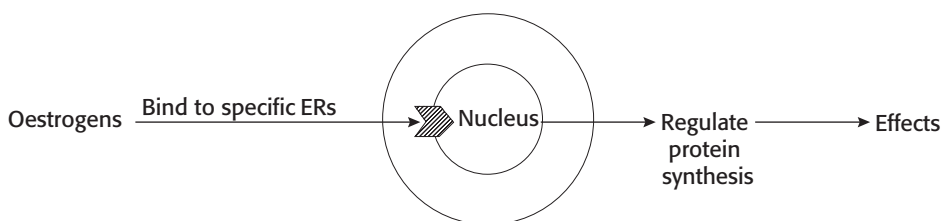


Fig. 9.9 Mechanism of action of oestrogens. ERs, oestrogen receptors.

Types and location of oestrogen receptors (ERs): The ERs are ER α and ER β . Many tissues contain both subtypes. ER α – predominantly in uterus, vagina, ovary, breast, hypothalamus and blood vessels; ER β – predominantly in prostate and ovaries.

Pharmacokinetics

Oestrogens are available for oral, parenteral, transdermal and topical administration. Natural oestrogens are not effective orally due to high first-pass metabolism.



All these natural oestrogens undergo glucuronide and sulphate conjugation. The metabolites are excreted in urine and bile. In the intestine, they undergo deconjugation with the help of bacterial flora and are reabsorbed resulting in enterohepatic cycling.

Actions of Oestrogens and Progestins are described in [Table 9.2](#).

Table 9.2 ■ **Actions of oestrogens and progestins**

Oestrogens	Progestins
Help in the growth and development of sex organs in females; they stimulate the development of secondary sex characters	Important for the maintenance of pregnancy
Responsible for the proliferative phase of endometrium and have negative feed-back control mainly on anterior pituitary	Responsible for secretory phase of the endometrium and have negative feedback control on both hypothalamus and anterior pituitary
Promote rhythmic contractions of fallopian tubes and myometrium	Decrease tubal motility and uterine contractions
Cervical secretion becomes thin, watery and alkaline, which facilitates entry of spermatozoa	Cervical mucus becomes thick, more viscous and acidic, which is hostile to sperm penetration
Stimulate the growth of ducts and stroma in breast	Stimulate proliferation of acini in breast
Metabolic actions: Oestrogens decrease the rate of resorption of bone by inhibiting the activity of osteoclasts; they increase plasma high-density lipoprotein (HDL) and decrease LDL levels; they cause sodium–water retention and oedema (mineralocorticoid activity)	Metabolic actions: Long-term use of progestins may decrease glucose tolerance; progestins increase circulating LDL levels; they stimulate lipoprotein lipase activity and favour fat deposition; they also produce sodium and water retention
They enhance coagulability of blood by increasing the clotting factors (II, VII, IX and X) and decreasing antithrombin III	They increase body temperature
They induce synthesis of progesterone receptors	They inhibit the synthesis of oestrogen receptors

Therapeutic Uses of Oestrogens (Fig. 9.10)

1. **Oral contraceptive:** The most common use of synthetic oestrogens is for contraception, often in combination with a progestin (for details, see p. 326).

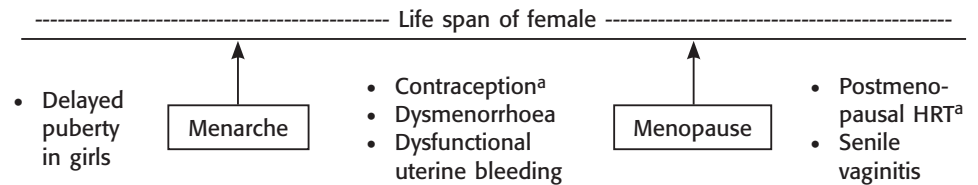


Fig. 9.10 Therapeutic uses of oestrogens in females. ^aMost common indications of oestrogens.

2. **Postmenopausal hormone replacement therapy:** The signs and symptoms in postmenopausal women are due to cessation of normal ovarian function. They are vasomotor symptoms, sleep disturbances, genital atrophy and osteoporosis leading to fractures. The incidence of cardiovascular disease is more in postmenopausal women.

Short-term oestrogen therapy is used to relieve menopausal symptoms such as hot flushes, night sweats, depression, irritability and sleeplessness. The main objective of long-term oestrogen therapy in postmenopausal women is to prevent or delay osteoporosis (oestrogens decrease the rate of resorption of bone by inhibiting the activity of osteoclasts) and atherosclerosis (oestrogens increase plasma HDL and decrease LDL levels). Hormone replacement therapy (HRT) reduces the incidence of coronary artery disease and Alzheimer disease. To avoid the risk of endometrial and breast cancer, a progestin (medroxyprogesterone or norethisterone) is given for the last 12–14 days of each month. Oestrogen alone is used in hysterectomized women. The most effective oestrogens in preventing osteoporosis are conjugated oestrogens (sulphate esters of natural oestrogens – oral preparation). Transdermal oestradiol patch can be used – systemic side effects are less.

Drawbacks of HRT: Increased incidence of venous thromboembolism and gallstones, uterine bleeding, mood changes, breast cancer, etc.

3. **Senile vaginitis:** Topical oestrogens are commonly used.
4. **Dysmenorrhoea:** Oestrogens in combination with progestins can be used to suppress ovulation in patient with dysmenorrhoea. (The anovulatory cycles are painless.)
5. **Delayed puberty in girls:** In patients suffering from Turner syndrome and hypopituitarism, oestrogens are used for the development of secondary sexual characteristics and to avoid osteoporosis. Usually cyclic treatment is given.
6. **Carcinoma of prostate:** Oestrogens are palliative. Fosfestrol is a prodrug of oestrogen, which is concentrated in the prostate and gets activated to stilboestrol by acid phosphatase in prostatic tissue. GnRH agonists are preferred to oestrogens.

Tibolone has oestrogenic, progestogenic and weak androgenic activities and does not cause endometrial proliferation. It can be used continuously for HRT without cyclic progesterone.

Adverse Effects of Oestrogens

They are nausea, vomiting, breast tenderness, water retention with oedema and weight gain, increased incidence of endometrial and breast cancer, thromboembolic complications, increased incidence of gallstones and liver disease. The dose of oestrogen used in HRT is low (approximately one-fifth of oral contraceptive dose), hence the side effects are less severe.

Antioestrogens and Selective Oestrogen-Receptor Modulators

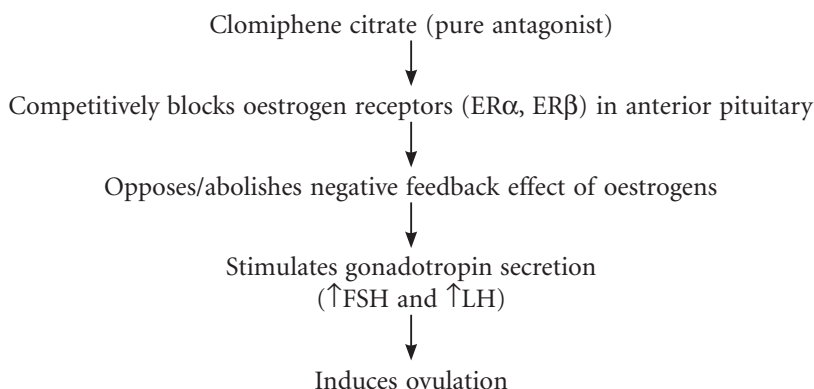
Antioestrogens compete with natural oestrogens for receptors in target organs. They include clomiphene citrate and fulvestrant.

CLOMIPHENE CITRATE

PH1.40

It is a nonsteroidal compound and has antioestrogenic effect.

Mechanism of Action

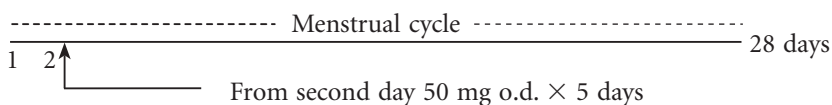


Pharmacokinetics

Clomiphene is well absorbed on oral administration. It has a long plasma half-life due to high plasma protein binding and accumulation in fatty tissues.

Uses

1. Infertility: Clomiphene citrate is used for the treatment of infertility due to anovulation. Cyclical therapy is recommended. Clomiphene should not be used for more than six cycles because of risk of ovarian cancer. Schedule of clomiphene therapy is given below.



2. Assisted reproduction therapy (ART) and gamete intrafallopian transfer (GIFT) technique.
3. Male infertility: It is used to increase the sperm count and testosterone secretion.

Adverse Effects

They include hot flushes, nausea, vomiting, headache, loss of hair, hyperstimulation syndrome, multiple pregnancy, ovarian cyst, ovarian malignancy, weight gain, breast discomfort, etc.

FULVESTRANT

- Pure oestrogen antagonist.
- Useful in breast carcinoma, not responding to tamoxifen.

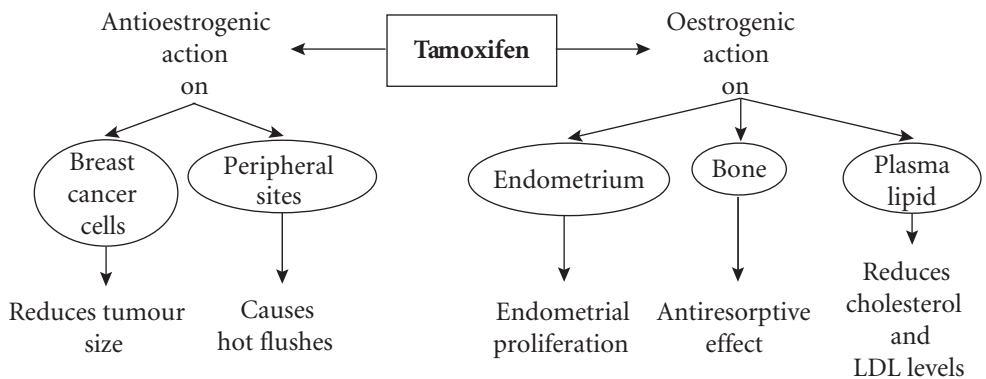
SELECTIVE OESTROGEN-RECEPTOR MODULATORS

Tamoxifen, raloxifene and ormeloxifene are selective oestrogen-receptor modulators (SERMs) and have tissue-selective actions; oestrogen-like actions in some and oestrogen antagonistic actions in other tissues.

TAMOXIFEN

It is a nonsteroidal compound with a selective ER-modulating effect.

Actions



1. **Uterus:** It causes endometrial proliferation.
2. **Bone:** It decreases the rate of resorption of bone by inhibiting the activity of osteoclasts.
3. **Plasma lipids:** It reduces blood cholesterol and LDL levels and decreases the risk of cardiovascular disease.

Pharmacokinetics

Tamoxifen is well absorbed on oral administration, metabolized in liver, excreted into the gut via bile and undergoes enterohepatic cycling.

Uses

Tamoxifen is used orally in carcinoma of breast in both premenopausal and postmenopausal women.

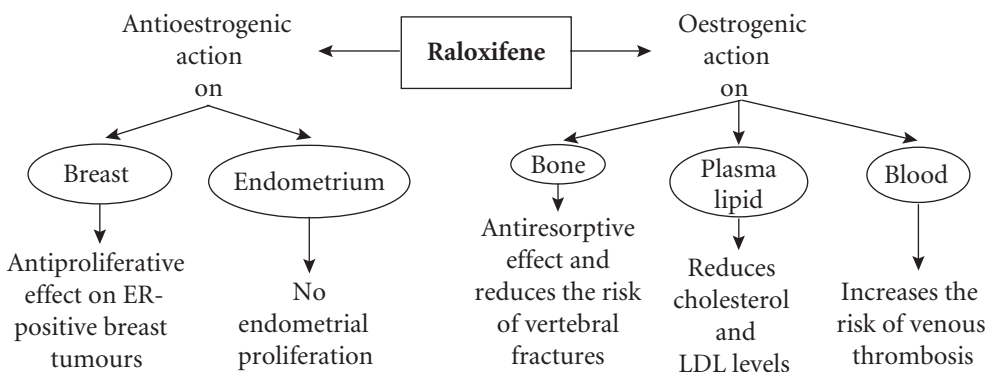
Adverse Effects

Nausea and vomiting are common. The other side effects are hot flushes, increased risk of endometrial cancer and venous thrombosis.

RALOXIFENE

Raloxifene has high affinity for both ER α and ER β .

Actions



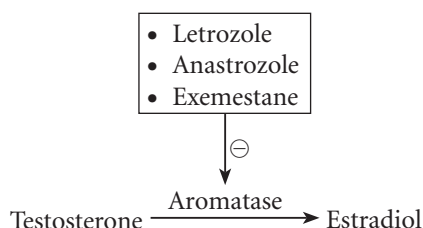
Raloxifene is rapidly absorbed after oral administration but has poor bioavailability due to extensive first-pass metabolism. It is used for prevention and treatment of osteoporosis in postmenopausal women. The adverse effects are hot flushes, leg cramps, increased incidence of deep vein thrombosis and pulmonary embolism. It does not increase the risk of endometrial cancer.

ORMELOXIFENE

Ormeloxifene, a selective oestrogen-receptor modulator, has antagonistic effect on breast and uterus. It is useful for the treatment of dysfunctional uterine bleeding. Adverse effects include headache, weight gain and nausea.

AROMATASE INHIBITORS

- *Exemestane* (steroidal agent) causes irreversible inhibition; *letrozole* and *anastrozole* (nonsteroidal agents) cause reversible inhibition of aromatase. They are administered orally.
- They decrease oestrogen levels by inhibiting aromatase enzyme – useful in breast carcinoma; hot flushes are common adverse effects.
- Unlike tamoxifen, there is **no** endometrial hyperplasia, venous thromboembolism, and unfavourable effect on lipid profile. But it causes bone loss. It should not be administered to premenopausal women.



Progestins

Natural progestin, progesterone, is secreted by corpus luteum of the ovary in the second half of the menstrual cycle, and by placenta during pregnancy. Actions of progestins are described in [Table 9.2](#) (see p. 320).

MECHANISM OF ACTION

Same as other steroidal hormones. The density of progesterone receptors is controlled by oestrogens.

PREPARATIONS

1. *Natural progestin*: Progesterone
2. *Synthetic progestins* include progesterone and 19 – nortestosterone derivatives ([Table 9.3](#))

The progesterone derivatives have weak anti-ovulatory effect. Desogestrel, gestodene and norgestrel have potent anti-ovulatory effect, minimal/no androgenic effect, no unfavourable effect on lipid profile.

Table 9.3 ■ Synthetic progestins

Progesterone derivatives	19-Nortestosterone derivatives
• Medroxyprogesterone acetate • Hydroxyprogesterone caproate • Megestrol acetate	• Norethindrone (norethisterone) • Norgestrel • Levonorgestrel • Desogestrel • Gestodene • Norgestimate

PHARMACOKINETICS

Progesterone is not effective orally because of extensive first-pass metabolism. It is usually given by i.m. route in oil base. Micronized progesterone and synthetic progestin preparations are effective orally.

USES

Progestins are commonly used for contraception and HRT of postmenopausal women (Fig. 9.11).

1. **Contraception:** Progestins are used in contraception as combined pill (oestrogen-progestogen), minipill, postcoital pill, injectable preparations, implants and intra-uterine contraceptive devices. For details, see under contraceptives (see p. 326).
2. **Dysfunctional uterine bleeding:** Oral progestins (norethisterone or norethynodrel) are used. A high initial dose is used to arrest bleeding after which maintenance dose is given for 20 days. Withdrawal bleeding occurs in 2–5 days after stoppage of therapy. The cyclic treatment can be continued for 3–6 months.
3. **Endometriosis:** The classical symptoms are dysmenorrhoea, dyspareunia, menorrhagia and infertility. Continuous long-term treatment with oral progestins causes regression of the lesion by inducing anovulatory cycles.
4. **HRT in postmenopausal women:** Progestins are combined with oestrogens for long-term HRT in women with an intact uterus to prevent endometrial proliferation and subsequent carcinoma.
5. **Endometrial carcinoma:** They are used in advanced metastatic endometrial carcinoma.
6. **Postponement of periods:** Either progestins or combined oral contraceptive pills should be started 3 days before the expected period and continued till required time as needed. The withdrawal bleeding occurs within 72 hours after stoppage of the drug.

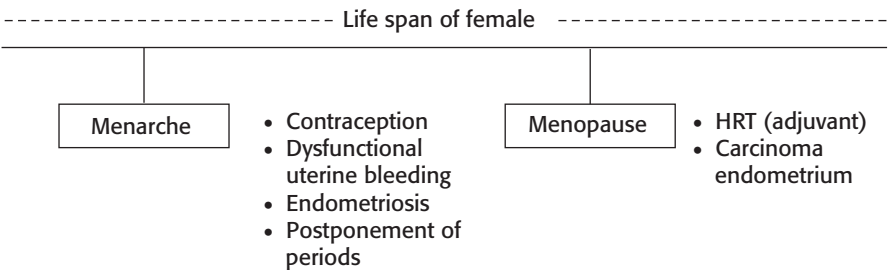


Fig. 9.11 Uses of progestins.

ADVERSE EFFECTS

The adverse effects are acne, fluid retention, weight gain, depression, irregular periods, hirsutism, increase in blood glucose levels (levonorgestrel) and increased risk of breast cancer on prolonged use. The older progestins cause altered plasma lipid levels; hence, there is an increased risk of cardiovascular diseases. The newer progestins have little or no adverse effect on lipid levels.

Antiprogesterin

Mifepristone is a competitive antagonist of progesterone and has luteolytic property. It also has antiglucocorticoid and antiandrogenic activities. Mifepristone is orally effective, has long plasma half-life, metabolized in liver, excreted in bile and undergoes enterohepatic cycling.

USES

1. *Termination of pregnancy*: Mifepristone is used in combination with prostaglandins (PGs) for termination of early pregnancy. A single oral dose of 600 mg of mifepristone, followed 48 hours later by gemeprost (PGE₁) 1 mg vaginal pessary, raises the success rate to 95%.
2. *Contraception*: It has been used as a postcoital contraceptive. It causes sloughing and shedding of decidua and brings about abortion.
3. Used for the *induction of labour* in cases of intrauterine fetal death.
4. For *cervical ripening* before abortion or induction of labour.
5. *Hypercortisolism*: It has antiglucocorticoid activity, hence useful in Cushing syndrome.

ADVERSE EFFECTS

These are nausea, vomiting, diarrhoea, abdominal pain, headache, uterine bleeding and teratogenicity.

Hormonal Contraceptives

PH1.39

Hormonal contraception (Fig. 9.12) is one of the most effective contraceptive methods available today. Progestin (norethynodrel) was used in the first contraceptive trial by Pincus and his colleagues in 1950s.

ORAL CONTRACEPTIVES (Table 9.4, P. 327)

They include combined pills, minipills and postcoital pills.

Combined Oestrogen and Progestin Preparations (Combined Pill)

The combined oral contraceptive pill is widely used; it is the most effective reversible method of contraception.

In combined pill

- Oestrogen used: ethinyl oestradiol.
- Commonly used progestins: Norethindrone, levonorgestrel, norgestimate, norgestrel, desogestrel and gestodene.

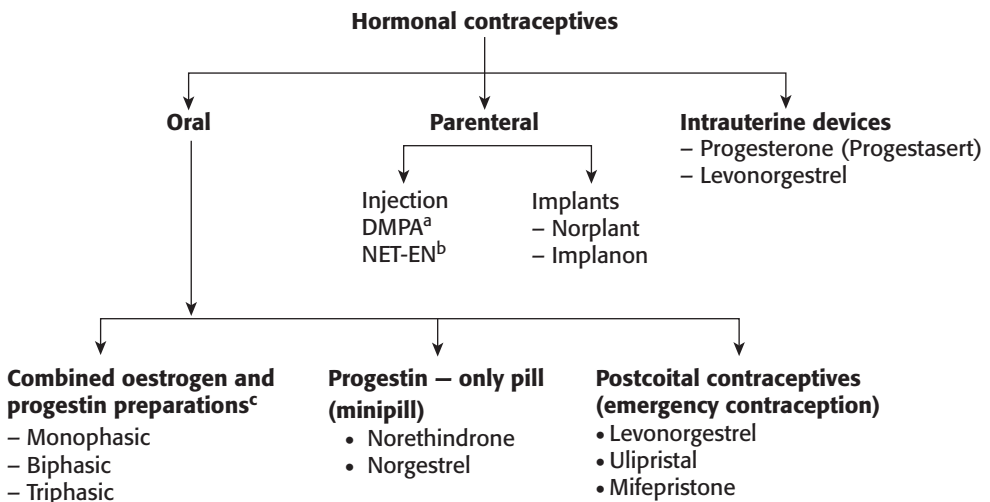


Fig. 9.12 Classification of hormonal contraceptives. ^aDepot medroxyprogesterone acetate; ^bNorethisterone enanthate; ^cCombined pill – oestrogen (ethinyl oestradiol) + progesterone (desogestrel/levonorgestrel/norgestrel/norgestimate, etc.).

- The combination is synergistic. In addition, progestins inhibit oestrogen-induced endometrial proliferation → decrease risk of endometrial carcinoma.
- Each pill (**monophasic**) taken throughout the treatment period has a fixed amount of oestrogen and progestin.
- In **biphasic preparation**, the dose of oestrogen is kept constant but progestogen varies according to the phase of the menstrual cycle. In **triphasic preparation**, the dose of oestrogen is slightly more in mid-cycle but doses of progestin increase in three successive phases of menstrual cycle.

The oestrogen content of pills usually ranges from 20 to 30 mcg and the progestin content from 0.1 to 1 mg in monophasic pills. Preparations containing less than 30 mcg of oestrogen are referred to as 'low-dose' pills. The progestins namely desogestrel, gestodene and norgestimate are 'lipid friendly', as they increase HDL level and reduce atherogenic risk. They have potent antioviulatory effect.

Table 9.4 ■ Oral contraceptive preparations

Brand name	Oestrogen (mcg)	Progestin (mg)
1. Combined oestrogen and progestin preparations (combined pill)		
• Nelova	Ethinyl oestradiol (35)	Norethindrone (1.0)
• Yasmin	Ethinyl oestradiol (30)	Drospirenone (3)
• Ovral-L	Ethinyl oestradiol (30)	Levonorgestrel (0.15)
• Novelon	Ethinyl oestradiol (30)	Desogestrel (0.15)
• Mala-D	Ethinyl oestradiol (30)	Norgestrel (0.3)
2. Minipill (progestin-only pill)		
• Micronor	–	Norethindrone (0.35)
• Norgest	–	Norgestrel (0.075)

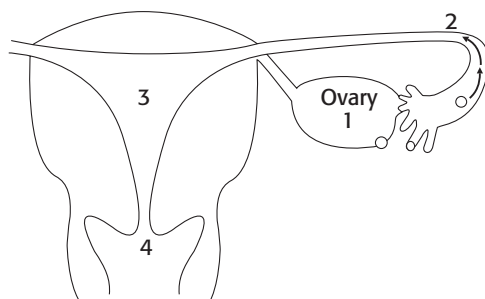


Fig. 9.13 Mechanism of action of contraceptives.

Mechanism of Action of Combined Contraceptive Pill. The following are the mechanism of action of contraceptives (Fig. 9.13). The numerals 1, 2, 3 and 4 shown in the figure are described in the following ways:

1. Both oestrogen and progestin act synergistically on hypothalamic–pituitary axis by negative feedback mechanism and inhibit the release of FSH and LH, which leads to inhibition of ovulation.
2. Cause tubal and uterine contractions that may interfere with fertilization.
3. Make the endometrium less suitable for implantation.
4. Thick, viscid cervical mucus secretion prevents sperm penetration (progestins).

Schedule for Use of Combined Pill. The schedule for use of combined pill is shown in Fig. 9.14.

The combined oral contraceptive pill is usually started from first day of menstrual cycle (i.e. the day bleeding starts) and continued till day 21. Days 22–28 is oral contraceptive pill–free period (7 days). The next day (i.e. after day 28) is taken as day 1 and the course of the combined pill repeated as above till required period of contraception.

The combined pill can also be started from fifth day of menstrual cycle, continued for 21 days followed by a gap of 7 days, following which it is continued again.

If a woman on combined oral contraceptive pills fails to take a tablet, she should take two tablets the next day and continue rest of the pills as prescribed. If she misses more than two tablets, she should stop the treatment, use alternate method of contraception and restart course of pills from next cycle.

Contraindications of Combined Oral Contraceptives. Absolute contraindications include thromboembolic disorders, malignancy of genital tract, severe hypertension, cardiac diseases, porphyria and active liver disease.

Relative contraindications are obesity, diabetes, migraine, mild hypertension, uterine fibroid, etc.

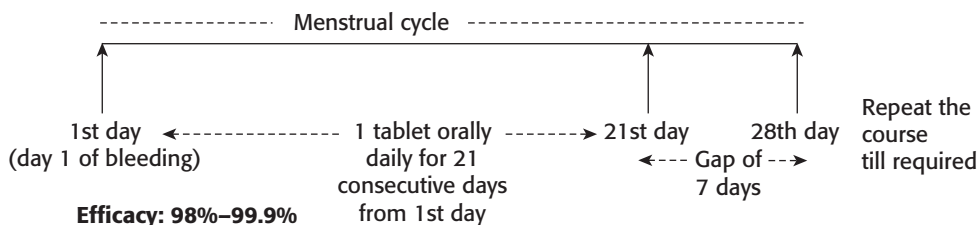


Fig. 9.14 Schedule for use of combined pill.

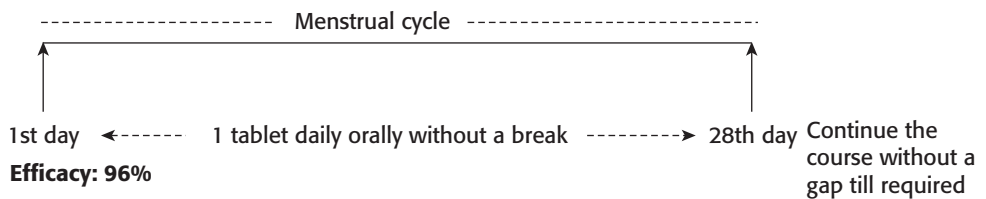


Fig. 9.15 Schedule for use of minipill.

Progestin-Only Pill (Minipill)

Minipill contains very low dose of a progestin (norethindrone or norgestrel) only. It may be used in women if oestrogens are contraindicated. The schedule for use of minipill is shown in Fig. 9.15.

Mechanism of Action of Minipill. It acts by altering cervical mucus, interfering with implantation and inhibiting ovulation. It may cause menstrual irregularities and there is increased risk of ectopic pregnancy.

Postcoital Pill (Emergency Contraception)

It interferes with implantation and also has antioviulatory effect. Drugs that can be used for postcoital contraception are levonorgestrel, ulipristal and mifepristone. They are mainly used following rape, unprotected intercourse or accidental rupture of condom during coitus.

- (a) Levonorgestrel tablet 0.75 mg (two doses, Fig. 9.16): Oral administration of levonorgestrel is effective, if taken within 72 hours of unprotected intercourse (morning after pill).

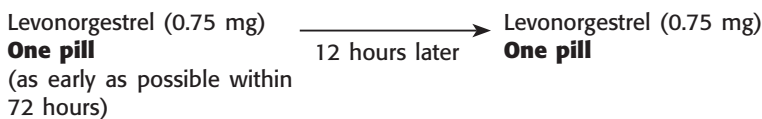


Fig. 9.16 Schedule for the use of postcoital contraceptive.

Note: Levonorgestrel 1.5 mg can be taken as a single dose within 72 hours of unprotected intercourse.

- (b) Mifepristone (antiprogesterin) 600 mg as a single dose can be used as postcoital pill.
 (c) Ulipristal (selective progesterone-receptor modulator, SPRM) 30 mg as a single dose is effective up to 5 days following unprotected sex. It has antioviulatory effect and can block implantation. It may cause headache.

Beneficial Effects of Contraceptives

- Unwanted pregnancy is avoided.

Noncontraceptive Beneficial Effects

- Relieve dysmenorrhoea and premenstrual tension.
- Prevent iron-deficiency anaemia by reducing menstrual loss.
- Reduce incidence of pelvic inflammatory disease and endometriosis.
- Protect against ovarian and endometrial carcinoma.
- Reduce incidence of benign breast tumours and ovarian cysts.

PARENTERAL CONTRACEPTIVES

Injectable Contraceptives

1. Depot medroxyprogesterone acetate (DMPA): 150 mg deep i.m. once in 3 months.
2. Norethindrone enanthate (NET-EN): 200 mg i.m. once in 2 months.

Advantages

1. Regular oral medication is avoided, so patient compliance is better.
2. Can be used safely during lactation.
3. Decreased risk of endometrial cancer on prolonged administration.

Disadvantages. Injectable contraceptives cause menstrual irregularities, headache, mood changes, weight gain, osteoporosis, decrease in HDL and increase in LDL levels. Return of fertility after stoppage is usually delayed for several months (6–8 months).

Implants

Norplant. It is a subdermal implant which consists of six flexible rods containing 216 mg of levonorgestrel. The contraceptive effect lasts for 5 years but fertility is restored almost immediately on removal. Implants may be associated with infection, local irritation and pain at the insertion site. The other side effects are headache, mood changes, weight gain and acne.

Implanon. It is a subdermal single rod containing 68 mg of desogestrel. The contraceptive effect lasts for 3 years.

DEVICES*Intrauterine devices:*

- (a) Levonorgestrel device: It is a 'T'-shaped device inserted into the uterine cavity and the contraceptive effect lasts for 5 years.
- (b) Progestasert: Intrauterine device containing progestogen can be inserted into the uterine cavity. The efficacy is low and the device has to be replaced yearly.

ADVERSE EFFECTS OF HORMONAL CONTRACEPTIVES

Most of the side effects with combined oral pills are dose related. The current low-dose preparations have minimal side effects.

1. Nausea, vomiting, headache, breakthrough bleeding, which occurs initially during therapy but subside following continuous use.
2. Weight gain, fluid retention, acne and pigmentation of skin occur later.
3. Impaired glucose tolerance and alteration in lipid profile was observed with high-dose contraceptives and is rare with low dose, newer preparations.
4. Blood pressure may increase following long-term use. It is less common with low-dose preparations.
5. Long-term adverse effects include increased incidence of venous thromboembolic disease especially in women with risk factors for thromboembolism like smoking; risk of myocardial infarction and stroke in women with coexisting diabetes or hypertension.
6. Increased risk of gallstones, benign liver tumours and breast cancer on prolonged use.

DRUG INTERACTIONS

Rifampin, phenytoin and carbamazepine induce hepatic microsomal enzyme system, enhance metabolism of oral contraceptives and can cause failure of contraception. Hence, when the woman is on rifampin, phenytoin, etc., alternative forms of contraception should be used.

Oral contraceptives × tetracyclines/ampicillin.

Oestrogens are conjugated in liver and excreted via bile into the gut, where they are deconjugated by bacterial flora and then reabsorbed. Antibiotics (tetracyclines, ampicillin) are incompletely absorbed in the gut, so they destroy the bacteria, therefore, reduce deconjugation and reabsorption of oral contraceptives, leading to contraceptive failure.

Nonsteroidal Contraceptive

Centchroman (ormeloxifene): It is a synthetic nonsteroidal contraceptive and has oestrogen antagonistic effect. It is taken orally twice weekly for 12 weeks, and weekly thereafter. It prevents implantation through endometrial changes. The return of fertility occurs within 6 months of stoppage of the drug. It has no teratogenic, carcinogenic or mutagenic effects. It has a long plasma half-life.

MALE CONTRACEPTIVES

Some of the drugs tried as male contraceptives are oestrogens, progestins, androgens, antiandrogens, GnRH analogues, gossypol, etc.; but the results are not satisfactory.

Corticosteroids

PH1.38

Adrenal gland has cortex and medulla. Adrenal cortex secretes steroidal hormones; adrenal medulla secretes adrenaline and noradrenaline. Hormones of adrenal cortex are given in [Table 9.5](#).

Synthesis and release of glucocorticoids is controlled by pituitary ACTH, which in turn is stimulated by corticotrophin-releasing factor (CRF) produced by hypothalamus. Glucocorticoids have negative feedback control on ACTH and CRF secretion ([Fig. 9.17](#)).

Mineralocorticoid (e.g. aldosterone) release is controlled by the renin–angiotensin system. There is a diurnal variation in the rate of release of ACTH and cortisol

Table 9.5 ■ Anatomical and functional divisions of adrenal cortex

	Zona glomerulosa	Zona fasciculata	Zona reticularis
Hormones secreted	Mineralocorticoids: Aldosterone Desoxycorticosterone	Glucocorticoids: Hydrocortisone (cortisol)	Androgens
Main actions	Regulate water and electrolyte balance	Carbohydrate, protein and fat metabolism, anti-inflammatory, immunosuppressant and antiallergic actions	
Hypersecretion	Primary hyperaldosteronism (Conn syndrome)	Cushing syndrome	Adrenogenital syndrome (precocious puberty)
Deficiency of adrenal cortical hormones (chronic)	← Addison disease →		

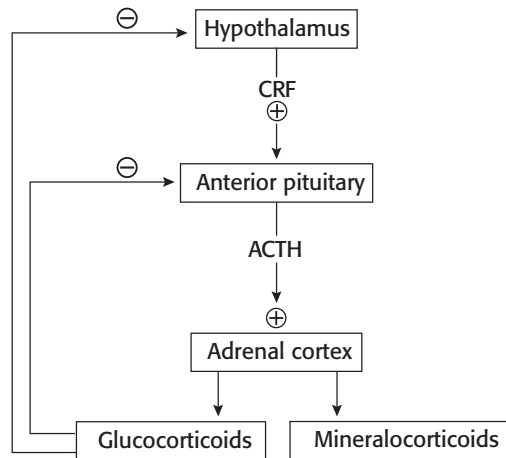
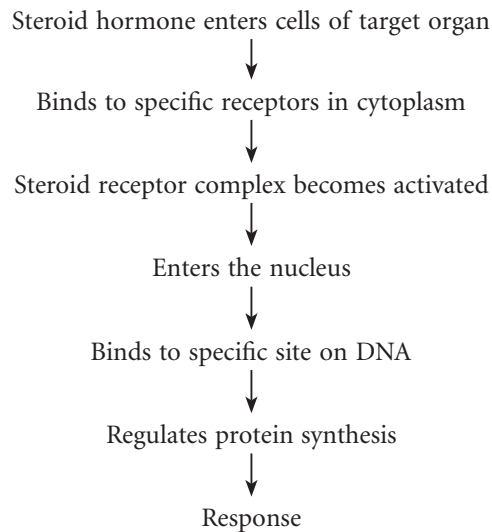


Fig. 9.17 Regulation of synthesis and secretion of corticosteroids. CRF, corticotropin-releasing factor; ACTH, adrenocorticotropic hormone; $\oplus$, stimulation; $\ominus$, inhibition.

(circadian rhythm). The plasma cortisol levels are highest in the early hours of morning and lowest in the late evening. During stress, glucocorticoids secretion is increased.

MECHANISM OF ACTION OF STEROID HORMONES

The mechanism of action of steroid hormones is given in [Fig. 9.18](#).



CLASSIFICATION OF CORTICOSTEROIDS

For classification and important features of corticosteroids, see [Table 9.6, p. 334](#).

PHARMACOLOGICAL ACTIONS

Corticosteroid with predominant sodium- and water-retaining property, e.g. aldosterone and desoxycorticosterone are mineralocorticoids. Corticosteroid with predominant liver

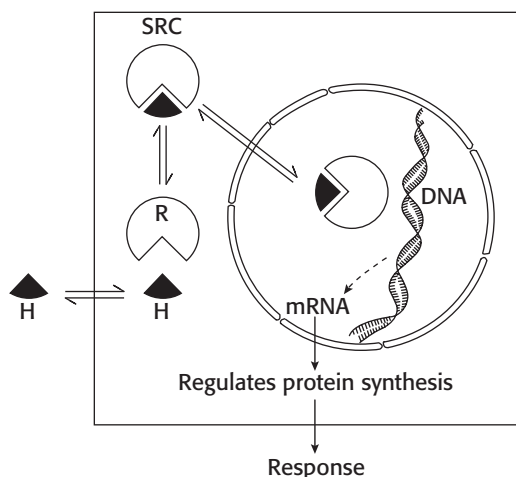
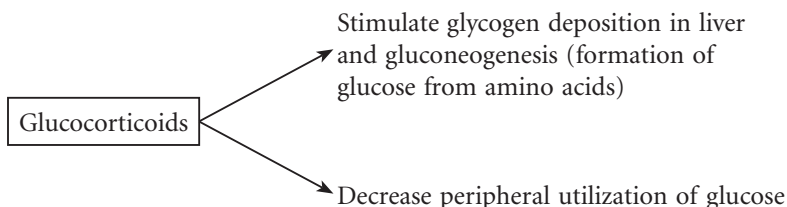


Fig. 9.18 Mechanism of action of steroid hormones. H, hormone; R, receptor; SRC, steroid receptor complex.

glycogen deposition and gluconeogenic effects, e.g. hydrocortisone (cortisol) and cortisone, are glucocorticoids (Table 9.6). The two actions (mineralocorticoid and glucocorticoid) are not completely separated in naturally occurring steroids, whereas synthetic preparations are available with selective action.

Carbohydrate Metabolism



The net result is (i) hyperglycaemia, (ii) decreased tissue sensitivity to insulin and (iii) diabetes may be exacerbated. Therefore, glucocorticoids are (relatively) *contraindicated in diabetics*.

Lipid Metabolism

Prolonged use of glucocorticoids causes redistribution of body fat that is deposited over the neck, face, shoulder, etc., resulting in 'moon face', 'buffalo hump' and 'fish mouth' with thin limbs.

Protein Metabolism

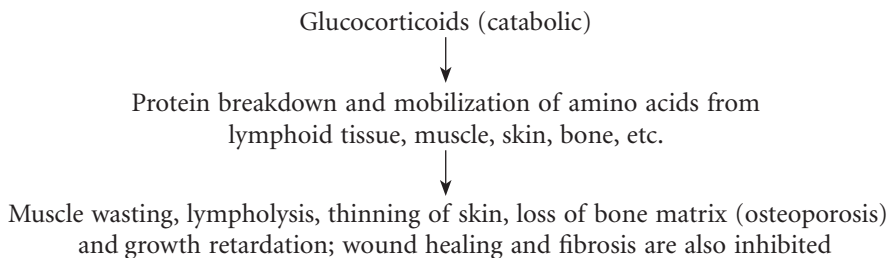


Table 9.6 ■ Comparison of corticosteroids using hydrocortisone as a standard

Agent	Activity		Equivalent dose (mg) (anti-inflammatory)	Uses and route of administration
	Anti-inflammatory	Salt retaining		
1. Glucocorticoids				
(a) Short acting (8–12 hours)				
(i) Hydrocortisone (cortisol)	1	1	20	It has a rapid onset but short duration of action. It is the drug of choice for replacement therapy in acute adrenal insufficiency. Other uses are status asthmaticus and anaphylactic shock (emergency uses) <i>Routes:</i> Oral, i.m., i.v., intra-articular and topical.
(ii) Cortisone	0.8	0.8	25	It is cheap; prodrug, converted to hydrocortisone after metabolism in liver; rarely used at present.
(b) Intermediate acting (12–36 hours)				
(i) Prednisolone	4	0.8	5	It is the most commonly used preparation for allergic, inflammatory, autoimmune disorders and in malignancies. It causes less HPA axis suppression if given once daily in the morning. <i>Routes:</i> Oral, i.m., intra-articular and topical.
(ii) Prednisone	4	0.8	5	It is a prodrug, gets converted to prednisolone in liver; less efficacious.
(iii) Methylprednisolone	5	0.5	4	It is used for its anti-inflammatory and immunosuppressant effects; as high-dose pulse therapy in renal transplant, pemphigus vulgaris, etc. <i>Routes:</i> i.m., i.v., retention enema in ulcerative colitis.
(iv) Triamcinolone ^a	5	0	4	More potent and relatively more toxic than prednisolone. It has no mineralocorticoid activity <i>Routes:</i> Oral, i.m., intra-articular and topical.

(v) Deflazacort	4	0	6	Lacks mineralocorticoid activity; lower risk of growth retardation in children than other glucocorticoids <i>Route:</i> oral.
(c) Long acting (36–72 hours)				Long acting; have highly potent anti-inflammatory and immunosuppressant effects. Have no mineralocorticoid activity
(i) Betamethasone ^a	30	0	0.75	They cause severe HPA axis suppression. Used in allergic and inflammatory conditions; cerebral oedema due to neoplasm, where water retention is undesirable and to promote lung maturation in fetus when premature delivery is anticipated <i>Routes:</i> Oral, i.v., i.m. and topical
(ii) Dexamethasone ^a	30	0	0.75	
Local acting glucocorticoids				They have local action
(i) Beclomethasone	+	–	–	It is used by inhalation in bronchial asthma, as nasal spray for allergic rhinitis; as ointment for skin and mucous membrane lesions. HPA axis suppression is minimal
(ii) Budesonide	+	–	–	Same as beclomethasone, but is more potent than beclomethasone
(iii) Fluticasone	+	–	–	It is used by inhalation for asthma and chronic obstructive pulmonary disease (COPD); orally for inflammatory bowel disease; as ointment for skin and mucous membrane lesions
2. Mineralocorticoids				
(i) Desoxycorticosterone acetate (DOCA)	0	100	–	It has selective mineralocorticoid activity and is used in Addison's disease as replacement therapy
(ii) Fludrocortisone	10	125	2	Has potent mineralocorticoid activity. It is used with hydrocortisone for replacement therapy in Addison's disease
(iii) Aldosterone	0.3	3000	–	Not used

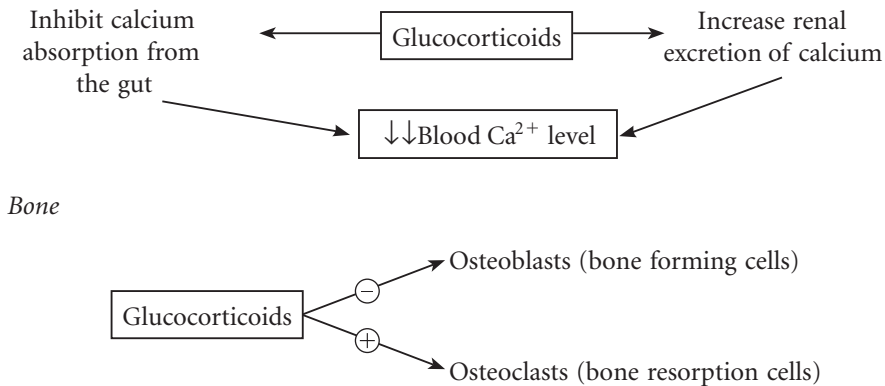
^a'am' containing drugs and deflazacort have no mineralocorticoid activity. +, Activity present; –, Activity absent. **Topical glucocorticoids for dermatological conditions: Betamethasone, clobetasol, mometasone, hydrocortisone, desonide, etc.**

Electrolyte and Water Metabolism

Glucocorticoids have weak mineralocorticoid action, cause sodium and water retention; promote potassium excretion. Thus, prolonged use of these drugs may cause oedema and hypertension. Some of the synthetic glucocorticoids (dexamethasone, betamethasone and triamcinolone) have no sodium- and water-retaining property.

Calcium Metabolism (Anti-Vitamin D Action)

Prolonged use of these drugs may lead to osteoporosis and pathological fracture of vertebral bodies.

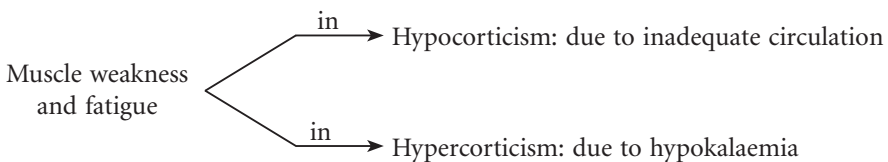


CARDIOVASCULAR SYSTEM

Glucocorticoids have sodium and water retaining property; exert a permissive effect on pressor action of adrenaline and angiotensin. On chronic administration, these drugs may cause hypertension and worsening of CCF (congestive cardiac failure).

SKELETAL MUSCLE

Corticosteroids are required for the normal function of skeletal muscles. Weakness occurs in both hypocorticism and hypercorticism.



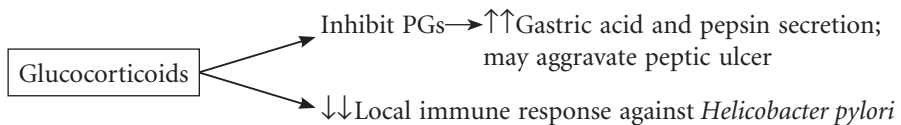
Prolonged use of glucocorticoids may cause muscle wasting and weakness (steroid myopathy).

CENTRAL NERVOUS SYSTEM

Corticosteroids have a number of indirect effects on CNS through maintenance of (i) blood pressure, (ii) blood glucose concentration and (iii) electrolyte levels.

They also have direct effects on CNS and influence mood and behaviour. Patients with Addison disease show depression, irritability and even psychosis. On the other hand, glucocorticoid therapy can cause euphoria, insomnia, restlessness and psychosis.

GASTROINTESTINAL TRACT

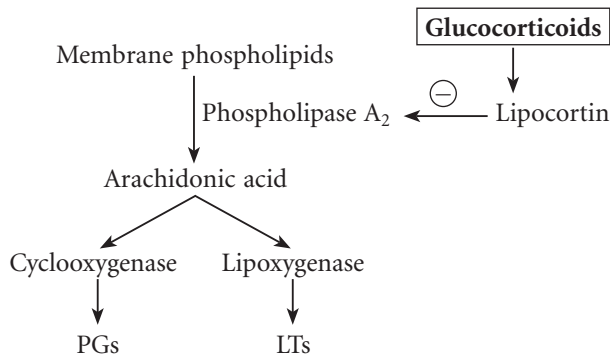


BLOOD AND LYMPHOID TISSUE

Glucocorticoid therapy leads to a decrease in the number of circulating lymphocytes, eosinophils, basophils and monocytes. This is due to redistribution of cells. They have a marked lympholytic action, therefore are used in lymphomas and leukaemias.

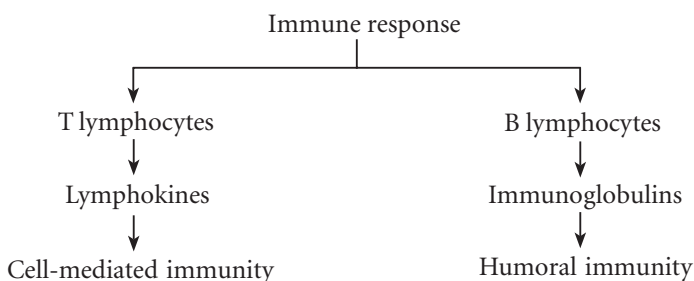
ANTI-INFLAMMATORY EFFECT

They have powerful anti-inflammatory and immunosuppressant effects. They prevent or suppress the clinical features of inflammation such as redness, heat, pain and swelling. At tissue level, they suppress the early phenomena (capillary permeability, oedema, cellular infiltration and phagocytosis) and late responses like capillary proliferation, collagen deposition, fibroblast activity and scar formation.



1. Glucocorticoids induce a protein called lipocortin which inhibits phospholipase A₂; hence, PGs, leukotrienes (LTs) and PAF are not formed.
2. Production of cytokines like IL-1, IL-6 and TNF- α necessary for initiating inflammation is inhibited.
3. Chemotaxis is suppressed.
4. Glucocorticoids stabilize lysosomal membrane and prevent release of inflammatory mediators.
5. Glucocorticoids inhibit expression of various adhesion molecules on endothelial cells, thus inhibiting leucocyte migration to site of injury.

IMMUNOSUPPRESSANT EFFECT



Glucocorticoids have immunosuppressant effect. They inhibit both B-cell and T-cell lymphocyte functions and this results in impairment of humoral and cell-mediated immunity. Cell-mediated responses are suppressed indirectly by inhibiting the production of cytokines, including TNF- α and interleukins. They also suppress all types of hypersensitivity or allergic reactions.

ADVERSE REACTIONS

A single dose of glucocorticoids is practically harmless, rather they are life-saving drugs in conditions like anaphylactic shock and acute adrenal insufficiency. The use of glucocorticoids in supraphysiological doses for more than 2–3 weeks causes a number of undesirable effects. Most of the adverse effects are extension of their pharmacological actions.

1. **Metabolic effects:** Hyperglycaemia, or aggravation of pre-existing diabetes.
2. **Cushing's habitus:** Abnormal fat distribution causes peculiar features with moon face, buffalo hump and thin limbs.
3. **GIT:** Peptic ulceration, sometimes with haemorrhage or perforation.
4. **Salt and water retention:** Mineralocorticoid effect may cause oedema, hypertension and even precipitation of CCF, particularly in patients with primary hyperaldosteronism. This can be minimized by using synthetic steroids like dexamethasone and betamethasone.
5. **Muscle:** Steroid treatment can cause hypokalaemia leading to muscle weakness and fatigability. Long-term steroid therapy leads to steroid myopathy.
6. **Bone:** Osteoporosis with pathological fractures of vertebral bodies is common. Ischaemic necrosis of femoral head can also occur.
7. **Growth retardation** in children is more common with dexamethasone and betamethasone.
8. **Eye:** Glaucoma and cataract may occur on prolonged therapy.
9. **CNS:** Behavioural disturbances like nervousness, insomnia, mood changes and even psychosis may be precipitated.
10. **Long-term therapy** with steroids leads to immunosuppression, which makes the patient vulnerable to opportunistic infections like fungal (candidiasis, cryptococcosis), viral (herpes, viral hepatitis) and bacterial (reactivation of latent tuberculosis). Inhalational steroids can cause local irritation and fungal infection of upper respiratory tract, which can be prevented by the use of spacer and by rinsing the mouth after inhalation.
11. **Hypothalamic–pituitary–adrenal (HPA) axis suppression:** The most dangerous side effect of long-term steroid therapy is HPA axis suppression. Long-term use of corticosteroids in large doses will decrease ACTH secretion through negative feedback effect on hypothalamus and pituitary and gradually cause adrenal cortical atrophy. Hence, abrupt stoppage of glucocorticoid therapy following prolonged use leads to:
 - Flaring up of the underlying disease being treated.
 - Withdrawal symptoms like fever, myalgia, arthralgia and malaise.
 - Acute adrenal insufficiency on exposure to stress which manifests as anorexia, nausea, vomiting, abdominal pain, hypotension, dehydration, hyponatraemia, hyperkalaemia, etc.

Therefore, important precautions to be taken during long-term steroid therapy to minimise HPA axis suppression are as follows:

- (a) Whenever possible, topical use is preferred.
- (b) Short- or intermediate-acting steroids (e.g. hydrocortisone, prednisolone) should be preferred.

- (c) Give steroids as a single morning dose at 8 a.m.; if the daily dose is high, administer two-third of the dose in the morning and one-third in the evening, which will mimic endogenous hormone levels and minimize chances of HPA axis suppression.
- (d) Try alternate-day steroid therapy in chronic conditions like bronchial asthma, nephrotic syndrome and systemic lupus erythematosus (SLE).
- (e) Withdrawal of steroids after long-term (>2 weeks) treatment should be very slow to allow recovery of normal adrenocortical function. The doses of steroid should be tapered gradually and then stopped. It will take days/weeks or even longer for HPA axis to recover after stoppage of therapy. During this period, patient will require treatment with steroids on exposure to stress.

Note: If a patient on long-term steroid therapy is exposed to stress like infections and major surgery, the dose of steroids administered should be increased to combat stress (as adrenals will fail to increase glucocorticoid secretion on account of HPA axis suppression).

THERAPEUTIC USES OF GLUCOCORTICOIDS

Replacement Therapy

1. **Acute adrenal insufficiency:** It is a medical emergency. It is treated with i.v. hydrocortisone and i.v. normal saline with 5% glucose to correct fluid and electrolyte imbalance. Precipitating causes such as trauma, infection or haemorrhage should be treated.
2. **Chronic adrenal insufficiency:** Treated with oral hydrocortisone (two-third of the daily dose is given in the morning and one-third in the evening) along with adequate salt and water.
3. **Adrenogenital syndrome and adrenal virilism:** Corticosteroids are helpful. The beneficial effect is due to suppression of pituitary ACTH, which in turn reduces adrenal androgens. A highly potent glucocorticoid like dexamethasone is preferred.

Nonendocrine Diseases. Corticosteroids are an important group of drugs used clinically in a variety of diseases. Because of their dramatic symptomatic relief, they are often misused. Nonendocrine diseases require supraphysiological doses of steroids. The beneficial effects of glucocorticoids are mainly due to their anti-inflammatory and immunosuppressant effects. They also have anti-allergic and lympholytic properties.

1. **Rheumatoid arthritis:** They produce an immediate and dramatic symptomatic relief in rheumatoid arthritis, but they do not halt progression of the disease. By their anti-inflammatory effects, they decrease the swelling, redness, pain and improve mobility of joints. Intra-articular injection is preferred only if one or two joints are involved. Steroid can be given as adjunct to nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs).
2. **Osteoarthritis:** They are rarely used in osteoarthritis. Intra-articular injection is recommended for acute episodes involving one or two joints.
3. **Rheumatic fever:** Glucocorticoids produce more rapid symptomatic relief than aspirin and are indicated in cases with carditis and CCF. Prednisolone is given along with aspirin and should be continued until the ESR comes to normal; then the steroid is tapered off gradually.
4. **Gout:** They are reserve anti-inflammatory drugs in acute gout not responding to NSAIDs.

5. **Allergic diseases:** The manifestations of allergic diseases, such as hay fever, reactions to drugs, urticaria, contact dermatitis, angioneurotic oedema and anaphylaxis, can be suppressed by glucocorticoids, but they have slow onset of action. Hence, severe reactions such as anaphylaxis and angioneurotic oedema require immediate therapy with adrenaline. In hay fever and mild allergic reactions, antihistamines are the preferred drugs.
6. **Bronchial asthma:** Glucocorticoids have anti-inflammatory and antiallergic effects; hence, they reduce mucosal oedema and bronchial hyperreactivity. They help to prevent and reverse tolerance to β_2 -agonists. In acute severe asthma, i.v. hydrocortisone is given along with nebulized β_2 -agonist and ipratropium bromide. If a chronic asthmatic needs steroid, it is better to give inhalational preparations like beclomethasone, budesonide or fluticasone because they cause minimal systemic adverse effects.
7. **Collagen diseases:** Collagen diseases such as polymyositis, polyarteritis nodosa, polymyalgia rheumatica and dermatomyositis can be controlled with large doses of glucocorticoids. Steroid with negligible salt- and water-retaining property is preferred.
8. **Renal disease:** Glucocorticoids are the first-line drugs in nephrotic syndrome.
9. **Ocular diseases:** They are frequently used to suppress inflammation in the eye, thus prevent damage to vision. Agents may be administered topically, subconjunctivally, systemically or by retrobulbar injection, depending upon the condition. Steroids are contraindicated in herpes simplex keratitis and ocular injuries.
10. **Skin diseases:** Glucocorticoids dramatically relieve itching, pain and inflammation in allergic and other dermatoses. To minimize systemic effects, topical steroids are preferred. Systemic steroid therapy is needed in severe conditions like exfoliative dermatitis, dermatomyositis and pemphigus. Psoriasis, keloids and hypertrophic scar are sometimes treated by intralesional injection of steroids.
11. **Haematological disorders:** Autoimmune haemolytic anaemias usually respond to glucocorticoids. Because of their lympholytic action, glucocorticoids are used to treat certain malignancies, leukaemia, lymphomas, Hodgkin disease, multiple myeloma, etc., usually in combination with antineoplastic drugs.
12. **Cerebral oedema:** The effectiveness of glucocorticoids in cerebral oedema depends upon the underlying cause. They are very effective when the oedema is caused by brain tumours, metastatic lesions and tubercular meningitis. They are least effective when the cerebral oedema is due to head injury. A steroid without salt and water retaining activity (e.g. dexamethasone) is preferred.
13. **Intestinal diseases:** They are used in ulcerative colitis when the patient is not responding to other forms of treatment. Methylprednisolone can be administered as retention enema during acute episodes.
14. **Shock:** Prompt intensive treatment with i.v. glucocorticoids may be life saving in septic shock.
15. **Organ transplantation:** Glucocorticoids are used to prevent as well as treat graft rejection.
16. **Hypercalcaemia** of malignant diseases, sarcoidosis and vitamin D intoxication responds to prednisolone.
17. **Other uses** include Bell palsy, acute polyneuritis and myotonia.
18. **Dexamethasone** can be used to test the HPA function.

RELATIVE CONTRAINDICATIONS FOR THE USE OF CORTICOSTEROIDS

1. Hypertension	7. Epilepsy
2. Diabetes mellitus	8. Psychosis
3. Peptic ulcer	9. Congestive cardiac failure
4. Tuberculosis	10. Renal failure
5. Herpes simplex keratitis	11. Glaucoma
6. Osteoporosis	

Metirapone: It blocks formation of hydrocortisone, hence useful to test the integrity of HPA axis and to treat hypercortisolism due to adrenal tumours.

Mifepristone: It has antiglucocorticoid, antiandrogenic actions and is a competitive antagonist of progesterone. It is useful in adrenal carcinoma.

Insulin and Oral Antidiabetic Agents

PH1.36

Diabetes mellitus (DM) is a clinical syndrome characterized by hyperglycaemia due to absolute or relative deficiency of insulin. Lack of insulin affects the metabolism of carbohydrate, protein and fat.

Type 1 DM: The aetiology is immunological or idiopathic. It appears when more than 90% of β -cells of pancreas are destroyed by an autoimmune process. The peak incidence is around 15 years. In type 1 DM, there is insulin deficiency. Insulin is essential for all patients with type 1 DM.

Type 2 DM: Genetic influence is much more powerful in type 2 DM. It is the commonest form of diabetes. Overeating, obesity, underactivity and ageing are the main risk factors. Type 2 DM is associated with increased hepatic production of glucose and resistance of target tissues to the action of insulin.

Hormones of pancreas: There are four types of cells in islets of Langerhans: β (B)-cells secrete insulin, α (A)-cells secrete glucagon, δ (D)-cells secrete somatostatin and F (PP)-cells secrete pancreatic polypeptide.

INSULIN

Insulin was discovered by Banting and Best. Insulin is synthesized by the β -cells of pancreatic islets from a single-chain polypeptide precursor called preproinsulin, which is converted to proinsulin. Insulin is formed by the removal of C-peptide from proinsulin by proteolysis. Insulin consists of two peptide chains called A and B (Fig. 9.19). These two chains are connected by two disulphide bridges. C-peptide (connecting peptide) can produce immunogenic reactions.

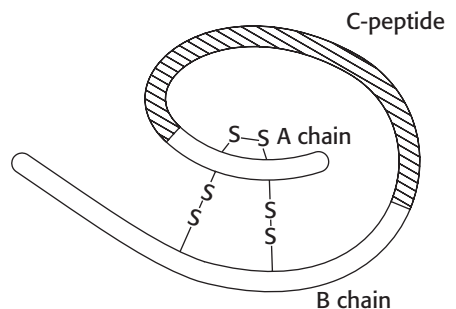


Fig. 9.19 Structure of proinsulin.

Regulation of Insulin Secretion

Insulin secretion is regulated by chemical, neural and hormonal mechanisms.

Chemical. Glucose, amino acids and fatty acids in the blood stimulate β -cells and release insulin (Fig. 9.20). Ingestion of nutrients (carbohydrate/protein/fat) causes

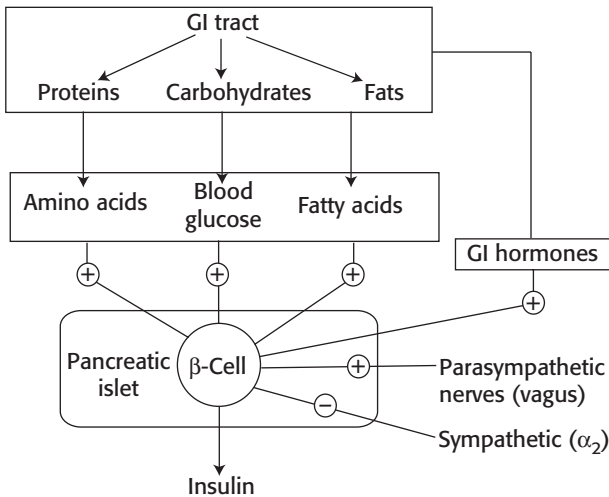


Fig. 9.20 Regulation of insulin secretion.

release of gut peptides (incretins) like GLP-1 (glucagon-like peptide) and GIP (glucose-dependent insulinotropic polypeptide) which promote the secretion of insulin. Oral nutrients (including glucose) are more effective in stimulating incretin secretion as compared to their intravenous infusion.

Neural. Both parasympathetic and sympathetic fibres supply the islet cells. Parasympathetic stimulation causes increase in insulin secretion and lowers raised blood glucose level. The islet cells have both α -adrenergic and β -adrenergic receptors. Adrenergic β_2 -stimulation increases insulin release and the blood glucose falls. Adrenergic α_2 -activation causes hyperglycaemia by inhibiting the release of insulin.

Hormonal. Counter-regulatory hormones like adrenaline, cortisol and glucagon promote glucose release from liver. Glucagon stimulates whereas somatostatin inhibits insulin release (Fig 9.21).

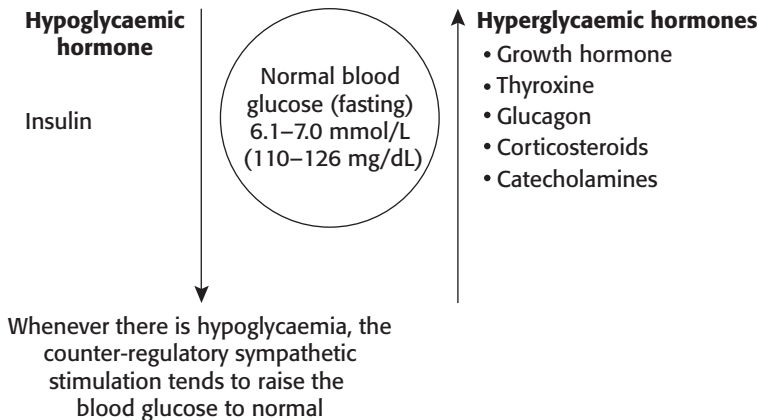


Fig. 9.21 Effect of various hormones on blood glucose level.

Actions of Insulin (Fig. 9.22)

Insulin has profound effects on the metabolism of carbohydrate, fat and protein. It facilitates the entry of glucose into all cells of the body. However, entry of glucose into RBCs, WBCs, liver and brain cells can occur independent of insulin. Exercise also facilitates entry of glucose into muscle cells without the need for insulin.

1. Insulin inhibits hepatic glycogenolysis and gluconeogenesis; inhibits lipolysis in adipose tissue.
2. Insulin enhances entry of amino acids into muscles and cells – promotes protein synthesis in muscle, lipogenesis, hepatic and muscle glycogenesis.
3. Insulin also promotes peripheral utilization of glucose and K^+ uptake into the cells.

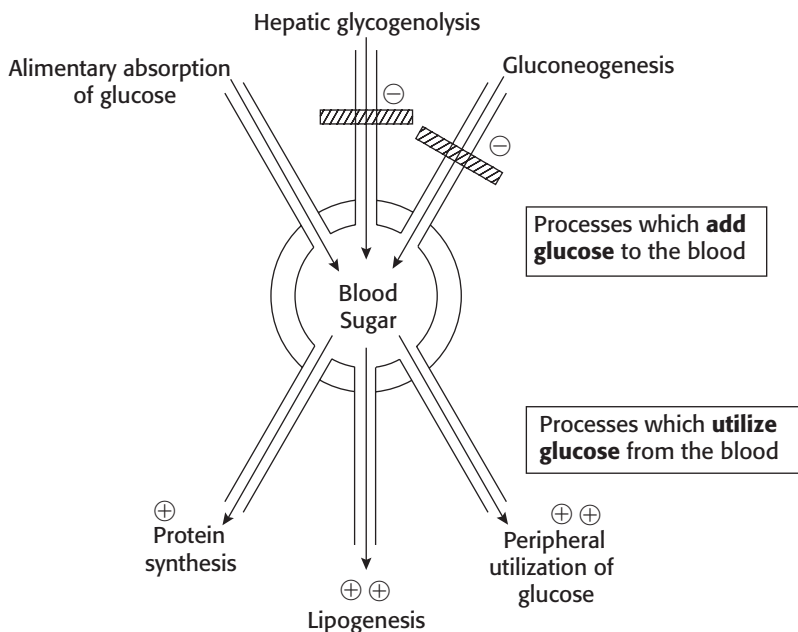


Fig. 9.22 Actions of insulin. ⊕, stimulation; ⊖, inhibition.

Mechanism of Action of Insulin

Insulin binds to specific receptors (tyrosine kinase receptor) present on the cell membrane. The receptor consists of two α and two β subunits (Fig. 9.23). The α subunits are entirely extracellular, whereas the β subunits are transmembrane proteins with tyrosine kinase activity. Binding of insulin to the α subunit activates tyrosine kinase activity of

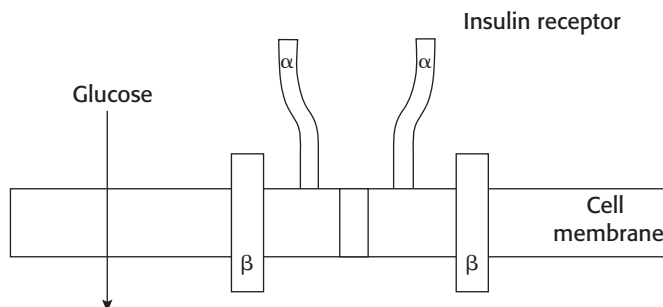


Fig. 9.23 Mechanism of action of insulin.

the β subunits resulting in phosphorylation of tyrosine residues of the receptor. This results in a complex series of phosphorylation–dephosphorylation reactions, which promotes entry of glucose into the cell and mediates various actions of insulin.

Pharmacokinetics

Insulin is destroyed by proteolytic enzymes in the gut, hence, not effective orally. Insulin is administered usually by subcutaneous (s.c.) route, but in emergencies, regular (soluble) insulin is given by i.v. route. After i.v. injection, soluble insulin is rapidly metabolized by the liver and kidney with a half-life of about 6 minutes.

Insulin Preparations

Conventional Insulin Preparations

1. **Bovine (beef) insulin:** It differs from human insulin by three amino acid residues and is antigenic to man.
2. **Porcine (pig) insulin:** It differs from human insulin by only one amino acid residue and is less immunogenic than bovine insulin.

These preparations are antigenic as they contain pancreatic proteins, proinsulin, etc. Hence, they are not used.

Monocomponent Insulins

Monocomponent insulins are purified insulins. They are less antigenic than conventional preparations, cause less insulin resistance and lipodystrophy at injection site, e.g. monocomponent porcine regular insulin, monocomponent porcine isophane insulin, etc.

Conventional porcine insulin $\xrightarrow{\text{Purification techniques}}$ Monocomponent pork insulin

(Purified insulins: insulin preparations with <10 ppm proinsulin contamination)

Human Insulins

They are produced by recombinant DNA technology using *Escherichia coli* or yeast. They have the same amino acid sequence as endogenous insulin. They are least immunogenic; insulin resistance and lipodystrophy at the site of injection are rare, e.g. human regular insulin and human NPH insulin. Purified human insulins are the commonly used insulin preparations.

Insulin Analogues

They are produced by DNA recombinant technology. The amino acid sequence is slightly different from endogenous insulin. Though actions are similar, pharmacokinetic profile is altered. They are either fast and short acting or slow and long acting.

Insulin Preparations Based on Onset and Duration of Action (Table 9.7)

Rapidly Acting Insulin Analogues. (Modification in B chain), e.g. insulin lispro, insulin aspart and insulin glulisine.

- They have less tendency to form hexamers (unlike regular insulin).
- On s.c. administration: quickly dissociate into monomers $\rightarrow$ rapidly absorbed $\rightarrow$ rapid onset of action within 5–15 minutes; peak effect in 1 hour. They are administered just before meals.
- Duration of action is about 4 hours; lower risk of late postprandial hypoglycaemia.
- Immunogenicity and binding to insulin receptor is similar to human regular insulin.

Table 9.7 ■ Insulin preparations based on onset and duration of action

Class	Type	Onset	Peak effect (hours)	Duration of action (hours)
I. Rapid-acting insulins	1. Insulin lispro	0.25 hour (15 minutes)	1–1.5	3–4
	2. Insulin aspart	0.25 hour (15 minutes)	1–1.5	3–4
	3. Insulin glulisine	0.25 hour (15 minutes)	1–2	3–4
II. Short-acting insulin	Regular soluble insulin (crystalline)	0.5–1 hour	2–4	6–8
III. Intermediate-acting insulin	NPH ^a (isophane)	1–2 hours	6–10	10–20
IV. Long-acting insulins	1. Insulin glargine	2–4 hours	— ^b	20–24
	2. Insulin detemir	1–4 hours	— ^b	20–24

^aNPH, neutral protamine Hagedorn.^bPeak is minimal.**Short-Acting Insulin*****Regular (Soluble) Insulin***

- Short acting, soluble, crystalline zinc insulin.
- Forms hexamers; after s.c. injection, it is slowly absorbed → onset of action is within 30 minutes; administered 30–45 minutes before meals.
- Duration of action is 6–8 hours.
- Available as 40 U/mL, 100 U/mL and 500 U/mL.
- Can be administered by s.c., i.m. and i.v. routes.

Intermediate-Acting Insulin***NPH (Neutral Protamine Hagedorn) Insulin or Isophane Insulin***

- Intermediate-acting insulin.
- Insulin complexed with protamine and zinc; dissociates slowly on s.c. administration → onset of action is delayed and duration of action is 10–20 hours.
- Cloudy solution.
- Given s.c. once or twice daily.

Long-Acting Insulins***Long-Acting Insulin Analogues.*** For example, insulin glargine and insulin detemir.***Insulin Glargine***

- On s.c. administration: precipitates and is slowly absorbed → delayed onset of action (24 hours) with ‘peakless’ plasma concentration.
- Lower risk of nocturnal hypoglycaemia than NPH insulin.
- Administered once daily.
- Cannot be mixed with other human insulins because of its acidic pH.
- Fasting blood glucose levels better controlled than NPH insulin.
- Should be avoided in pregnant diabetics.

Insulin Detemir

- On s.c. injection: binds to albumin in blood → prolonged duration of action.
- Minimal peak level.
- Usually given twice daily.

INSULIN THERAPY

Insulin is the main drug for all patients with type 1 DM, and for patients with type 2 DM who are not controlled by diet and oral antidiabetic drugs. The main goal of insulin therapy is to maintain the fasting blood glucose concentration between 90 and 120 mg/dL and postprandial glucose level below 150 mg/dL.

Concentration of Insulin

Insulin preparations are available in a concentration of 100 U/mL or 40 U/mL. Regular insulin is also available in 500 U/mL. Insulin dosage is measured in units (U). All insulin preparations are administered by s.c. route. Regular insulin can be given by i.v. route in diabetic ketoacidosis to get rapid effect.

Insulin Regimens

Various regimens of mixture of insulins are used for therapy. The split mixed regimen – often, a split dose of 70:30 NPH/regular insulin mixture is administered before breakfast and before dinner. Another regimen (intensive regimen) consists of administration of long-acting insulin either before breakfast or at bedtime and injection of short-acting insulin before each meal (preprandial). Intermediate- and long-acting insulins maintain basal insulin levels; preprandial insulin provides postprandial needs of insulin.

Mixed Insulin Preparations

- Intermediate-acting insulin takes several hours to achieve effective plasma concentration. Hence, they are combined with regular insulin/rapidly acting insulin analogues.
- NPH (intermediate-acting insulin) + regular insulin. They can be mixed in the same syringe.
- Stable premixed insulin mixtures are available, e.g. NPH 70% + regular insulin 30%.
- Premixed preparations of NPH with insulin lispro/aspart are unstable. Hence, protamine is complexed with insulin lispro to form neutral protamine lispro (NPL) and with aspart resulting in neutral protamine aspart (NPA), which are intermediate acting like NPH insulin.

Premixed combination of NPL and insulin lispro:

- 75% NPL/25% insulin lispro.
- 50% NPL/50% insulin lispro.

Premixed combination of NPA and insulin aspart: 70% NPA/30% insulin aspart.

Long-acting insulin analogues (glargine and detemir) should not be mixed with regular insulins or rapidly acting insulin analogues. They should be administered separately.

Insulin Administration

- Insulin syringes and needles.
- Pen devices: They are convenient to carry; a preset amount is delivered subcutaneously.
- Insulin pumps are available for continuous s.c. insulin infusion. Short-acting insulin, e.g. regular insulin is used. An advantage is that it is programmed to deliver

insulin to maintain basal levels and also a bolus dose prior to meals. It is expensive and there could be mechanical problems with the pump.

Indications for Insulin

1. Type 1 DM
2. Diabetic ketoacidosis
3. Nonketotic hyperglycaemic coma
4. Diabetes during pregnancy
5. Stress of surgery, infections and trauma (temporarily to tide over trauma, infection, surgery, etc.) in diabetics
6. Patients with type 2 DM in addition to oral antidiabetic drugs

Site of Administration

Insulin is usually administered subcutaneously in the abdomen, buttock, anterior thigh or dorsal arm.

Complications of Insulin Therapy

1. Hypoglycaemia is the most common and dangerous complication. Prolonged hypoglycaemia may cause permanent brain damage. Hypoglycaemia can occur in any diabetic and may be due to delay in taking food, too much physical activity or excess dose of insulin.

Symptoms of hypoglycaemia are

- (a) Autonomic symptoms: They occur initially and are due to counter-regulatory sympathetic stimulation – sweating, tremor, palpitation, anxiety and tachycardia.
- (b) Neuroglycopenic symptoms like headache, blurred vision, confusion, loss of fine motor skill and abnormal behaviour. They usually occur at lower plasma glucose levels.

With further lowering of blood glucose levels, convulsions and loss of consciousness can occur.

Treatment: All these manifestations are relieved by administration of glucose.

If the patient is conscious, oral glucose or if the hypoglycaemia is severe (unconscious patient) 50 mL of 50% dextrose is injected intravenously.

Glucagon 1 mg i.v. or adrenaline 0.2 mg s.c. may be given for severe hypoglycaemia.

2. Allergic reactions are rare; they may cause local skin reactions (swelling, redness) at the site of injection and may be due to minor contaminants.
3. Lipodystrophy (either atrophy or hypertrophy) may occur at the site of injection. It may be avoided by using purified insulin preparations and changing the injection site by rotation.
4. Oedema due to salt and water retention.

Insulin Resistance. It is a state in which there is decreased response of peripheral tissues to insulin. Acute insulin resistance develops during stressful conditions like trauma, infection, surgery and psychological stress. Dose of regular insulin should be increased.

Diabetic Ketoacidosis

Diabetic ketoacidosis is a complication of type 1 DM. It is rare in type 2 DM. The common precipitating factors are infection, trauma, severe stress, etc. The clinical features are anorexia, nausea, vomiting, polyuria, abdominal pain, hypotension, tachycardia, hyperventilation, altered consciousness or coma in untreated cases. Diabetic ketoacidosis is a medical emergency.

Management of Diabetic Ketoacidosis

- Insulin replacement: Regular insulin is administered as intravenous bolus in a dose of 0.2–0.3 U/kg followed by 0.1 U/kg/hour i.v. infusion. Blood glucose levels should decrease by 10% in the first hour. Monitoring of blood glucose levels should be done for optimal insulin replacement. Once patient becomes conscious, insulin can be administered subcutaneously.
- Fluid replacement: Initially, normal saline is infused intravenously at 1 L/h; then rate of infusion is gradually decreased depending on the requirement of the patient. Once blood glucose levels fall to about 250 mg/dL, 5% glucose in ½ N saline is administered to prevent development of hypoglycaemia and cerebral oedema.
- Potassium: Following insulin therapy and correction of acidosis, potassium shifts into the cells resulting in hypokalaemia. Potassium chloride 10–20 mEq/h is infused after 4 hours of initiation of insulin therapy. Serum potassium and ECG should be monitored to determine potassium replacement.
- Sodium bicarbonate i.v. is administered if required.
- Phosphate: Patients with severe hypophosphataemia require phosphate replacement.
- Antibiotics to treat associated infection, if any.

Hyperosmolar Nonketotic Diabetic Coma

It is a medical emergency. It is characterized by severe hyperglycaemia (in the absence of ketosis), hyperosmolality and dehydration. The general principle of treatment is same as for diabetic ketoacidosis except that the patient needs more and faster fluid replacement. There is a high mortality rate of about 50% in spite of intensive therapy.

Drug Interactions

1. β -Blockers $\times$ insulin (see Fig. 2.25, p. 94).
2. Salicylates $\times$ insulin: Salicylates exert hypoglycaemic effect by increasing the sensitivity of pancreatic β -cells to glucose and potentiating insulin secretion.

ORAL ANTIDIABETIC DRUGS (Table 9.8)

1. Sulphonylureas
 - (a) First generation: Tolbutamide
 - (b) Second generation: Glyburide (glibenclamide), glipizide, gliclazide, glimepiride
2. Biguanide: Metformin
3. Meglitinide analogue: Repaglinide
4. D-phenylalanine derivative: Nateglinide
5. Thiazolidinediones: Pioglitazone
6. α -Glucosidase inhibitors: Acarbose, miglitol, voglibose
7. Dipeptidyl peptidase-4 (DPP-4) inhibitors: Sitagliptin, saxagliptin, alogliptin, linagliptin, vildagliptin, teneligliptin
8. SGLT-2 (sodium–glucose co-transporter-2) inhibitor: Dapagliflozin, canagliflozin

Other Antidiabetic Agents (Parenteral)

- GLP-1 analogue: Exenatide, albiglutide, dulaglutide, liraglutide, lixisenatide.
- Others: Pramlintide

Note:

- Biguanides and thiazolidinediones are insulin sensitizers.
- Sulphonylureas, meglitinides, DPP-4 inhibitors and GLP-1 analogues are insulin secretagogues.

Table 9.8 ■ Oral and other antidiabetic drugs: dosage and duration of action

Drug	Daily dose	Duration of action (hours)	Other points
I. Sulphonylureas (given orally half an hour before food)			
• Tolbutamide	0.5–2 g, in two or three divided doses	6–12	Short acting, low potency and least likely to cause hypoglycaemia
• Chlorpropamide	0.1–0.5 g, as a single dose	48–72	Incidence of hypoglycaemia is more because of long duration of action, has disulfiram-like action, increases the release of ADH, hence useful in neurogenic diabetes insipidus.
• Glibenclamide (glyburide)	1.25–20 mg, single or two divided doses	12–24	Hypoglycaemia is common because of long duration of action. The active metabolite accumulates in renal failure.
• Gliclazide	40–320 mg, single or in two divided doses	12–24	It is a commonly used second-generation sulphonylurea with antiplatelet effect.
• Glipizide	5–40 mg, one to two doses	12–18	Shorter acting, lower potency and is preferred in elderly patients.
• Glimepiride	1–8 mg, single dose	Up to 24	Used once daily as monotherapy or in combination with insulin. It causes less hypoglycaemia than glibenclamide.
II. Biguanide			
Metformin	500 mg orally three times daily, given with food (maximum dose is 2.5 g/day)	8–12	Metformin is used in patients with type 2 DM, either alone or in combination with sulphonylurea/insulin/other antidiabetics. It is not used in patients with type 1 DM and is contraindicated in patients with hepatic insufficiency and alcoholism. Lactic acidosis is less common than with phenformin.
III. Meglitinide analogue			
Repaglinide	0.25–4 mg orally in two divided doses, given 15 minutes before breakfast and dinner	3	Repaglinide can be used in combination with metformin. It is rapid acting. Less risk of hypoglycaemia because of short duration of action. It may be useful in patients with renal impairment or in the elderly.

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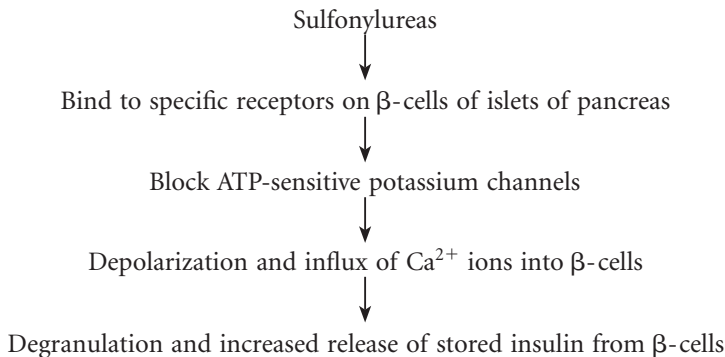
Table 9.8 ■ Oral and other antidiabetic drugs: dosage and duration of action—cont'd

Drug	Daily dose	Duration of action (hours)	Other points
IV. D-Phenylalanine derivative			
Nateglinide	60–120 mg orally t.d.s., given just before food	2–4	Has rapid onset and short duration of action. Side effects are hypoglycaemia and weight gain.
V. Thiazolidinediones			
• Rosiglitazone	2–8 mg orally daily	Up to 24	Cause fluid retention, weight gain and can precipitate CHF. The drug should be avoided in patients with liver and heart disease and bladder cancer.
• Pioglitazone	15–45 mg orally daily	Up to 24	
VI. α-Glucosidase inhibitors			
Acarbose	50 mg orally b.d. gradually increased to 100 mg t.d.s. just before food	4	Side effects are flatulence, fullness and diarrhoea
VII. GLP-1 receptor agonist			
• Exenatide	5–10 mcg, subcutaneously b.d. 1 hour before breakfast and dinner	6	May cause nausea
• Albiglutide	30–50 mg	1 week	Causes weight loss; long acting
• Dulaglutide	0.5–1.5 mg	1 week	
• Liraglutide		24	
VIII. DPP-4 inhibitors			
• Sitagliptin	Oral, 100 mg o.d.	24	Can cause allergic reactions, pancreatitis.
• Saxagliptin	Oral, 2.5 mg/5 mg o.d.	24	May have drug interactions
• Vildagliptin	50 mg orally o.d.	24	No significant drug interactions
IX. SGLT-2 inhibitors			
• Dapagliflozin	5 mg orally o.d.	Terminal half-life: 12.9	Glycosuria can lead to urinary tract infection
X. Amylin analogue			
• Pramlintide	60–120 mcg t.d.s. subcutaneously before food	2	Useful in type 1 and type 2 diabetes mellitus. Nausea and hypoglycaemia can occur.

Sulphonylureas. Sulphonylureas are divided into two generations. All these drugs have the same mechanism of action, but differ in potency and duration of action. The second-generation drugs are more potent than first-generation drugs.

Mechanism of Action

1. Sulphonylureas stimulate insulin secretion from β -cells of pancreas. It is an insulin secretagogue.



For successful therapy with sulphonylureas, at least 30% functioning β -cells are necessary. Sulphonylureas are ineffective in type 1 DM because of absence of functioning β -cells in the islets of pancreas.

2. Sulphonylureas increase the sensitivity of peripheral tissues to insulin by increasing the number of insulin receptors.
3. They reduce the release of glucagon.

Pharmacokinetics. Sulphonylureas are well absorbed after oral administration, highly bound to plasma proteins and have low volume of distribution. They are metabolized in liver and excreted mainly in urine.

Adverse Effects

1. Hypoglycaemia is common, particularly with glibenclamide and chlorpropamide due to their long duration of action. Glibenclamide is best avoided in elderly patients because of the high risk of hypoglycaemia.
2. GI disturbances like nausea, vomiting, diarrhoea and flatulence.
3. Weight gain is due to stimulation of appetite.
4. Allergic reactions: Skin rashes, itching and photosensitivity.
5. Teratogenicity: Sulphonylureas are not safe during pregnancy.
6. Chlorpropamide has disulfiram-like action, hence, produces intolerance to alcohol.

Use. Sulphonylureas are useful in patients with type 2 DM.

Drug Interactions

1. **Sulphonylureas $\times$ salicylates/sulphonamides:** These drugs are highly bound to plasma proteins and displace sulphonylureas from the plasma protein-binding site, resulting in an increase in free plasma concentration of sulphonylureas – potentiate the effects of sulphonylureas (severe hypoglycaemia).
2. **Propranolol $\times$ sulphonylureas:** Propranolol by blocking hepatic β_2 -receptors, inhibits glycogenolysis and delays recovery from hypoglycaemia. Propranolol also masks the symptoms of sulphonylurea-induced hypoglycaemia, such as tachycardia and palpitation (by blocking β_1 -receptors of the heart) and tremors (by blocking β_2 -receptors in skeletal muscle).

3. **Rifampicin, phenobarbitone × sulphonylureas:** Rifampicin and phenobarbitone are enzyme inducers; hence, they accelerate the metabolism of sulphonylureas and reduce their effects.
4. **Warfarin, sulphonamides × sulphonylureas:** They inhibit the metabolism of sulphonylureas, thereby, increase the plasma levels of sulphonylureas leading to severe hypoglycaemia.

Biguanides. Metformin is the only biguanide used clinically.

Mechanism of Action. The mechanism of action of biguanides is shown in Fig. 9.24.

Metformin

1. It activates the enzyme AMP-dependent protein kinase (AMPK). This results in
 - a. Decreased hepatic gluconeogenesis (major action).
 - b. Increased peripheral utilization of glucose in skeletal muscle and fat resulting in glycogen storage in the skeletal muscle, increased fatty acid oxidation and decreased lipogenesis.
2. Inhibition of alimentary absorption of glucose.

Biguanides do not affect insulin release; they improve tissue sensitivity to insulin.

Pharmacokinetics. Metformin is taken orally, well absorbed through GI tract and is excreted mostly unchanged in urine.

Adverse Effects. Adverse effects are metallic taste, anorexia, nausea, vomiting, diarrhoea, loss of weight and skin rashes. Lactic acidosis is the most serious complication but is rare with metformin. Prolonged use can cause vitamin B₁₂ deficiency due to malabsorption. Metformin usually does not cause hypoglycaemia even in large doses.

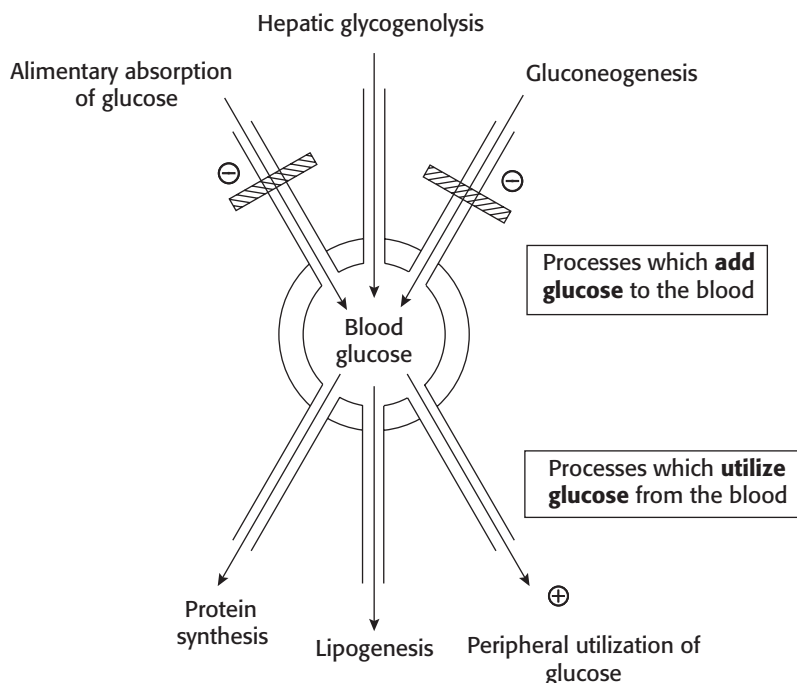


Fig. 9.24 Mechanism of action of biguanides. ⊕, stimulation; ⊖, inhibition.

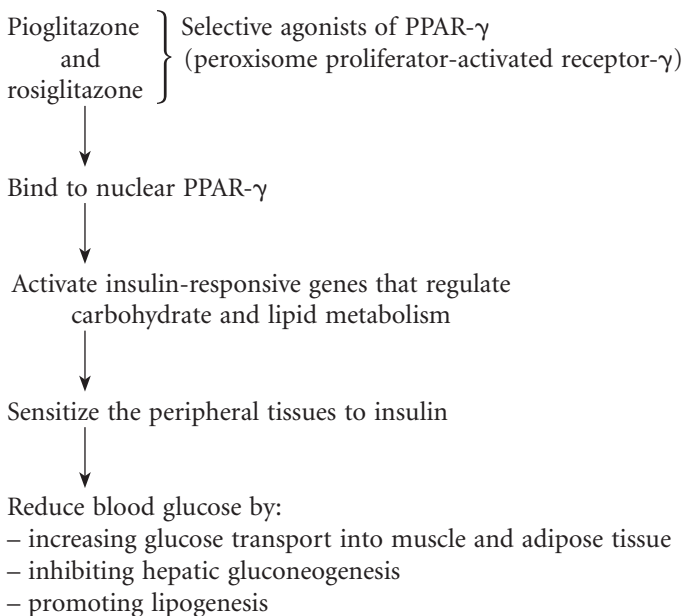
Use. Metformin is used in patients with type 2 DM either alone or in combination with other antidiabetic agents. Hypoglycaemia is rare. It protects against vascular complications of diabetes.

Meglitinide Analogue (Repaglinide) and D-Phenylalanine Derivative (Nateglinide). Repaglinide and nateglinide are structurally unrelated to sulphonylureas but their mechanism of action is similar to sulphonylureas. They stimulate insulin release by closure of ATP-sensitive potassium channels in β -cells of islets of pancreas $\rightarrow$ depolarization $\rightarrow$ insulin release. Repaglinide and nateglinide are well absorbed from GI tract, metabolized mainly in the liver and should be avoided in patients with hepatic failure. They have rapid onset but short duration of action. They are less potent than sulphonylureas. They are used only in type 2 DM to control postprandial hyperglycaemia.

The main side effects of repaglinide are weight gain and hypoglycaemia, but the episodes are less frequent; meglitinide causes nausea and flu-like symptoms.

Dipeptidyl Peptidase-4 Inhibitors. Sitagliptin, alogliptin and linagliptin inhibit DPP-4 competitively whereas saxagliptin and vildagliptin bind covalently with the enzyme. They inhibit the enzyme DPP-4 $\rightarrow$ prevent inactivation of GLP-1 $\rightarrow$ increase plasma concentration of GLP-1 $\rightarrow$ increases insulin secretion, suppresses glucagon release, and improves control of fasting and postprandial hyperglycaemia. They do not affect gastric emptying, satiety and body weight. They are administered orally as adjuvants in patients with type 2 DM. Allergic reactions can occur with sitagliptin. Hepatotoxicity may occur with vildagliptin. Drug interactions are rare with vildagliptin. Risk of hypoglycaemia is low.

Thiazolidinediones. They increase sensitivity of peripheral tissues to insulin.



Other Actions. Pioglitazone reduces serum triglyceride and increases HDL levels.

Pharmacokinetics. Pioglitazone is almost completely absorbed from GI tract, highly bound to plasma proteins (95%) and metabolized in the liver.

Adverse Effects. Nausea, vomiting, anaemia, oedema, weight gain, and precipitation of heart failure in patients with low cardiac reserve; rarely hepatotoxicity and bladder cancer may occur. There is an increased risk of cardiovascular events with rosiglitazone. Its use has been suspended in some countries.

Use. Pioglitazone is used alone or in combination with sulphonylureas/metformin in patients with type 2 DM.

α -Glucosidase Inhibitors. These drugs should be given just before food.

Acarbose, Miglitol and Voglibose. They reduce intestinal absorption of carbohydrates by inhibiting the enzyme α -glucosidase in the brush border of the small intestine and reduce postprandial hyperglycaemia. They are mainly used in obese patients with type 2 DM. Side effects are mainly on GI tract: flatulence, fullness and diarrhoea.

GLP-1 Analogues (e.g. Exenatide, Liraglutide, Albiglutide, Dulaglutide, Lixisenatide). GLP-1, an incretin, is released from the gut after meals. It stimulates glucose-dependent insulin secretion, suppresses glucagon release and slows gastric emptying. It is degraded by DPP-4; its plasma half-life is 1–2 minutes; hence, it cannot be used therapeutically. GLP-1 analogues are resistant to DPP-4. Their action is similar to GLP-1. They are injected s.c. 1 hour before breakfast and dinner in type 2 DM patients. They are mainly used as adjuncts to other antidiabetic agents. This results in better glycaemic control, reduction in HbA_{1c} and body weight. They may help to prevent progression of β -cell failure in type 2 diabetes. Extended-release s.c. preparation of exenatide is available. Liraglutide is longer acting. Albiglutide and dulaglutide are long acting with a duration of 1 week. The main side effect is nausea. They usually do not cause hypoglycaemia, but it may occur when used in combination with other antidiabetic agents.

Pramlintide. It is a synthetic analogue of amylin (islet amyloid polypeptide). It decreases glucagon secretion, delays gastric emptying, suppresses appetite and decreases body weight. Pramlintide (as an adjuvant) is administered subcutaneously in patients with type 1 and type 2 DM just before meals. Nausea and hypoglycaemia are common adverse effects.

Sodium–Glucose Co-Transporter-2 Inhibitors. For example, dapagliflozin, canagliflozin and empagliflozin $\rightarrow$ inhibit SGLT-2 in renal proximal tubule $\rightarrow$ inhibit glucose reabsorption $\rightarrow$ glycosuria, $\downarrow$ blood glucose levels. SGLT-2 inhibitors are used as adjunct medication for better glycaemic control. Adverse effects include urinary tract infection.

Agents Affecting Calcium Balance

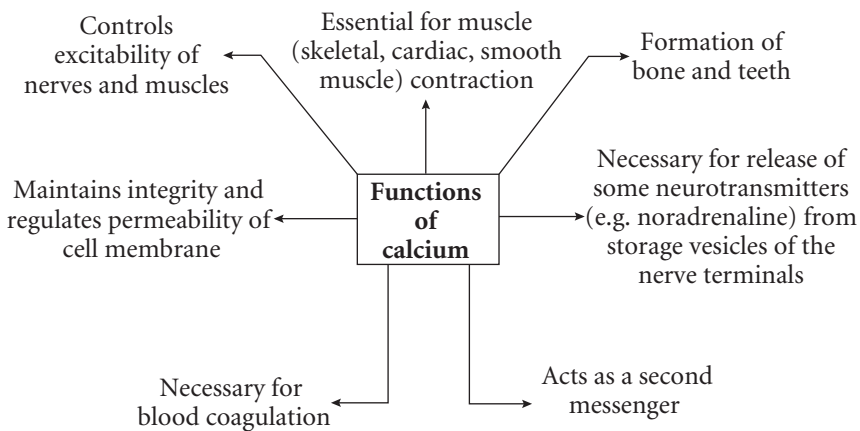
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CALCIUM

About 99% of calcium of our body is in bone and teeth. Calcium metabolism is chiefly regulated by three hormones: parathormone (PTH), vitamin D and calcitonin. PTH plays a central role in regulating calcium homeostasis. Calcium metabolism is also

intimately connected with phosphorus and magnesium metabolism. The normal serum calcium level is 9–11 mg/dL.

Functions of Calcium



Preparations of Calcium

Oral. Calcium gluconate, calcium citrate, calcium lactate and calcium carbonate. Calcium carbonate is cheap, tasteless and is preferred because of its high percentage of calcium.

Parenteral

Intravenous calcium gluconate: Nonirritant, hence it is preferred.

Intravenous calcium chloride: Highly irritant and causes tissue necrosis.

Therapeutic Uses of Calcium Salts

1. To correct calcium deficiency:
 - (a) In growing children, pregnant and lactating women
 - (b) In dietary deficiency
 - (c) In postmenopausal osteoporosis
 - (d) In rickets and osteomalacia along with vitamin D
 - (e) In long-term corticosteroid therapy along with vitamin D
 - (f) After removal of parathyroid tumour
2. Intravenous calcium gluconate (10%) in tetany
3. Calcium carbonate is used as antacid
4. Intravenous calcium gluconate may be useful in treating urticaria and dermatoses

PARATHYROID HORMONE

PTH is a polypeptide hormone, which is synthesized by chief cells of the parathyroid gland. PTH secretion is chiefly controlled by the concentration of free Ca^{2+} in plasma – low-plasma Ca^{2+} stimulates secretion and vice versa.

PTH activates, via G-protein-coupled receptors, adenylyl cyclase enzyme present in the cell membrane, which, in turn, increases the intracellular cAMP and Ca^{2+} concentration leading to various effects.

Causes of hypoparathyroidism

- Following thyroidectomy
- Idiopathic
 - Genetic
 - Autoimmune

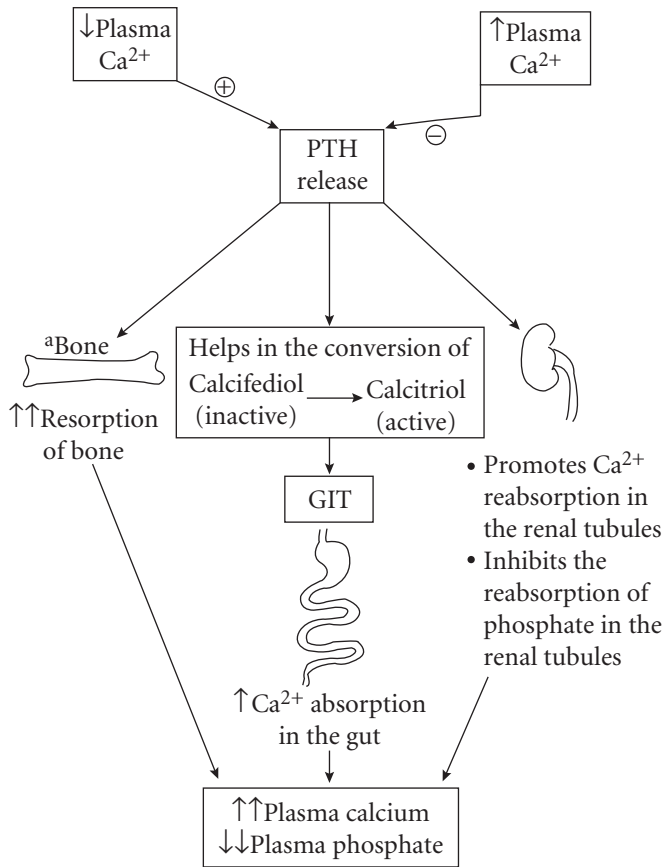
Clinical features of acute hypoparathyroidism

- Hypocalcaemia
- Tetany
- Carpopedal spasm
- Laryngospasm
- Tingling of lips, hands, muscles
- Convulsions

Clinical features of chronic hypoparathyroidism

- Loss of hair
- Brittle finger nails
- Caries of teeth
- Cataract
- Anxiety and depression

Actions of PTH



^aLow intermittent doses of PTH stimulates bone formation.

Hypoparathyroidism (Deficiency of Parathyroid Hormone)

Treatment

1. Emergency treatment of acute attack (hypoparathyroid tetany)
 - (a) 10% calcium gluconate 10–20 mL given i.v. slowly until tetany ceases.
 - (b) Oral calcium salts should be started as soon as possible.
2. Treatment of chronic hypoparathyroidism
 - (a) The treatment of choice is vitamin D₂ (ergocalciferol).
 - (b) Oral calcium salts should be started as soon as possible.

Hyperparathyroidism

Hyperparathyroidism is characterized by increased levels of parathormone, often due to parathyroid tumour. There is hypercalcaemia and hypercalciuria. Treatment involves surgical removal of the tumour. Some of the cases of hyperparathyroidism can be treated with cinacalcet.

Cinacalcet (Calcimimetic Agent)

- Binds to receptors on parathyroid gland → ↓ PTH secretion → ↓ serum Ca²⁺ levels.
- Route: Oral.
- Use: Hypercalcaemia due to parathyroid tumour; secondary hyperparathyroidism due to renal disease.
- Adverse effect: Hypocalcaemia.

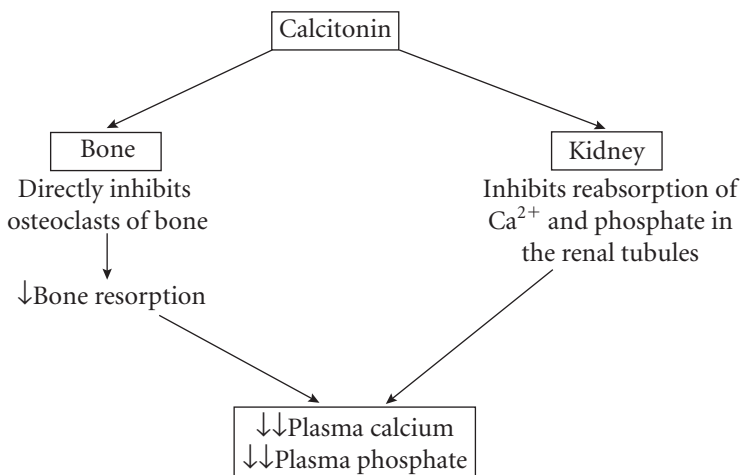
Teriparatide

- Recombinant preparations of PTH.
- Route: Administered subcutaneously, once daily.
- Stimulates bone formation.
- Use: Treatment of severe osteoporosis – improves bone mineral density
- Adverse effect: Hypercalcaemia
- Expensive.

Calcitonin

Calcitonin is synthesized by the 'C' cells of the thyroid. It is a peptide hormone. The main actions of calcitonin are to lower serum calcium and phosphate by direct action on bone and kidney. Calcitonin secretion is stimulated when the serum calcium level becomes high and vice versa.

Actions of Calcitonin (Generally Opposite to That of PTH)



Preparations of Calcitonin

1. Porcine (natural) calcitonin – antigenic – can lead to production of antibodies.
2. Synthetic salmon calcitonin.
3. Synthetic human calcitonin.

Calcitonin is given by s.c. or i.m. route. Salmon calcitonin is also available as nasal spray.

Therapeutic Uses

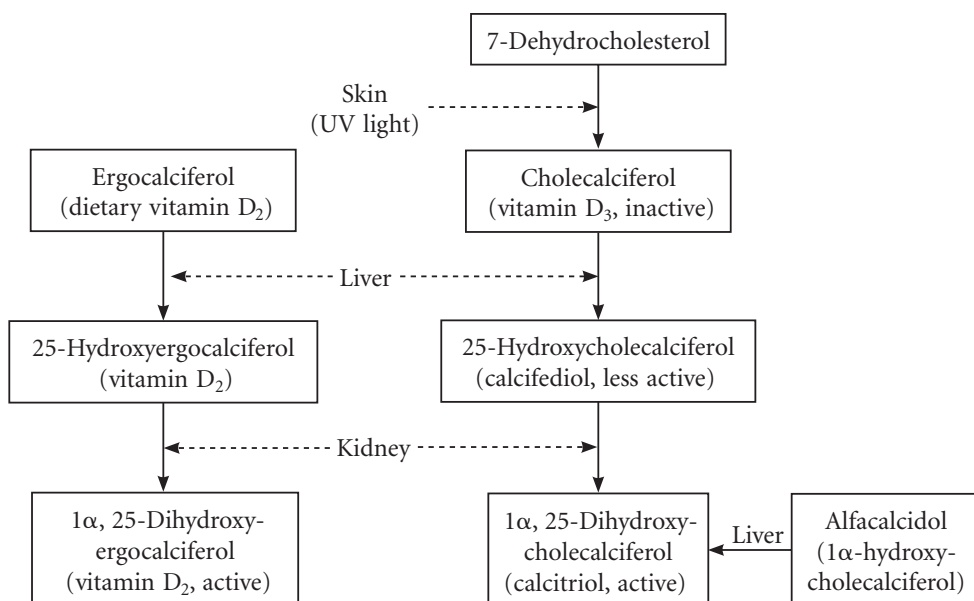
1. In hypercalcaemic states (e.g. associated with neoplasia).
2. In Paget disease of bone: Chronic use of calcitonin relieves pain and reduces some of the neurological complications, but bisphosphonates are the treatment of choice.
3. In postmenopausal osteoporosis and corticosteroid-induced osteoporosis: Salmon calcitonin is used as nasal spray along with calcium and vitamin D supplements.

Adverse effects are nausea, vomiting, flushing and pain at the site of injection.

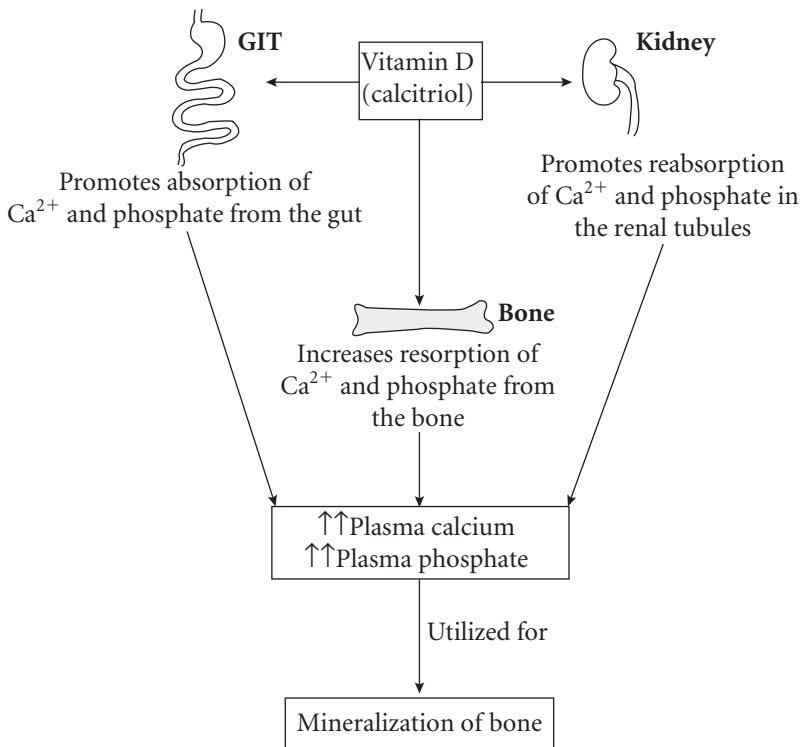
VITAMIN D

Vitamin D is a fat-soluble vitamin. It is a prohormone, which is converted in the body into a number of biologically active metabolites that function as true hormone. Vitamin D, together with PTH, plays a central role in the maintenance of plasma calcium and bone formation. Vitamin D is found in fish liver oils and dairy products; it is also synthesized in the skin on exposure to sunlight.

Pathways of Vitamin D Production



Actions of Vitamin D



Vitamin D deficiency causes rickets in children and osteomalacia in adults. Hypervitaminosis D may occur due to acute large dose or long-term use of vitamin D. The signs and symptoms of hypercalcaemia are nausea, weakness, fatigue and polyuria. If hypercalcaemia persists, calcium salts are deposited in the kidney, resulting in renal failure and renal stones. Treatment includes immediate stoppage of vitamin D, low-calcium diet, intravenous hydration and administration of glucocorticoids.

Preparations of Vitamin D

- Ergocalciferol (vitamin D₂): Oral capsules 400 IU/day for prevention of rickets in children and osteomalacia in adults.
 - Cholecalciferol (vitamin D₃): Oral and i.m. injection.
 - Calcitriol: Active form of vitamin D. Oral capsules and solution.
 - Alfacalcidol
 - Dihydrotachysterol
- } Prodrugs, orally effective; do not require activation in the kidney; are rapidly biotransformed into calcitriol in liver. They are effective in renal bone disease and hypoparathyroidism.
- Calcipotriol: It is used topically in psoriasis.

Therapeutic Uses of Vitamin D

1. Prevention (400 IU/day) and treatment (4000 IU/day) of nutritional rickets and osteomalacia.
2. Renal rickets: It is associated with chronic renal failure; hence, the conversion of calcifediol to calcitriol does not occur. It is treated with calcitriol or alfacalcidol.

3. Vitamin D–dependent rickets: It is an inborn error of vitamin D metabolism. There is a failure of conversion of calcifediol to calcitriol. It responds to calcitriol or alfacalcidol.
4. Vitamin D–resistant rickets and osteomalacia: They are X-linked disorders of calcium and phosphate metabolism. They are treated with large doses of vitamin D and phosphate.
5. In hypoparathyroidism, there is hypocalcaemia and hyperphosphataemia. Calcitriol and alfacalcidol are effective for temporary treatment of hypocalcaemia.
6. Administration of vitamin D with calcium in senile or postmenopausal osteoporosis improves calcium balance and may reduce the risk of fractures.
7. Vitamin D analogue, calcipotriol, is used topically in the treatment of psoriasis.

Bisphosphonates

Bisphosphonates are analogues of pyrophosphate. They are Pamidronate (i.v. infusion), Alendronate (oral), Zoledronate (i.v. infusion), Etidronate (oral, i.v.), Tiludronate (oral), Risedronate (oral), etc. (Mnemonic: PAZET)

MECHANISM OF ACTION

Bisphosphonates exert antiresorptive effect. They:

- Have high affinity for calcium in the bone → accumulate in areas of bone resorption → taken up by osteoclasts → inhibits ability of osteoclasts to form ruffled border and promotes their apoptosis.
- Interfere with mevalonate pathway of cholesterol synthesis which is required for normal function of osteoclasts (this is the important mechanism of action for alendronate, risedronate, etc.).

PHARMACOKINETICS

Bisphosphonates are highly polar, hence, poorly absorbed through GI tract; a part of the absorbed drug is incorporated into bone and remains for long from months to years. The free drug is excreted unchanged in urine. Zoledronate has less irritant effect on injected vein; it is administered once a year.

USES

1. Paget disease of bone: Bisphosphonates are the treatment of choice for Paget disease. They are usually given cyclically. They reduce bone pain and decrease alkaline phosphatase level.
2. For prevention and treatment of postmenopausal osteoporosis: These drugs improve bone mineral density and reduce incidence of vertebral fracture.
3. To prevent corticosteroid-induced osteoporosis along with oral calcium carbonate.
4. Hypercalcaemia of malignancy: Bisphosphonates control hypercalcaemia by inhibiting bone resorption. Zoledronate is most potent and is the drug of choice for malignant hypercalcaemia.
5. Bisphosphonates are also useful to control hypercalcaemia of hyperparathyroidism.
6. To relieve pain of lytic bone lesions.

ADVERSE EFFECTS

They include nausea, vomiting, diarrhoea, heartburn, oesophagitis, peptic ulcer, fever, myalgia, hypocalcaemia, headache and skin rashes. Oral bisphosphonates should be taken with plenty of water and the patient should remain upright for at least 30 minutes to prevent oesophagitis. Flu-like symptoms can occur on parenteral administration. Rarely, osteonecrosis of the jaw may occur.

DRUGS USEFUL IN HYPERCALCAEMIA

Bisphosphonates and mithramycin (inhibit bone resorption), glucocorticoids ($\downarrow$ Ca²⁺ absorption and $\uparrow$ its excretion), furosemide.

Strontium Ranelate. It inhibits bone resorption and is used for treatment of osteoporosis.

Denosumab. It is a monoclonal antibody useful for treatment of osteoporosis. Bone resorption is inhibited. It is administered s.c. once in 6 months.

Drugs Acting on Uterus

Uterine Stimulants and Relaxants

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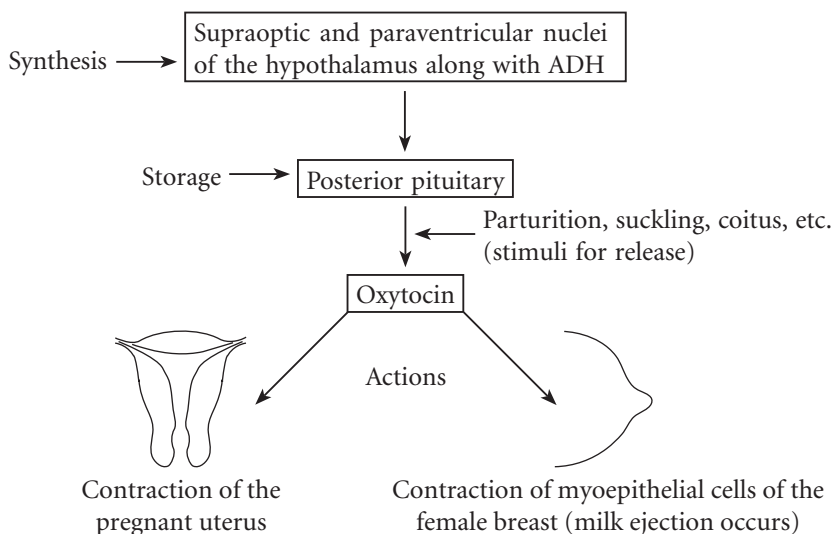
UTERINE STIMULANTS (OXYTOCICS, ECBOLICS)

Oxytocics are drugs that cause uterine contraction. They include:

- Oxytocin
- Ergot derivatives: Ergometrine and methylergometrine
- Prostaglandins: PGE_2 , $\text{PGF}_{2\alpha}$, 15-methyl $\text{PGF}_{2\alpha}$ and misoprostol (PGE_1)

Oxytocin

It is a hormone synthesized in the hypothalamus along with antidiuretic hormone (ADH) and stored in neurohypophysis. The storage, release and actions of oxytocin are shown below:



Pharmacological Actions

1. **Uterus:** Oxytocin stimulates contraction of the pregnant uterus.

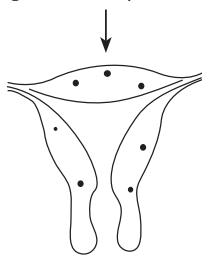
Uterine sensitivity to oxytocin is increased by oestrogens and decreased by progestins. Oestrogens increase oxytocin receptors.

- Nonpregnant uterus is relatively insensitive to oxytocin.
- In early pregnancy, uterus is fairly resistant to oxytocin. High dose of oxytocin is required to stimulate the uterus. The sensitivity of uterus to oxytocin gradually increases during pregnancy, especially in the last half, with a sharp rise near term. Oxytocin increases both force and frequency of uterine (only fundus and body) contractions.

With intravenous infusion of low dose of oxytocin, there is a period of complete relaxation between uterine contractions. This helps to maintain blood flow to the placenta and fetus, thereby preventing fetal asphyxia. Large doses of oxytocin further increase the force and frequency of uterine contractions, which can lead to fetal asphyxia.

Mechanism of Action

Oxytocin binds to specific G-protein–coupled receptors on myometrium



This leads to:

- Generation of IP_3 (inositol triphosphate)
- Release of Ca^{2+} from intracellular stores
- Increased production of PGs by endometrium

Contraction of the pregnant uterus

2. **Breast:** Oxytocin contracts myoepithelial cells of the breast and causes milk ejection.
3. **Kidney:** Oxytocin (high doses) → ADH-like action → decreased urine output. Water intoxication may occur if large amount of fluids is administered along with oxytocin.
4. **Cardiovascular system:** Oxytocin (high doses) → vasodilatation and transient hypotension → reflex tachycardia and flushing.

Preparations and Route of Administration

- Oxytocin is not effective orally since it is a peptide.
- Synthetic oxytocin is commonly used; administered as intravenous infusion or intramuscularly.
- Syntometrine (1 mL contains oxytocin 5 IU + ergometrine 500 mcg), intramuscularly.

Uses

1. **Induction of labour:** Oxytocin is the drug of choice for induction of labour. It is administered by i.v. infusion. The starting dose should be low and the rate of infusion is monitored and adjusted according to response. During oxytocin infusion, uterine contractions, maternal blood pressure (BP), fetal and maternal heart rate should be monitored.

Oxytocin is preferred for induction of labour because:

- (a) The dose (rate of infusion) can be adjusted according to the response.
- (b) It has a short plasma half-life. Its action can be terminated by stopping the infusion immediately, if there are signs of uterine hyperstimulation/fetal distress.

- (c) At low doses, there is a period of complete relaxation between the uterine contractions. This helps to maintain blood flow to the placenta and fetus, thereby preventing fetal asphyxia.
 - (d) It does not interfere with fetal descent, as it does not contract the lower segment. Cephalopelvic disproportion, placenta praevia, previous classical caesarean section, transverse fetal lie, fetal distress, etc. should be excluded prior to administration of oxytocin.
2. **Postpartum haemorrhage (PPH):** Oxytocin is used for prevention (i.m. or i.v. infusion) and treatment (i.v. infusion) of PPH. It contracts uterine smooth muscle resulting in compression of the blood vessels as they pass through the myometrium – bleeding is arrested. Oxytocin has fewer side effects than ergot derivatives and is preferred to them for prevention and treatment of PPH.
 3. Oxytocin (i.v. infusion) is also used to increase intensity, frequency and duration of uterine contractions, if they are not adequate (uterine inertia), during labour. It should not be used to enhance uterine contractions, if labour is progressing satisfactorily.
 4. Intranasal oxytocin may be useful in breast engorgement. Oxytocin stimulates the myoepithelial cells resulting in milk let down.

Adverse Effects

1. Uterine hyperstimulation: Overdosage of oxytocin can cause strong uterine contractions which can result in uterine rupture, fetal asphyxia or even fetal death.
2. If large amount of fluids is infused along with oxytocin, water intoxication (headache, vomiting, drowsiness and convulsions) can occur.
3. High dose of oxytocin may cause hypotension and reflex tachycardia.

Carbetocin

It is an analogue of oxytocin with a longer duration of action. It is useful for the prevention of uterine atony following caesarean section and for prevention of PPH.

Ergot Derivatives

Ergometrine and Methylergometrine (Methergine). Ergometrine (ergonovine) is a natural ergot alkaloid. Methylergometrine is a semisynthetic derivative. They have similar pharmacological actions, but methylergometrine has more potent effect on uterus than ergometrine.

Pharmacological Actions

1. **Uterus:** Ergometrine and methylergometrine stimulate uterine contractions involving both upper and lower segments. Force, frequency and duration of contractions are increased. At low doses, contractions are rhythmic with a period of relaxation in between. But at higher doses, the contractions become more powerful, basal tone is increased and uterus passes into a state of sustained tonic contraction – uterine tetany.
2. **GIT:** In high doses, they can increase peristaltic movements.
3. **CVS:** They have weak vasoconstrictor effect. In therapeutic doses, they can increase BP, but it is not significant.

Pharmacokinetics. Ergometrine and methylergometrine are administered parenterally or orally. They have a rapid onset of action – within a minute of i.v., 3–5 minutes after i.m. and 15–20 minutes after oral administration. They are metabolized in liver and excreted in urine.

Therapeutic Uses of Ergometrine and Methylergometrine

1. Ergometrine and methylergometrine are used for prevention and treatment of **PPH**. For prophylaxis, they are usually given after the delivery of anterior shoulder. Methylergometrine is preferred to ergometrine, as it has more potent effect on the uterus.

These drugs are useful in PPH because they cause sustained contractions of the uterine smooth muscle resulting in compression of blood vessels and arrest of bleeding. Methylergometrine 0.2 mg i.m. is administered prophylactically to prevent PPH and 0.2 mg i.v. to control PPH. A combination of ergometrine with oxytocin can be used to treat PPH.

2. After caesarean section, methylergometrine is administered to **prevent uterine atony** and control bleeding.
3. Ergometrine and methylergometrine are used orally to **hasten the involution of the uterus** when it is delayed.

Adverse Effects. Nausea, vomiting and rise in BP especially in hypertensive patients. They may interfere with lactation as they decrease prolactin secretion.

Contraindications. These include hypertension, peripheral vascular disease, sepsis, preeclampsia and eclampsia.

Prostaglandins

PGE₁ (misoprostol) and PGE₂ (dinoprostone) promote ripening and dilatation of the cervix, thus useful for induction of labour.

Prior use of prostaglandins (oral, vaginal), during induction of labour with oxytocin produces synergistic effect on uterine contractility. There should be at least 4–6 hours gap between their administration.

Misoprostol and carboprost stimulate uterine contractions and can be used to prevent/treat PPH. Misoprostol is administered orally/sublingually, while carboprost is given intramuscularly.

Uterine Relaxants (Tocolytics; Fig. 10.1)

Tocolytics are drugs that inhibit uterine contractions.

β-ADRENERGIC AGONISTS

The selective β₂-agonists used as uterine relaxants are isoxsuprine, salbutamol, terbutaline and ritodrine. They can cause tachycardia, palpitations, arrhythmias, pulmonary

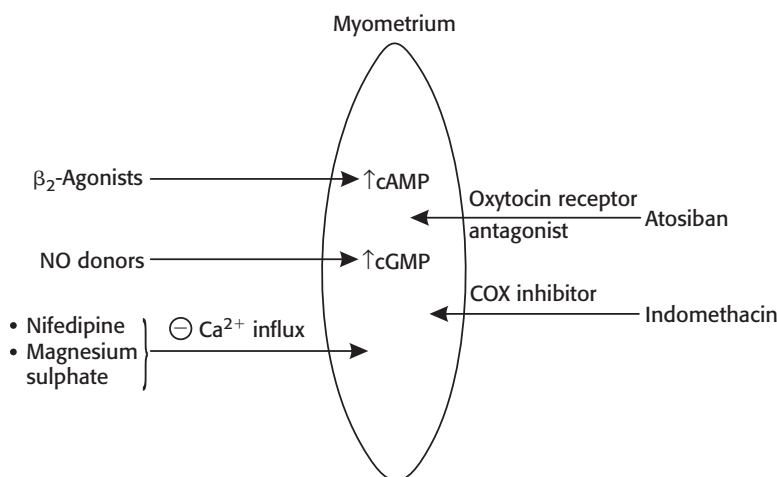


Fig. 10.1 Mechanism of action of tocolytics. NO, nitric oxide; COX, cyclooxygenase; ⊖, inhibition.

oedema, hyperglycaemia and hypokalaemia. They should be avoided in pregnant women with diabetes or heart disease. During acute phase, they are administered by i.v. infusion. For prophylactic therapy, they are given orally.

CALCIUM CHANNEL BLOCKERS

Nifedipine acts by inhibiting the influx of Ca^{2+} ions into the myometrial cells. It is used orally as tocolytic. Side effects are fewer than β_2 -agonists.

ATOSIBAN (OXYTOCIN-RECEPTOR ANTAGONIST)

It competitively blocks the oxytocin receptors of the uterus and induces uterine relaxation. It is given by i.v. infusion. Side effects are less as compared to β_2 -agonists.

PROSTAGLANDIN SYNTHESIS INHIBITORS

NSAIDs, like indomethacin, produce tocolytic effect by inhibiting prostaglandin synthesis. But they are not used because of adverse effects, such as premature closure of ductus arteriosus with subsequent development of pulmonary hypertension. These drugs can be used for relief of dysmenorrhoea, but not to delay labour. Both beneficial and adverse effects of these drugs are due to inhibition of PG synthesis.

MAGNESIUM SULPHATE

Magnesium sulphate is given by i.v. infusion. It has a depressant action on uterine smooth muscle, central nervous system (CNS) and myocardium. It is used to control convulsions and BP in toxemia of pregnancy. It is useful when β_2 -agonists are contraindicated. The side effects are hypotension, hypothermia, cardiac arrhythmias, CNS and respiratory depression.

PROGESTERONE

It has relaxant effect on the uterus. Progestins are used in the treatment of threatened abortion.

NITRIC OXIDE DONORS

Nitroglycerin and other nitrates have tocolytic action, but they may cause maternal hypotension.

OTHERS

Halothane, a fluorinated inhalational general anaesthetic, has a potent tocolytic effect.

USES OF TOCOLYTICS

1. To delay preterm labour
2. Threatened abortion
3. Dysmenorrhoea

Chemotherapy

General Considerations

PH1.42

CHEMOTHERAPY

Chemotherapy is the treatment of infectious diseases or malignancy with drugs which destroy microorganisms or cancer cells preferentially with minimal damage to host tissues. The infection may be due to bacteria, virus, fungi, protozoa or helminths.

BACTERICIDAL AGENTS

They kill or destroy microorganisms, e.g. penicillins, cephalosporins and aminoglycosides.

BACTERIOSTATIC AGENTS

They inhibit the growth and multiplication of microorganisms, e.g. sulphonamides, tetracyclines, chloramphenicol and erythromycin.

At high concentration, some of the 'static' drugs may produce 'cidal' effect; for example, chloramphenicol is a bacteriostatic drug, but at high concentrations it is bactericidal against *Haemophilus influenzae* and *Neisseria meningitidis*.

ANTIMICROBIAL AGENTS

Antimicrobial agents (AMAs) are naturally obtained, semisynthetic and synthetic drugs that act against microorganisms. Natural sources include bacteria (bacitracin, colistin, polymyxin B, aztreonam), fungi (penicillin, cephalosporin, griseofulvin) and actinomycetes (tetracyclines, chloramphenicol, aminoglycosides, macrolides).

ANTIBIOTICS

Antibiotics are substances obtained from microorganisms that kill or inhibit growth of other microorganisms at a very low concentration.

MINIMUM INHIBITORY CONCENTRATION

Minimum inhibitory concentration (MIC) is the minimum concentration of an AMA that prevents visible growth of a microorganism.

Classification of Antimicrobial Agents

I According to their type of action

(a) Bactericidal agents

- Penicillins
- Cephalosporins
- Aminoglycosides
- Fluoroquinolones
- Rifampin
- Metronidazole

(b) Bacteriostatic agents

- Tetracyclines
- Chloramphenicol
- Sulphonamides
- Dapsone
- Erythromycin
- Clindamycin

II According to their spectrum of activity

(a) Narrow-spectrum antibiotics

- Penicillin G
- Aminoglycosides

(b) Broad-spectrum antibiotics

- Tetracyclines
- Chloramphenicol

III According to their mechanism of action (Fig. 11.1)

1. Drugs that inhibit cell wall synthesis, e.g. penicillins, cephalosporins, carbapenems, bacitracin, vancomycin, cycloserine
2. Drugs that affect cell membrane function, e.g. amphotericin B (AMB), nystatin, polymyxin
3. Drugs that inhibit protein synthesis, e.g. chloramphenicol, tetracyclines, erythromycin, linezolid, clindamycin
4. Drugs that alter protein synthesis by misreading of mRNA code and premature termination of mRNA translation, e.g. aminoglycosides
5. Drugs that inhibit viral DNA synthesis, e.g. acyclovir, ganciclovir, zidovudine
6. Drugs that affect DNA function, e.g. rifampin, rifabutin
7. Drugs that inhibit DNA gyrase, e.g. fluoroquinolones (FQs)
8. Antimetabolites, e.g. sulphonamides, dapsone, trimethoprim, pyrimethamine

RESISTANCE TO ANTIMICROBIAL AGENTS

It is said to occur when the microorganism does not respond to the AMA which would normally kill or inhibit its growth. The resistance may be *natural* or *acquired*. Natural resistance is genetically determined, e.g. normally, gram-negative bacilli are not affected by penicillin G.

In acquired resistance, microbes that initially respond to an AMA develop resistance later to the same AMA by mutation or gene transfer. Mutation is a permanent alteration

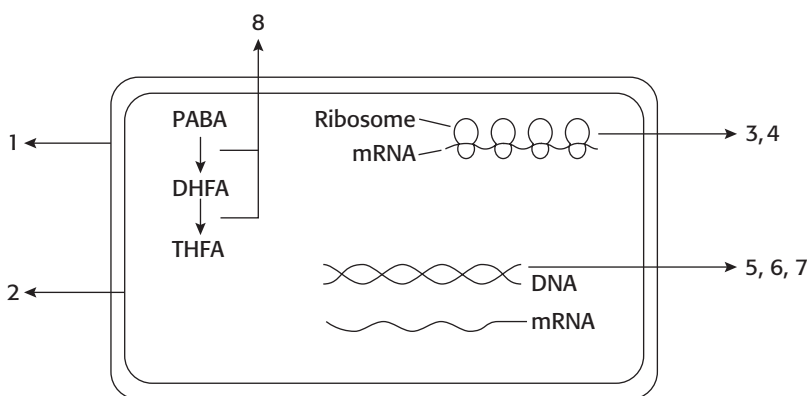


Fig. 11.1 Classification of antimicrobials based on their mechanism of action. PABA, *para*-aminobenzoic acid; DHFA, dihydrofolic acid; THFA, tetrahydrofolic acid.

in the sequence of DNA. Resistance can be single-step mutation (e.g. resistance of *Staphylococcus* to rifampin) or multistep mutation (mutation in a gene, which results in resistance, occurs in more than one step; the microorganism becomes gradually less sensitive to the drug, e.g. resistance to erythromycin). The transfer of genes for drug resistance occurs by the following mechanisms:

Transduction. There is transfer of DNA, carrying a gene for resistance, from one bacterium to another through bacteriophage, e.g. resistance of strains of *Staphylococcus aureus* to antibiotics is mediated via transduction.

Transformation. The resistance carrying genetic material, which is released into the environment by resistant bacteria, is taken up by other sensitive bacteria which then become resistant to the AMA, e.g. penicillin G resistance in pneumococci.



Conjugation. Conjugation is the transfer of genetic material carrying resistance between bacteria by direct contact through sex pilus, e.g. *Escherichia coli* resistance to streptomycin.

Development of Resistance to Antimicrobial Agents. There are several mechanisms by which an organism can develop resistance to an AMA. The important mechanisms are as follows:

1. *Production of inactivating enzymes:* For example, staphylococci, gonococci and *E. coli* produce β -lactamases that can destroy some of the penicillins and cephalosporins.
2. *An efflux pump mechanism:* It is a mechanism that prevents the accumulation of the drug in the microorganism, e.g. resistance of gram-positive and gram-negative bacteria to tetracyclines, chloramphenicol, macrolides, etc.
3. *Decreased entry of AMA into the organism* due to alteration in the channel/transporter required for its entry into the organism.
4. *Alteration of the binding site:* For example, change in penicillin-binding proteins (PBPs) in case of certain pneumococci with decreased affinity for penicillins.
5. *Absence of metabolic pathway:* For example, sulphonamide-resistant bacteria can utilize preformed folic acid without the need for usual metabolic steps.

Cross-Resistance. Organisms that develop resistance to an AMA may also show resistance to other chemically related AMAs. The cross-resistance among AMAs could be either one-way or two-way. Cross-resistance among tetracyclines and sulphonamides is usually 'two-way'.



The 'one-way' resistance is seen between neomycin and streptomycin. Neomycin-resistant organisms are resistant to streptomycin but streptomycin-resistant organisms may be sensitive to neomycin.



- Prevention of Development of Resistance to Antimicrobial Agents.** It is done by:
- 1. Selecting right AMA.
 - 2. Giving right dose of the AMA for proper duration.
 - 3. Proper combination of AMAs, e.g. in tuberculosis (TB), multidrug therapy (MDT) is used to prevent development of resistance to antitubercular drugs by mycobacteria.

SUPERINFECTION (SUPRAINFECTION)

It is defined as the occurrence of a new infection due to antimicrobial therapy for another infection. The causative organism of superinfection should be different from that of the primary disease. Most of the AMAs – especially broad-spectrum antibiotics (tetracyclines and chloramphenicol), clindamycin, ampicillin, etc. – alter the normal bacterial flora, as a result of which the host-defence mechanism is impaired. Hence, pathogenic organisms invade the host, multiply and produce superinfection. The causative organism may be fungi or bacteria.

Pathogenesis. Superinfection is associated with suppression/change of normal flora in the body following treatment with certain antimicrobials. The pathogenesis of superinfection is described in Fig. 11.2.

The sites involved in superinfection are those body cavities that have direct communication with the exterior, i.e. rectum, oral cavity, vagina, lower urinary tract, upper respiratory tract, etc. (Table 11.1).

Factors Predisposing to Superinfection. Superinfection is common in immunocompromised conditions, such as diabetes, malignancy and AIDS, and also during prolonged

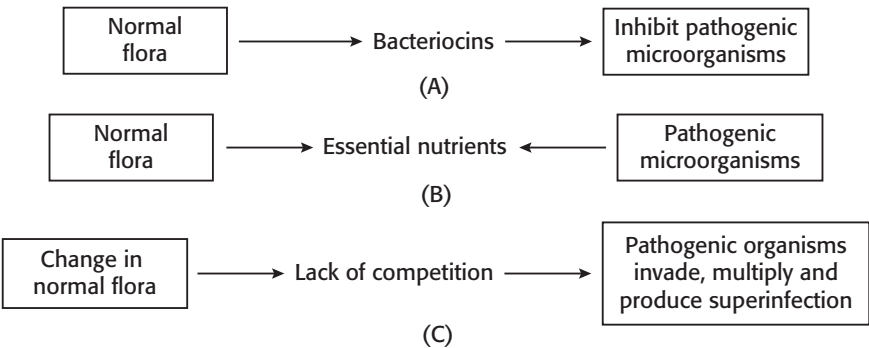


Fig. 11.2 Pathogenesis of superinfection. (A) Absence of bacteriocins promotes growth of pathogens. (B) Alteration in normal flora favours utilization of nutrients by pathogens.

Table 11.1 ■ Microorganisms causing superinfection and its treatment

Manifestations	Microorganisms	Treatment
Diarrhoea, oral thrush	<i>Candida albicans</i>	Nystatin, clotrimazole, fluconazole
Pseudomembranous enterocolitis	<i>Clostridium difficile</i>	Metronidazole, vancomycin
Urinary tract infection	<i>Escherichia coli</i> , <i>Proteus</i> , <i>Pseudomonas</i>	Ciprofloxacin, gentamicin, carbenicillin

corticosteroid therapy. It can be minimized by (i) using specific AMAs, (ii) avoiding unnecessary use of AMAs and (iii) use of probiotics, e.g. *Lactobacillus*.

CHEMOPROPHYLAXIS

Chemoprophylaxis is the administration of AMAs to prevent infection or to prevent development of disease in persons who are already infected (see Table 11.2). The ideal time to initiate therapy is before the organism enters the body or at least before the development of signs and symptoms of the disease.

Indications for Chemoprophylaxis

- 1. To prevent endocarditis in patients with valvular lesion before undergoing surgical procedures: Surgical procedure → mucosal damage → bacteraemia → affects damaged valve → endocarditis.
- 2. To protect healthy persons: Chloroquine/mefloquine is used for chemoprophylaxis of malaria for those travelling to malaria endemic area.
- 3. To prevent infection in patients undergoing organ transplantation: Oral FQs can be used.
- 4. To prevent opportunistic infections in immunocompromised patients, e.g. cotrimoxazole is used to prevent *Pneumocystis jiroveci* pneumonia in AIDS patients.
- 5. Prior to surgical procedures: AMAs are administered to all patients prior to major surgical procedures or implantation of prosthetic devices and in diabetic patients or patients on prolonged corticosteroids to prevent wound infection after surgery.
- 6. To prevent infection in patients with burns: Topical silver sulphadiazine and systemic antibiotics are used.

Table 11.2 ■ Chemoprophylactic regimens

Infection	Antimicrobial agent with dose and duration
1. Meningococcal and <i>Haemophilus influenzae</i> meningitis	Rifampin 600 mg orally, every 12 hours for four doses. Children 10 mg/kg orally, every 12 hours for four doses Rifampin is the most effective antimicrobial agent in eradicating the organism from nasopharynx, thus eliminating carrier state
2. Rheumatic fever	Benzathine penicillin G 1,200,000 units i.m. once a month and continued for lifetime
3. Tuberculosis	INH (isoniazid) 5 mg/kg orally, daily for 6 months
4. Chemoprophylaxis for endocarditis before surgical procedures	
^a Oral regimens	Amoxicillin 2 g, 1 hour before procedure
If patient is allergic to penicillin	Clindamycin 600 mg, 1 hour before procedure or Azithromycin 500 mg, 1 hour before procedure
^a Parenteral regimens	Ampicillin 2 g i.m. or i.v., 30 minutes before procedure or Cefazolin 1 g i.v. or i.m., 30 minutes before procedure
If patient is allergic to β-lactams	Clindamycin 600 mg i.v., 1 hour before procedure

INH, isonicotinic acid hydrazide.
^aThese regimens are also used for surgical prophylaxis.

7. *To prevent infection in patients with urinary catheter:* FQs are used in patients who are at high risk of infection.

Suggested Chemoprophylactic Regimens. The effectiveness of chemoprophylaxis depends on the selection of a specific AMA, its dosage, time of initiation and duration of antimicrobial therapy. The suggested chemoprophylactic regimens are listed in [Table 11.2](#).

Empirical therapy: It is the use of AMAs before identification of causative organism or availability of susceptibility test results, e.g. combination of cefotaxime, vancomycin and ampicillin is used as empirical therapy for suspected bacterial meningitis (before test results are available) to cover possible organisms likely to cause meningitis.

Definitive therapy: It involves the use of AMA after identification/susceptibility tests of the causative organism responsible for the disease.

COMBINATION OF ANTIMICROBIAL AGENTS

It is the simultaneous use of two or more AMAs for the treatment of certain infectious diseases.

Indications/Advantages of Antimicrobial Combinations

1. *To broaden the spectrum of activity in mixed bacterial infections:* Intra-abdominal, pulmonary, hepatic, pelvic, brain abscesses, etc., are often due to both aerobic and anaerobic organisms. Hence, they require antimicrobial combination therapy.
 - Metronidazole + ceftriaxone for brain abscess
2. *To broaden the spectrum of action in severe infections when the aetiology is not known:* Combination of cefotaxime, vancomycin and ampicillin is used for empirical therapy of suspected bacterial meningitis. Later, the AMA should be selected according to the type of organism, culture and sensitivity results.
3. *To increase antibacterial activity in the treatment of specific infections (for synergistic effect)*
 - Ampicillin (bactericidal) + gentamicin (bactericidal) for enterococcal endocarditis
 - Carbenicillin + gentamicin for infections due to *Pseudomonas*
Penicillins, by inhibiting bacterial cell wall synthesis, facilitate the entry of gentamicin into the bacterial cell (synergistic effect) resulting in more complete eradication of the organism.
 - Sulphamethoxazole + trimethoprim for *Pneumocystis jiroveci* pneumonia (see p. 377 for mechanism of action)
 - Rifampin (cidal) + dapsone (static) in leprosy – synergistic effect
4. *To prevent emergence of resistant microorganisms:* In TB, leprosy and HIV infection, combination therapy is used.
5. *To reduce duration of therapy:* MDT is used in TB and leprosy.
6. *To reduce adverse effects:* AMB and flucytosine in cryptococcal meningitis: The dose-dependent toxicity (especially nephrotoxicity) of AMB is decreased due to reduction in dosage (see p. 425).

Disadvantages of Antimicrobial Drug Combinations

1. *Increased toxicity,* e.g. vancomycin with tobramycin may cause enhanced nephrotoxicity.
2. *Increased cost.*
3. *Decreased antibacterial activity* due to improper combinations, e.g. in pneumococcal meningitis, activity of penicillin G (bactericidal) against pneumococci will decrease

if combined with tetracycline (bacteriostatic). Penicillins act mainly on rapidly multiplying bacteria; tetracycline inhibits multiplication of bacteria because of its static effect, thus reducing effect of penicillins.

4. Increased likelihood of superinfection.
5. Irrational combination of AMAs can lead to development of resistance.

List of Microorganisms

1. Gram-positive cocci: *S. aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Streptococcus β -haemolyticus*, *S. pneumoniae* (pneumococcus), *Enterococcus*
2. Gram-negative cocci: *Neisseria gonorrhoeae*, *N. meningitidis*
3. Gram-positive bacilli: *Bacillus anthracis*, *Corynebacterium diphtheriae*, *Clostridium tetani*, *Clostridium perfringens*, *Clostridium difficile*
4. Gram-negative bacilli: *E. coli*, *Enterobacter* spp., *Proteus*, *Pseudomonas*, *Salmonella*, *Shigella*, *H. influenzae*, *H. ducreyi*, *Klebsiella*, *Brucella*, *Vibrio cholerae*
5. Acid-fast bacilli: *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Mycobacterium avium* complex (MAC)
6. Spirochetes: *Treponema pallidum*, *Leptospira*
7. Others: *Rickettsia*, *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, *Helicobacter pylori*, etc.

SELECTION OF AN APPROPRIATE ANTIMICROBIAL AGENT (Fig. 11.3)

Patient Factors

1. **Age:** Use of chloramphenicol in premature infants may produce grey baby syndrome because metabolic functions of liver and renal excretion are not fully developed. Sulphonamides in neonates can cause kernicterus.
- Renal function declines with age; hence, elderly patients are more prone to ototoxicity and nephrotoxicity with aminoglycosides due to their reduced clearance by kidney.

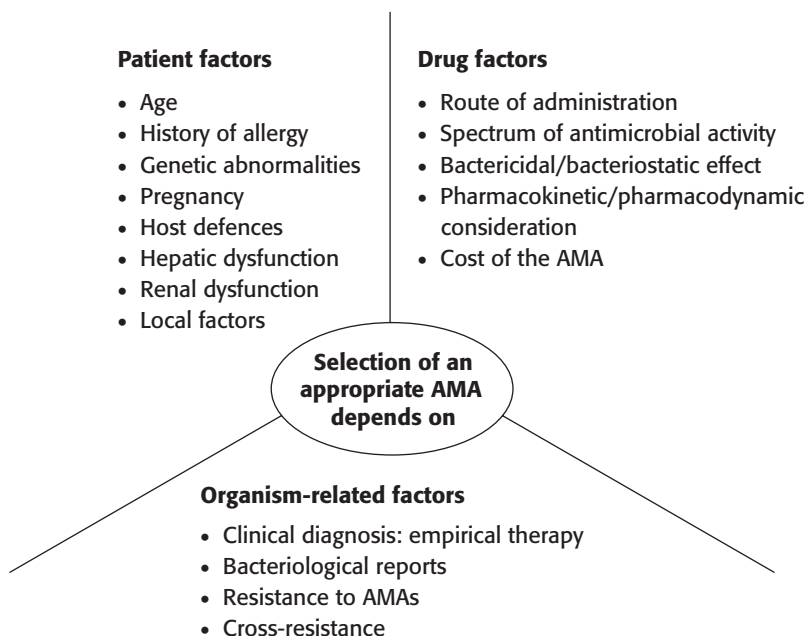


Fig. 11.3 Factors affecting selection of an antimicrobial agent.

2. **History of allergy:** In patients with history of asthma, allergic rhinitis, hay fever, etc., there is an increased risk of penicillin allergy; hence, such drugs should be avoided in them.
3. **Genetic abnormalities:** Primaquine, pyrimethamine, sulphonamides, sulphones, FQs, etc., may cause haemolysis in patients with G6PD deficiency.
4. **Pregnancy:** Most of the AMAs cross placental barrier and may affect the developing fetus. The risk of teratogenicity is highest during the first trimester. For example, use of tetracyclines during pregnancy may affect fetal dentition and bone growth. There is an increased incidence of hepatotoxicity with tetracycline in pregnant women.
5. **Host defences:** In immunocompromised patients (AIDS, leukaemias and other malignancies), normal defence mechanisms are impaired – bacteriostatic drugs may not be adequate; hence bactericidal agents should be used to treat infection.
6. **Hepatic dysfunction:** In patients with hepatic dysfunction, drugs like chloramphenicol, erythromycin and rifampin should be avoided or require dose reduction to minimize toxic effects.
7. **Renal dysfunction:** In renal failure, drugs that are eliminated via kidney can accumulate in the body and cause severe toxic effects. Hence, aminoglycosides, vancomycin, AMB, FQs, etc., should be avoided or require dose reduction in patients with impaired renal function.
8. **Local factors**
 - (a) Antimicrobial activity of sulphonamides is markedly reduced in the presence of pus.
 - (b) The activity of aminoglycosides is enhanced at alkaline pH.

Drug Factors

1. **Route of administration:** Depending on the severity and site of infection, AMAs have to be chosen. Some of the AMAs can be administered orally as well as parenterally. For mild-to-moderate infections, oral route is usually preferred, but for severe infections like endocarditis and meningitis, parenteral AMAs are preferred during initial stages of therapy. Some AMAs like aminoglycosides are not effective orally; they are administered parenterally for systemic infections.
2. **The spectrum of antimicrobial activity:** It is an important factor while selecting an AMA especially during empirical therapy.
3. **Bactericidal/bacteriostatic effect:** Bactericidal drugs kill organisms, while static drugs inhibit growth and multiplication. In immunocompromised states, the host-defence mechanisms are impaired; hence, bactericidal drugs are required even for trivial infections.
4. **Cost of AMA:** The cost of treatment has to be considered while selecting an AMA. The expensive antimicrobials should not be used routinely when alternative cheaper and effective AMAs are available.
5. **Pharmacokinetic/pharmacodynamic considerations**
 - Time-dependent inhibition: This is observed with certain AMAs like β -lactams and glycopeptides. Their antimicrobial action depends on the duration of time the drug concentration remains above the MIC in the dosing interval. Thus, they are administered in multiple doses.
 - Concentration-dependent killing: For aminoglycosides and FQs, the antimicrobial effect depends on the ratio of peak plasma concentration to MIC.

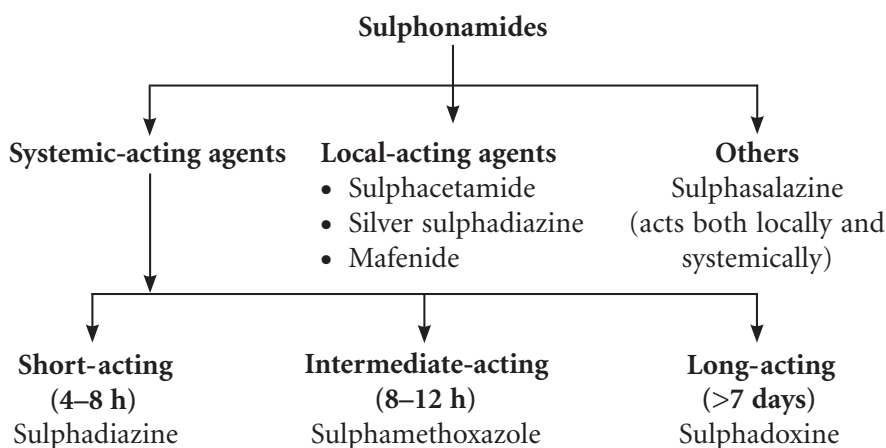
A single daily dose of aminoglycosides is as/more effective than multiple doses.

- Ability to penetrate into the infected area
 - Ability to cross the blood–brain barrier (BBB): Clindamycin is effective against anaerobes, but not useful for anaerobic brain abscess as it does not reach cerebrospinal fluid (CSF) and brain. Anaerobic brain abscess can be treated effectively with third-generation cephalosporins or combination of metronidazole and chloramphenicol.
 - Levofloxacin attains good concentration in the lung, skin/soft tissues and urinary tract – produces high cure rates in community-acquired pneumonia, skin infections, etc.

Organism-Related Factors. In severe infections, empirical therapy with antimicrobial drug combination should be initiated depending on the clinical diagnosis. Later, the AMA should be selected according to the type of organism, culture and sensitivity reports. The bacterial resistance to AMAs and cross-resistance should also be considered while selecting an AMA.

Sulphonamides

Sulphonamides were the first effective AMAs used in the treatment of bacterial infections in humans. They are derivatives of sulphanilamide (*para*-aminobenzene sulphonamide) and are synthetic compounds (Fig. 11.4).



Mechanism of Action. *para*-Aminobenzoic acid (PABA) is a precursor of folic acid which is essential for growth and multiplication of many bacteria. Sulphonamides, being structurally similar to PABA, competitively inhibit folate synthase enzyme and prevent the formation of folic acid, thereby producing bacteriostatic effect. They are not effective in the presence of pus as it is rich in PABA, purines and thymidine. Mammalian

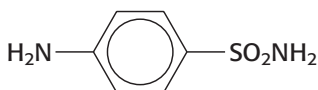
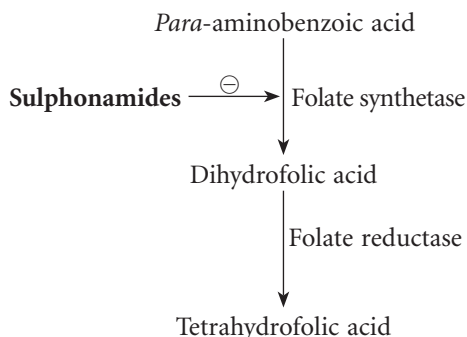


Fig. 11.4 Basic structure of sulphonamides.

cells do not synthesize folic acid, but utilize folic acid present in diet, hence are unaffected by sulphonamides.



Bacterial Resistance to Sulphonamides. Most of the bacteria have developed resistance to sulphonamides. It could be due to:

1. Decreased affinity of folate synthetase for the drug
2. Efflux of the drug by bacteria
3. Development of alternate metabolic pathway for folate synthesis

Pharmacokinetics. All systemic-acting sulphonamides are well absorbed from the gut. They are bound to plasma proteins, particularly albumin. Sulphonamides are distributed in almost all tissues of the body including CSF. They cross placental barrier and reach fetal circulation; they are metabolized in liver mainly by acetylation. The acetylated products have no antibacterial activity but retain the toxic potential of the parent compound. Sulphonamides are excreted partly unchanged and partly as metabolic products.

Adverse Effects

1. The acetylated products of sulphonamides are poorly soluble in acidic urine and may cause crystalluria, haematuria or even obstruction to urinary tract. This may be avoided by taking plenty of water and alkalinizing the urine.
2. Hypersensitivity reactions include skin rashes, itching, drug fever and exfoliative dermatitis. Stevens–Johnson syndrome is the most severe type of hypersensitivity reaction characterized by fever, erythema multiforme and ulceration of mucous membranes.
3. In patients with glucose-6-phosphate dehydrogenase deficiency, sulphonamides may cause acute haemolytic anaemia.
4. Rarely cause hepatitis and suppression of bone marrow.
5. Use of sulphonamides in neonates, especially in premature babies, may cause displacement of bilirubin from plasma proteins. The free bilirubin can cross BBB and get deposited in the basal ganglia resulting in kernicterus.

Drug Interactions. Sulphonamides potentiate the effect of phenytoin, methotrexate (MTX), oral anticoagulants and oral hypoglycaemic agents (sulfonylureas) by inhibiting their metabolism and displacing them from plasma protein binding sites.

Therapeutic Uses. Sulphonamides alone are rarely used now for systemic infections. They are used in combination with other AMAs.

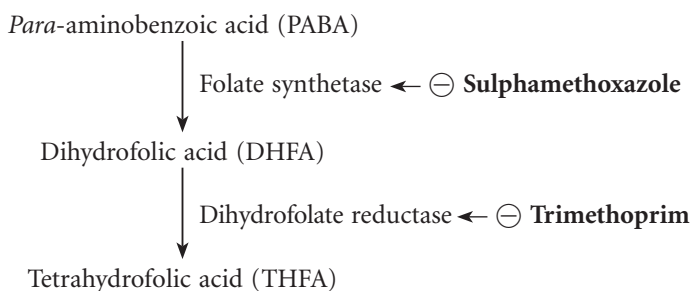
1. Sulphadoxine and pyrimethamine are used in combination with artesunate in the treatment of chloroquine-resistant *Plasmodium falciparum* malaria.
2. Sulphadiazine and pyrimethamine combination is the drug of choice for toxoplasmosis.
3. Nocardiosis: Sulphamethoxazole in combination with trimethoprim is used.

4. Sulphamethoxazole in combination with trimethoprim is used in the treatment of *P. jiroveci* infection in patients with AIDS.
5. Sodium salt of sulphacetamide is used exclusively for the treatment of ophthalmic infections. It is administered as eye drops or eye ointment. It is preferred because of:
 - (a) High aqueous solubility
 - (b) Neutral pH and nonirritant nature of the drug
 - (c) Good penetrability on topical administration
 - (d) Low incidence of hypersensitivity reactions
 - (e) Low cost
6. Silver sulfadiazine and mafenide are used topically for preventing infection of burn wound. Silver sulfadiazine slowly releases silver ions which are toxic to microorganisms. It is not effective in the presence of pus and tissue fluid.
7. Sulphasalazine is useful in the treatment of inflammatory bowel disease and rheumatoid arthritis.
8. Rheumatic fever: Sulphadiazine can be used for prophylaxis of rheumatic fever.

Cotrimoxazole

Cotrimoxazole is a World Health Organization (WHO)–approved fixed-dose combination of sulphamethoxazole and trimethoprim in the ratio of 5:1. It was introduced in late 1960s; even today, it is one of the commonly used AMAs.

Mechanism of Action



Cotrimoxazole (sulphamethoxazole and trimethoprim in a dose ratio of 5:1) produces **sequential blockade**, i.e. two drugs interfere with two successive steps in the same metabolic pathway; hence, their combination produces supra-additive effect. Sulphamethoxazole inhibits folate synthetase, whereas trimethoprim inhibits folate reductase enzyme. The pharmacokinetic properties of these two drugs match each other almost closely, hence are selected for combination. They have similar half-lives. Optimum synergistic effect is seen at a concentration ratio of 20:1 (sulphamethoxazole to trimethoprim) in blood and tissues. The advantages of this combination are the following:

1. Individually, both are bacteriostatic but the combination has cidal effect.
2. Chances of development of bacterial resistance is greatly reduced.

Pharmacokinetics. Cotrimoxazole is well absorbed after oral administration and is also available for parenteral use, widely distributed to various tissues including CSF and sputum, metabolized in liver and excreted mainly in urine; hence, dose reduction is needed in patients with renal insufficiency.

Adverse Effects. Cotrimoxazole is well tolerated in most patients. Most of the adverse effects are same as those of sulphonamides. The common adverse effects are skin rashes and

Table 11.3 ■ Preparations of cotrimoxazole

Strength of cotrimoxazole	Preparations
Sulphamethoxazole 400 mg + trimethoprim 80 mg	Oral, i.v.
Sulphamethoxazole 800 mg + trimethoprim 160 mg	Double strength (DS); oral, i.m.
Sulphamethoxazole 200 mg + trimethoprim 40 mg	Oral suspension
Sulphamethoxazole 100 mg + trimethoprim 20 mg	Paediatric tablet

gastrointestinal (GI) disturbances. Exfoliative dermatitis, erythema multiforme and Stevens–Johnson syndrome are rare. GI symptoms include nausea, vomiting, glossitis and stomatitis. Megaloblastic anaemia due to folate deficiency may occur rarely, especially in alcoholics and malnourished persons. Bone marrow suppression with leucopenia, neutropenia and thrombocytopenia occurs rarely. Cotrimoxazole is contraindicated in pregnancy.

The preparations of cotrimoxazole are shown in [Table 11.3](#).

Therapeutic Uses

- 1. Urinary tract infection (UTI):** Cotrimoxazole is effective for the treatment of acute uncomplicated lower UTIs due to gram-negative organisms such as *E. coli*, *Proteus* and *Enterobacter* spp. The usual dose is 800 mg sulphamethoxazole plus 160 mg of trimethoprim (cotrimoxazole double-strength tablet) b.d. for 3 days. It is useful for chronic and recurrent lower UTIs especially in women. Small doses of cotrimoxazole daily or thrice weekly are used for long-term prophylaxis in recurrent UTI. Cotrimoxazole can be used in the treatment of bacterial prostatitis as it is concentrated in prostatic tissue.
- 2. Respiratory tract infections:** Cotrimoxazole is useful for acute and chronic bronchitis due to *H. influenzae* and *Moraxella catarrhalis*. It is also useful for acute maxillary sinusitis and otitis media.
- 3. Bacterial diarrhoeas:** Cotrimoxazole may be used for GI infections due to *Shigella*, *E. coli* and *Salmonella* spp. But FQs are the preferred agents.
- 4. Pneumocystis jiroveci infection:** High doses of cotrimoxazole are used for treatment of infection due to *P. jiroveci* in immunocompromised patients. It is useful for treatment as well as prophylaxis of *P. jiroveci* pneumonia. Pentamidine, clindamycin, primaquine and atovaquone are the alternative drugs for *P. jiroveci* infection.
- 5. Nocardiosis:** Cotrimoxazole has been used in the treatment of infection due to *Nocardia* spp.
- 6. Chancroid:** It is caused by *H. ducreyi*. The drug of choice is azithromycin. Cotrimoxazole is equally effective. The alternative drugs are ceftriaxone and ciprofloxacin.
- 7. Typhoid fever** (see p. 382): Fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, etc.) or third-generation cephalosporins (ceftriaxone and cefoperazone) are the treatment of choice for typhoid fever. Cotrimoxazole may also be effective.

Quinolones and Fluoroquinolones

The first quinolone, nalidixic acid, is a urinary antiseptic. It is effective against gram-negative bacteria including *E. coli*, *Proteus*, *Klebsiella*, *Enterobacter*, *Salmonella* and *Shigella*, but not *Pseudomonas*. Nalidixic acid inhibits DNA gyrase enzyme and interferes with the replication of bacterial DNA. It is useful in the treatment of uncomplicated UTI due to

gram-negative bacteria and diarrhoea due to *Shigella* or *Salmonella*. The most common adverse effects are related to the GI tract, central nervous system (CNS) and skin.

Fluoroquinolones (FQs) are synthetic, fluorinated analogues of nalidixic acid. The important FQs are norfloxacin, ciprofloxacin, pefloxacin (first-generation FQs), ofloxacin, levofloxacin, gemifloxacin and moxifloxacin (second-generation FQs) (Table 11.4).

Mechanism of Action

DNA gyrase (topoisomerase II) in
gram-negative bacteria



Nicking, formation
of negative supercoils and
resealing of strands of DNA

Topoisomerase IV in
gram-positive bacteria



Nicking and separation of daughter
DNA strands following
DNA replication

FQs inhibit bacterial DNA synthesis (bactericidal). They inhibit DNA gyrase, thus blocking DNA replication in gram-negative bacteria. Inhibition of topoisomerase IV in gram-positive bacteria prevents separation of replicated DNA.

Antibacterial Spectrum

Ciprofloxacin is the prototype drug. It is highly effective against aerobic gram-negative organisms – *E. coli*, *Enterobacter*, *Proteus*, *Klebsiella*, *Salmonella*, *Shigella*, *H. ducreyi*, *H. influenzae*, *N. gonorrhoeae*, *N. meningitidis*, *V. cholerae* and *Campylobacter jejuni*.

It has activity against *S. aureus*, *Pseudomonas aeruginosa* and *M. tuberculosis*.

Most of the anaerobes, *Bacteroides fragilis*, *C. difficile*, etc. are resistant to ciprofloxacin.

Newer FQs like levofloxacin, gemifloxacin and moxifloxacin have greater activity against streptococci and some activity against anaerobes.

Pharmacokinetics. Ciprofloxacin is administered by oral, i.v. or topical routes. It is well absorbed from the gut, but food delays its absorption. It is widely distributed in the body, and reaches high concentration in kidney, lung, prostatic tissue, bile, macrophages, etc. It is excreted mainly in urine.

Adverse Effects

- The common adverse effects are related to the GI tract, e.g. nausea, vomiting and abdominal discomfort.
- CNS effects include headache, dizziness, insomnia, confusion, hallucinations and convulsions.
- Hypersensitivity reactions include skin rashes, urticaria, itching, eosinophilia and photosensitivity.
- Tenosynovitis and tendon rupture can occur especially in athletes.
- Moxifloxacin can cause prolongation of QT interval.
- FQs are contraindicated in pregnancy.
- FQs have caused cartilage damage in immature animals – hence, they should be avoided in young children.

Drug Interactions. Ciprofloxacin increases the plasma concentration of theophylline, warfarin, etc., by inhibiting their metabolism. Nonsteroidal anti-inflammatory drugs (NSAIDs) may potentiate CNS side effects of FQs – confusion, irritability and rarely convulsions may occur. Like tetracyclines, absorption of FQs is reduced by antacids, ferrous salts and sucralfate.

Other FQs have been discussed in Table 11.4.

Table 11.4 ■ Pharmacokinetics, antibacterial spectrum, uses and drug interactions of fluoroquinolones

Fluoroquinolone	Routes of administration	Oral bioavailability	Elimination $t_{1/2}$ (hours)	Antibacterial spectrum and uses	Drug interactions
First generation					
Norfloxacin	Oral, topical (eye)	30%–40%	4–6	Mainly against gram-negative organisms, but not <i>Pseudomonas</i> Uses: It is used mainly in the treatment of urinary tract infection and bacterial diarrhoeas due to <i>Escherichia coli</i> , <i>Shigella</i> , <i>Salmonella</i> , etc.	Inhibits metabolism of theophylline and warfarin
Ciprofloxacin	Oral, i.v. infusion, topical (eye drops, ointment)	70%	3–5	See pp. 379, 382	Inhibits metabolism of theophylline and warfarin
Pefloxacin	Oral, i.v. infusion	Almost 100%	7–14	Similar to ciprofloxacin, also effective against <i>Mycobacterium leprae</i> Uses: Typhoid, gonococcal infections, meningitis due to gram-negative organisms, UTI and bacterial diarrhoeas	Inhibits metabolism of theophylline and warfarin
Ofloxacin	Oral, i.v. infusion, topical (eye drops)	Almost 100%	4–7	Effective against gram-negative organisms. More active than ciprofloxacin against gram-positive organisms, <i>Chlamydia</i> , <i>Mycoplasma</i> and mycobacteria Uses: Tuberculosis (TB), leprosy, atypical pneumonia and bacterial conjunctivitis	Inhibits metabolism of theophylline but to a lesser extent

Second generation

Levofloxacin	Oral, i.v., topical (eye drops)	100%	8	Increased activity against <i>Streptococcus pneumoniae</i> , effective against gram-negative bacteria and anaerobes Uses: Community-acquired pneumonia, chronic bronchitis, typhoid, bacterial conjunctivitis, skin, soft-tissue and urinary tract infection	No interaction with theophylline and warfarin
Gemifloxacin	Oral	70%	8–10	Effective against <i>S. pneumoniae</i> and some anaerobes Uses: Community-acquired pneumonia, chronic bronchitis, sinusitis, otitis media and bacterial conjunctivitis	—
Moxifloxacin	Oral, i.v. infusion, topical (eye drops)	90%	12	More active against gram-positive bacteria including <i>S. pneumoniae</i> , <i>M. tuberculosis</i> and some anaerobes (<i>Bacteroides fragilis</i>) Uses: Community-acquired pneumonia, chronic bronchitis, sinusitis, otitis media and bacterial conjunctivitis	—
Prulifloxacin (prodrug)	Oral; converted to ulifloxacin (active)	Well absorbed	—	Effective against gram-positive and gram-negative organisms Uses: It is used mainly in the treatment of urinary tract infection and bronchitis	—

UTI, urinary tract infection.

Balofloxacin (oral) and pazufloxacin (i.v. infusion) are effective against both gram-positive and gram-negative organisms including methicillin-resistant *S. aureus* (MRSA). They are used in nosocomial infections.

Uses of Fluoroquinolones

1. **UTI:** FQs are one of the most commonly used AMAs for UTI. They are effective against gram-negative bacilli, such as *E. coli*, *Proteus* and *Enterobacter*. They also have moderate activity against *Pseudomonas* infection. FQs are superior to cotrimoxazole for the treatment of UTI. They are also effective for the treatment of bacterial prostatitis as they are concentrated in the prostatic tissue (ciprofloxacin 750 mg b.d. for 3 weeks for upper UTI).
2. **Prostatitis:** FQs are used in prostatitis as an alternative to cotrimoxazole.
3. **Bacterial diarrhoeas:** FQs are effective for a variety of GI infections caused by *E. coli*, *Shigella*, *Salmonella*, etc. For traveller's diarrhoea (due to *E. coli*), FQs are as effective as cotrimoxazole. Norfloxacin, ciprofloxacin or levofloxacin therapy for 3–5 days is adequate.
4. **Typhoid fever:** Ciprofloxacin (750 mg orally b.d. for 10 days) is the preferred drug for treatment of typhoid. It is bactericidal and causes rapid resolution of symptoms. Levofloxacin or ofloxacin can also be used. They are also effective in eliminating chronic carrier state of *Salmonella typhi* when therapy is continued for 4 weeks as they attain effective concentration in bile and intestinal mucosa. Multidrug-resistant (MDR) cases are treated with ceftriaxone (2 g i.v. for 7 days) or azithromycin (500 mg orally daily for 7 days).
5. **Sexually transmitted diseases**
 - *Gonococcal infections:* FQs were effective for the treatment of cervicitis and urethritis caused by *N. gonorrhoeae* but their use has declined because of high rates of resistance.
 - *Chancroid:* Ciprofloxacin in a dose of 500 mg b.d. for 3 days is effective.
 - Chlamydial cervicitis and urethritis can be treated with levofloxacin or ofloxacin.
6. **Skin, soft-tissue and bone infections** due to *S. aureus* and gram-negative bacilli require prolonged antimicrobial therapy. FQs can be used in combination with an agent effective against anaerobes especially in diabetic foot infections.
7. Ciprofloxacin can be used to **eradicate meningococci** from nasopharynx, thus eliminating the carrier state, but the preferred drug is rifampin.
8. **Mycobacterial infections:** In MDR-TB, atypical mycobacterial infections, MAC infection in AIDS patients and leprosy, FQs are used in combination with other AMAs.
9. **Prophylaxis and treatment of infections in neutropenic patients:** FQs can be used.
10. Ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin are used topically for **conjunctivitis** due to susceptible organisms.
11. **Respiratory infections:** Newer FQs (levofloxacin and moxifloxacin) are highly effective for community-acquired pneumonia and chronic bronchitis.
12. **Anthrax:** Ciprofloxacin is the preferred drug for treatment and prophylaxis of anthrax.

β-Lactam Antibiotics

β-Lactam antibiotics include penicillins, cephalosporins, carbapenems and monobactams. All of them have a β-lactam ring in their chemical structure (Fig. 11.5), hence the name β-lactam antibiotics.

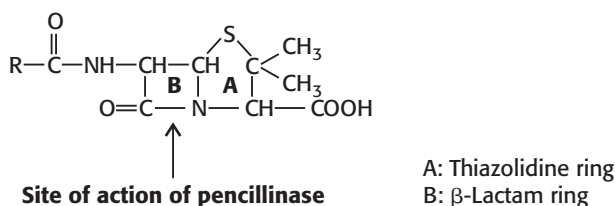


Fig. 11.5 Structure of penicillins.

Penicillins

Penicillin was the first antibiotic developed and used clinically. It was discovered accidentally by Alexander Fleming. The source of penicillin is the high-yielding *Penicillium chrysogenum*.

Mechanism of Action (Fig. 11.6). β -Lactam antibiotics produce bactericidal effect by inhibiting cell wall synthesis in susceptible bacteria.

Bacterial cell wall is composed of peptidoglycan which contains amino sugars, *N*-acetylmuramic acid (NAM) and *N*-acetylglucosamine (NAG). The enzyme, transpeptidase (a PBP), removes terminal alanine of one strand resulting in its linkage with glycine of adjacent strand. Cross-linking makes the cell wall rigid and stable.

β -Lactams, the structural analogues of D-alanine, inhibit transpeptidase, thus inhibiting cross-linking of peptidoglycans and cell wall synthesis. Cell wall-deficient forms are produced which undergo lysis (bactericidal action). β -Lactams exert their cidal effect when the bacteria are actively multiplying and synthesizing cell wall.

PBPs, consisting of transpeptidase, other enzymes and related proteins, are located in the cell membrane of bacteria. The cell wall in gram-positive bacteria is composed mainly of highly cross-linked peptidoglycan, which is 50–100 layers thick and is near the cell surface. In gram-negative bacteria, the peptidoglycan layer is only one to two molecules thick. In addition, there is an outer lipopolysaccharide layer. Hence, gram-negative organisms are less susceptible to penicillin than gram-positive organisms.

Mechanism of Bacterial Resistance to Penicillins. Bacteria develop resistance (i) by producing β -lactamases, which destroy the β -lactam ring, e.g. *S. aureus*, *E. coli*, gonococci and *H. influenzae*, (ii) due to altered PBPs which have less affinity for

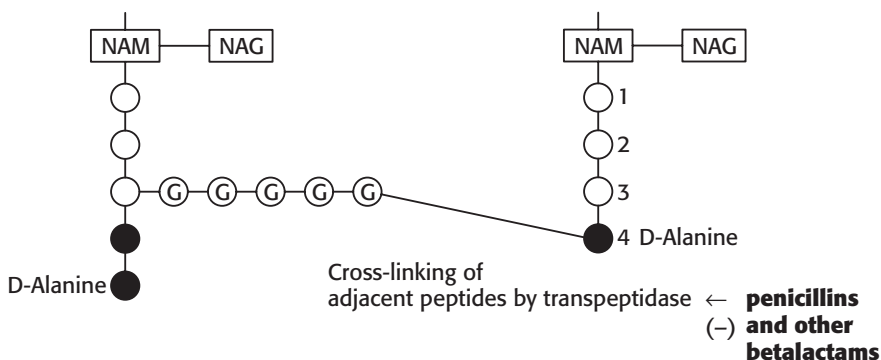


Fig. 11.6 Cross-linking of peptidoglycan residues and site of action of β -lactam antibiotics. (Source: Adapted from Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 12th ed).

β -lactams, e.g. *S. pneumoniae*, and (iii) due to decreased ability of the drug to penetrate to its site of action.

Pharmacokinetics. Most of the orally administered penicillin G is destroyed by gastric acid (acid labile); hence, penicillin G is usually given by i.v. route. It can also be administered by i.m. route but is painful. Penicillin G is widely distributed in body tissues, but poorly crosses BBB, although during meningitis, adequate amount reaches the CSF. Penicillin G is rapidly excreted in urine mainly by active tubular secretion. Since renal function is not completely developed in infants and neonates, excretion of penicillins is slow. The action of penicillins can be augmented and prolonged by giving probenecid simultaneously.

Preparations of Penicillin G. The duration of action of penicillin G is increased by combining it with poorly water-soluble compounds, such as procaine (procaine penicillin G) or benzathine (benzathine penicillin G) to yield aqueous suspensions. They are called repository or depot penicillins (Table 11.5 and Fig. 11.7).

Adverse Reactions. Penicillins are relatively safe. They may cause hypersensitivity reactions, such as skin rashes, urticaria, fever, dermatitis, bronchospasm, angioedema, joint pain, serum sickness or anaphylactic reaction.

The major manifestations of anaphylactic shock are severe hypotension, bronchospasm and laryngeal oedema. It is an immunoglobulin E (IgE)–mediated, immediate type of hypersensitivity reaction (type I hypersensitivity). It is not a dose-related adverse

Table 11.5 ■ Characteristic features of preparations of penicillin G

Penicillin	Route and dose	Duration of action	Special features
1. Penicillin G (benzyl penicillin, crystalline penicillin)	i.v., i.m. 20–24 million units (MU) daily	4–6 hours	Rapid onset of action, reaches high plasma concentration; mainly used in severe infections – meningitis, endocarditis, pneumonia, etc.
2. Repository penicillins (depot penicillins)			
• Procaine penicillin G	600,000–1,200,000 units (0.6–1.2 MU) i.m. daily	12–24 hours	Moderate plasma concentration, used in mild-to-moderate infections; less painful because of procaine component
• Benzathine penicillin G	600,000–2,400,000 units (0.6–2.4 MU), i.m. once a month	3–4 weeks	Slow onset but has longest duration of action among penicillins. Used in syphilis, rheumatic fever prophylaxis, etc.
• Fortified procaine penicillin G	300,000 units procaine penicillin G + 100,000 units penicillin G i.m.	12–24 hours	Rapid onset with high plasma concentration and longer duration of action; used in mild-to-moderate infections by sensitive organisms

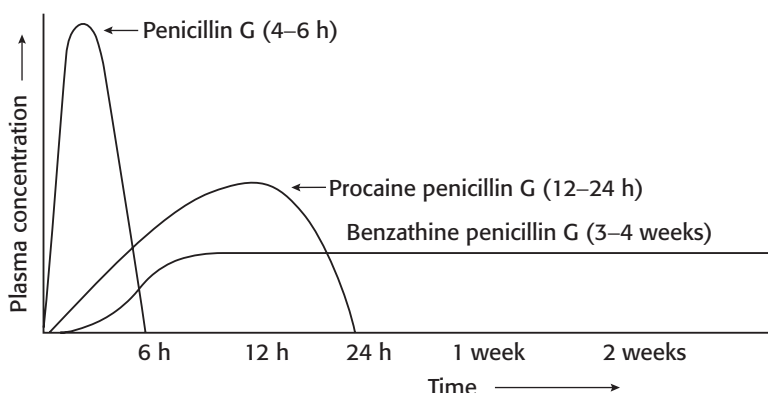


Fig. 11.7 Preparations of penicillin G with their duration of action and plasma concentration.

drug reaction and can occur with any dosage form of penicillin. Cross-reactivity can occur among penicillins and also among β -lactam antibiotics.

Treatment of Anaphylactic Shock

1. Inj. adrenaline 0.3–0.5 mL of 1:1000 solution intramuscularly
2. Inj. hydrocortisone 200 mg intravenously
3. Inj. diphenhydramine 50–100 mg intravenously or intramuscularly

Precautions

1. Before giving penicillin, history of previous administration and allergic manifestations, if any, must be noted.
2. In patients with history of asthma, allergic rhinitis, hay fever, etc., there is an increased risk of penicillin allergy; hence, it should be avoided in such cases.
3. Sensitivity test should be performed by an intradermal test on the ventral aspect of forearm. Itching, erythema and wheal formation are watched for. A negative skin test does not ensure absolute safety.
4. Inj. adrenaline and hydrocortisone should be kept ready before injecting penicillin to treat the anaphylactic reaction.

Other adverse effects of penicillins are pain and sterile abscess at the site of i.m. injection. Prolonged use of i.v. penicillin G may cause thrombophlebitis.

Jarisch–Herxheimer Reaction. It is an acute exacerbation of signs and symptoms of syphilis during penicillin therapy due to release of endotoxins from the dead organisms. The manifestations are fever, chills, myalgia, hypotension, circulatory collapse, etc. It is treated with aspirin and corticosteroids.

Therapeutic Uses. Owing to the risk of anaphylaxis as well as availability of better AMAs, the use of penicillin G has declined. For uses of PnG, see pp. 387 to 389.

Limitations/Drawbacks of Penicillin G

1. Acid labile – orally not very effective
2. Short duration of action (to overcome this, repository penicillins have been developed)
3. Narrow spectrum of antibacterial activity (mainly against gram-positive organisms)
4. Destroyed by penicillinase enzyme
5. Possibility of anaphylaxis

To overcome most of the above drawbacks, semisynthetic penicillins have been developed.

Semisynthetic Penicillins

The spectrum of action of semisynthetic penicillins, their route of administration and susceptibility to penicillinase is shown in Table 11.6.

Aminopenicillins

Uses of Aminopenicillins (see pp. 387 to 389)

Adverse Effects of Aminopenicillins. The adverse effects of ampicillin are similar to those of penicillin G but skin rashes and diarrhoea are more common.

Carboxypenicillins and Ureidopenicillins

They are carbenicillin, carbenicillin indanyl, ticarcillin (carboxypenicillins), mezlocillin and piperacillin (ureidopenicillins).

Uses (see p. 389)

Table 11.6 ■ Classification of penicillins with their spectrum of activity

Penicillins	Route of administration	Penicillinase susceptible/ resistant	Antimicrobial spectrum/uses
1. Natural penicillins			
(a) Penicillin G	i.v., i.m.	Susceptible	<i>Streptococcus pyogenes</i> , <i>S. viridans</i> , <i>N. meningitidis</i> , <i>B. anthracis</i> , <i>Corynebacterium diphtheriae</i> , <i>Clostridium</i> spp., spirochetes (<i>Treponema</i> , <i>Leptospira</i>), <i>Actinomyces</i> and most of the anaerobes (not <i>Bacteroides fragilis</i>)
(b) Procaine penicillin G	i.m.		
(c) Benzathine penicillin G	i.m.		
2. Semisynthetic penicillins			
(a) <i>Acid-resistant penicillin</i>			
Phoxymethyl penicillin (penicillin V)	Oral	Susceptible	Similar to penicillin G, attains very low plasma concentration, hence used only for mild streptococcal and pneumococcal infections, trench mouth
(b) <i>Penicillinase-resistant penicillins</i>		Resistant	Sensitive strains of <i>Staphylococcus aureus</i> and <i>S. epidermidis</i> infections (abscesses, cellulitis, pneumonia, etc.)
Methicillin	i.m., i.v.		
Oxacillin	Oral, i.m., i.v.		
Cloxacillin			
Dicloxacillin			

Table 11.6 ■ Classification of penicillins with their spectrum of activity—cont'd

Penicillins	Route of administration	Penicillinase susceptible/ resistant	Antimicrobial spectrum/uses
(c) <i>Extended-spectrum penicillins</i>			
• <i>Aminopenicillins</i>			
Ampicillin	Oral, i.m., i.v.	Susceptible	Antimicrobial spectrum extended to gram-negative bacilli; <i>Escherichia coli</i> , <i>Proteus</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Haemophilus influenzae</i> and <i>Helicobacter pylori</i> . Of all the oral β -lactams, amoxicillin is the most active agent against both penicillin-sensitive and penicillin-resistant <i>Streptococcus pneumoniae</i> . Ampicillin is highly effective against <i>Listeria monocytogenes</i>
Amoxicillin			
• <i>Carboxypenicillins</i>		Susceptible	Infections caused by <i>Pseudomonas aeruginosa</i> and <i>Proteus</i> spp.
Carbenicillin	i.m., i.v.		
Carbenicillin indanyl	Oral		
Ticarcillin	i.v.		
• <i>Ureidopenicillins</i>		Susceptible	<i>P. aeruginosa</i> , <i>Klebsiella</i> and Enterobacteriaceae infections (pneumonias, burns and UTIs)
Mezlocillin	i.m., i.v.		
Piperacillin	i.m., i.v.		

UTI, urinary tract infection.

Adverse Effects. They are similar to those of penicillin G. Congestive cardiac failure may be precipitated due to sodium content of carbenicillin sodium. It can also interfere with platelet function and cause bleeding.

Therapeutic Uses of Penicillins

1. Streptococcal Infections. Ampicillin and amoxicillin (Table 11.7) are effective for pharyngitis, sinusitis, otitis media, bronchitis, etc., caused by *S. pyogenes*, *S. pneumoniae* and *H. influenzae*. Among oral β -lactams, amoxicillin is the most effective agent against penicillin-sensitive and penicillin-resistant *S. pneumoniae*.

Rheumatic Fever. The causative organism is group A β -haemolytic *Streptococcus*. Procaine penicillin G 600,000 units i.m., once daily for 10 days, or benzathine penicillin G 1,200,000 units i.m. as a single dose is used for the treatment of rheumatic fever. For rheumatic fever prophylaxis, inj. benzathine penicillin G is the ideal agent. It is given in a dose of 1.2 million units i.m., once a month and continued for lifetime in high-risk people. Patients allergic to penicillin are treated with erythromycin or sulphadiazine.

Table 11.7 ■ Comparison between ampicillin and amoxicillin

Ampicillin	Amoxicillin
Semisynthetic, aminopenicillin	Semisynthetic, aminopenicillin
Acid stable; incompletely absorbed from the GI tract – alters intestinal flora; hence, diarrhoea is more common (superinfection)	Acid stable, completely absorbed from the GI tract; hence, the incidence of diarrhoea is less
Food decreases the absorption of ampicillin	Food does not decrease the absorption of amoxicillin
Effective against <i>Shigella</i> and <i>H. influenzae</i>	Less effective against <i>Shigella</i> and <i>H. influenzae</i>
Ampicillin reduces the effectiveness of oral contraceptives	Does not reduce the effectiveness of oral contraceptives
Dose: Ampicillin 250–500 mg q.i.d.	Dose: Amoxicillin 250–500 mg t.i.d.
GI, gastrointestinal.	

Subacute bacterial endocarditis (SABE): Ampicillin in combination with gentamicin has been used for the treatment of SABE. Amoxicillin is the most commonly used AMA for prophylaxis of bacterial endocarditis.

- Urinary tract infection (UTI)**: Fluoroquinolones are the preferred AMAs for UTIs. Ampicillin + gentamicin is useful in *E. coli* pyelonephritis.
- Meningitis**: At present, third-generation cephalosporins along with vancomycin are the drugs of choice for treatment of meningitis caused by *S. pneumoniae* or *N. meningitidis*, as the organisms have developed resistance to ampicillin. But ampicillin is very effective for meningitis due to *Listeria monocytogenes* in immunocompromised patients. Hence, the combination of ampicillin, vancomycin and third-generation cephalosporin is used for empirical therapy of bacterial meningitis.
- Bacillary dysentery**: FQs are the drugs of choice. Some cases may respond to ampicillin, but many strains have developed resistance to it.
- Typhoid fever**: A FQ or ceftriaxone is the drug of choice for typhoid. Ampicillin, cotrimoxazole or ciprofloxacin is useful for eradicating carrier state.
- Syphilis**: Penicillin G is the drug of choice for syphilis. *T. pallidum* is very sensitive to penicillin and is killed at very low concentration of the drug. Procaine penicillin G/ benzathine penicillin G is used for the treatment of early syphilis. For late syphilis, benzathine penicillin G is used. The alternative drugs are ceftriaxone, azithromycin and doxycycline. Penicillin is the drug of choice for treatment of syphilis in pregnancy.
- Diphtheria**: It is an acute infection of upper respiratory tract caused by *C. diphtheriae*. It is treated mainly with the specific antitoxin. Penicillin G helps to eliminate carrier state. Patients allergic to penicillin are treated with erythromycin.
- Clostridial infections (tetanus and gas gangrene)**: The main treatment is neutralization of the toxin by using human tetanus immunoglobulin. For gas gangrene, penicillin G is used as an adjunct to antitoxin.
- Gonococcal infections**: Penicillin was the drug of choice for gonococcal infections. Ampicillin with probenecid is effective against non-penicillinase-producing gonococcus.

Because of the emergence of resistant organisms, penicillins are not preferred at present. Third-generation cephalosporins, ceftriaxone or cefixime are the drugs of choice for uncomplicated gonococcal infections.

10. **Other infections:** Leptospirosis, anthrax, Lyme disease, actinomycosis, rat-bite fever, etc., are effectively treated with penicillin G.
11. **Anaerobic infections:** Amoxicillin/ampicillin/penicillin V is used in combination with metronidazole for treatment of acute necrotizing gingivitis (trench mouth).
12. ***H. pylori* infection:** Amoxicillin is used in combination with other drugs.
13. **Serious infections:** Bacteraemias, pneumonias, UTI, burns, etc., by *P. aeruginosa* and *Proteus* are more effectively treated with piperacillin/ticarcillin than by carbenicillin. Carbenicillin indanyl is used orally for the treatment of UTI caused by *P. aeruginosa* and *Proteus* spp. Ticarcillin is used in combination with β -lactamase inhibitor and an aminoglycoside for the treatment of mixed nosocomial infection.

Drug interactions of penicillins: Probenecid competes with β -lactams (penicillins and cephalosporins) for active tubular secretion and retards their excretion, thereby increasing the plasma concentration as well as the duration of action of β -lactams. Hence, simultaneous administration of probenecid and penicillin is useful in the treatment of bacterial endocarditis and gonococcal infections to enhance the therapeutic efficacy of β -lactams.

β -Lactamase Inhibitors (Table 11.8). They are clavulanic acid, sulbactam and tazobactam. They structurally resemble β -lactam molecules. β -Lactamase inhibitors bind to β -lactamases and inactivate them. Coadministration of these drugs with β -lactams increases the activity of β -lactams by preventing them from enzymatic destruction.

Clavulanic Acid. It is isolated from *Streptomyces clavuligerus*. It competitively and irreversibly inhibits β -lactamases produced by a wide range of gram-positive and gram-negative bacteria. After binding to the enzyme, clavulanic acid itself gets inactivated, hence called a 'suicide' inhibitor.

Table 11.8 ■ β -Lactamase inhibitors and their uses

Preparation (brand name)	Route(s) of administration	Uses
1. Clavulanic acid + amoxicillin	Oral, i.m., i.v.	Skin, soft-tissue, otitis media, respiratory and urinary tract infections caused by β -lactamase-producing strains of <i>S. aureus</i> , <i>E. coli</i> , <i>H. influenzae</i> and gonococci
2. Clavulanic acid + ticarcillin	i.m., i.v.	Mixed nosocomial infections due to aerobic gram-negative bacilli, <i>S. aureus</i> and <i>Bacteroides</i> spp.
3. Sulbactam + ampicillin	Oral, i.m., i.v.	Intra-abdominal and pelvic infections (mixed aerobic and anaerobic infections) due to β -lactamase-producing strains of <i>S. aureus</i> , gram-negative aerobes and anaerobes
4. Tazobactam + piperacillin	i.v.	Severe infections caused by β -lactamase-producing strains of gram-negative bacilli

Cephalosporins

The first cephalosporins were obtained from a fungus, *Cephalosporium acremonium*. Later, semisynthetic cephalosporins were developed. Cephalosporins are β -lactam antibiotics with 7-aminocephalosporanic acid nucleus. The mechanism of action and development of resistance are similar to those of penicillins. Like penicillins, cephalosporins also inhibit synthesis of bacterial cell wall and produce bactericidal effect. Cephalosporins have been divided into five generations.

Important features of first, second, third and fourth generation cephalosporins have been described in Table 11.9.

Fifth-generation cephalosporins: They are ceftaroline fosamil (i.v.) and ceftobiprole medocartil (i.v.). Both are prodrugs. They are active against gram-positive and gram-negative bacteria including MRSA, penicillin-resistant *S. pneumoniae*, *Enterococcus fecalis*, etc. They are indicated for treatment of complicated skin and soft-tissue infections and community-acquired pneumonia caused by resistant organisms.

Pharmacokinetics. Cephalosporins are administered either orally or parenterally (Table 11.9). These drugs are excreted mainly unchanged through kidney by either glomerular filtration or tubular secretion. Some cephalosporins are metabolized in the body before their excretion. Cefotaxime is deacetylated in the body before its excretion. Cefoperazone is mainly excreted through bile. Like penicillins, the active tubular secretion of cephalosporins is blocked by probenecid, resulting in higher blood levels and longer duration of action.

Adverse Effects

1. Hypersensitivity: The most common adverse effects are allergic reactions. They are skin rashes, urticaria and rarely anaphylaxis. Cross-reactivity to penicillin is seen in few patients.
2. GI disturbances mainly diarrhoea, vomiting and anorexia can also occur.
3. Pain at the site of i.m. injection mainly with cephalothin. Intravenous cephalosporins can cause thrombophlebitis.
4. Nephrotoxicity is also seen, particularly with cephaloridine, because of which it has been withdrawn. Coadministration of cephalothin and gentamicin increases the risk of nephrotoxicity.
5. Intolerance to alcohol (a disulfiram-like reaction) has been reported with cefotetan and cefoperazone.
6. Severe bleeding can occur due to either hypoprothrombinaemia (which responds to vitamin K therapy) or thrombocytopenia and/or platelet dysfunction, especially in patients with renal failure.

Table 11.9 ■ Antibacterial spectrum, pharmacokinetics and uses of cephalosporins

Cephalosporins	First generation	Second generation	Third generation	Fourth generation
1. Drugs	• Cephalexin (O) • Cefadroxil (O) • Cefazolin (i.m., i.v.) • Cephradine (O, i.m., i.v.) • Cephalothin (i.m.)	• Cefaclor (O) • Cefuroxime axetil (O) • Cefuroxime (i.m., i.v.) • Cefoxitin (i.m., i.v.) • Cefotetan (i.m.) • Cefprozil (O)	• Cefixime (O) • Cefpodoxime proxetil (O) • Ceftriaxone (i.m., i.v.) • Cefotaxime (i.m., i.v.) • Cefoperazone (i.m., i.v.) • Ceftazidime (i.m., i.v.) • Ceftizoxime (i.m., i.v.) • Cefdinir (O) • Ceftibuten (O)	• Cefepime (i.v.) • Cefpirome (i.m., i.v.)
2. Antibacterial spectrum				
• Against gram-positive organisms (except enterococci and MRSA)	+++	++	+	+
• Against gram-negative organisms	+ (<i>E. coli</i> , <i>K. pneumoniae</i>)	++ (<i>E. coli</i> , <i>K. pneumoniae</i> , <i>Proteus</i> , <i>H. influenzae</i>)	+++	+++
• Anaerobes	Effective against oral cavity anaerobes except <i>Bacteroides fragilis</i>	Effective against anaerobes including <i>B. fragilis</i> (cefotetan, cefoxitin)	Effective against anaerobes including <i>B. fragilis</i> (cefoperazone, ceftizoxime)	Not effective against <i>B. fragilis</i>
• Against <i>Pseudomonas</i>	Not effective	Not effective	Effective (cefoperazone, ceftazidime)	Effective (cefepime)
• Against <i>Salmonella</i>	Not effective	Not effective	Effective (ceftriaxone, cefoperazone)	
3. β -Lactamase enzyme	Among the first-generation agents, cefazolin is highly susceptible to staphylococcal β -lactamases	Cefoxitin and cefuroxime are resistant to β -lactamases produced by gram-negative organisms	Most of them are resistant to most of the β -lactamases (except cefoperazone) produced by gram-negative organisms	Same as third generation

Continued

Table 11.9 ■ Antibacterial spectrum, pharmacokinetics and uses of cephalosporins—cont'd

Cephalosporins	First generation	Second generation	Third generation	Fourth generation
4. Blood–brain barrier (BBB)	—	Some of the second-generation drugs (cefuroxime) cross BBB	Cefotaxime, ceftriaxone cross BBB and reach high concentration in CSF	Cross BBB
5. Uses	1. Skin and soft-tissue infections due to streptococci and <i>Staphylococcus aureus</i> 2. Surgical prophylaxis: Cefazolin is preferred because of its longer duration of action	1. Respiratory tract infections: Otitis media and sinusitis – oral cefuroxime axetil can be used 2. Cefoxitin and cefotetan are preferred for mixed (gram-negative bacteria and anaerobes) intra-abdominal and pelvic infections	Third-generation cephalosporins alone or with aminoglycosides are used in severe gram-negative infections 1. Pyelonephritis caused by gram-negative organisms: Ceftriaxone 2. Community-acquired pneumonia: Ceftriaxone, cefotaxime 3. Gonorrhoea: Ceftriaxone is the drug of choice, 250 mg i.m. as a single dose 4. Typhoid fever: Ceftriaxone and cefoperazone are very effective for the treatment of multidrug-resistant <i>Salmonella</i> infections 5. Meningitis caused by meningococci and <i>Haemophilus influenzae</i>: Inj. cefotaxime and ceftriaxone are the preferred drugs 6. Mixed aerobic and anaerobic infections seen in patients with malignancy 7. Septicaemia caused by gram-negative infections 8. Nosocomial infection: Third-generation drugs are useful 9. Syphilis: Ceftriaxone is an alternative drug	Same as third generation. They are reserve drugs for hospital-acquired resistant infections

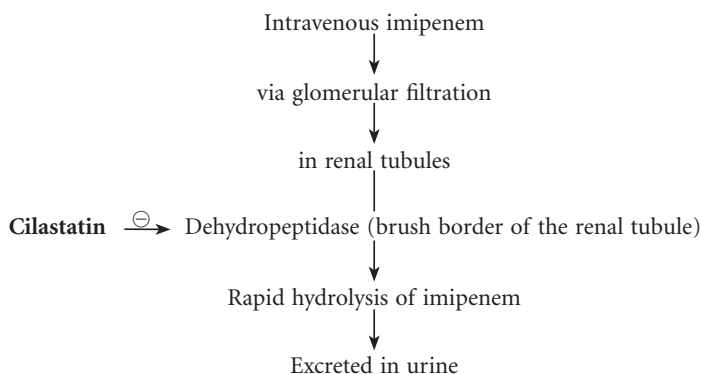
+, less active; ++, moderately active; +++, highly active; CSF, cerebrospinal fluid; MRSA, methicillin-resistant *S. aureus*.

Carbapenems

Examples are imipenem, meropenem, doripenem, ertapenem and faropenem.

IMIPENEM

Imipenem is a semisynthetic β -lactam antibiotic. Imipenem, like other β -lactam antibiotics, acts by inhibiting bacterial cell wall synthesis and produces bactericidal activity. It has a wide spectrum of antibacterial activity – gram-positive organisms like streptococci, staphylococci, enterococci, *Listeria* and *C. difficile* (anaerobe); and gram-negative organisms like *P. aeruginosa*, Enterobacteriaceae and *B. fragilis* (anaerobes). It is resistant to most β -lactamases.



Cilastatin, a dehydropeptidase inhibitor, increases the concentration of imipenem in urine. Hence, it is combined with imipenem. Imipenem–cilastatin combination increases the antibacterial efficacy.

Imipenem may exhibit cross-reactivity with penicillins and cephalosporins. Nausea, vomiting and skin rashes are the common side effects and, rarely, seizures have also been reported.

OTHER CARBAPENEMS

Meropenem and Doripenem

- Injected intravenously
- Not destroyed by dehydropeptidase – does not require cilastatin coadministration
- Seizures less likely
- Also effective against imipenem-resistant *P. aeruginosa*

Ertapenem

- Is administered parenterally (i.v. and i.m.)
- Has longer half-life than those of imipenem and meropenem – once-daily dose is used
- Less effective against *P. aeruginosa*

Faropenem

- Orally effective

USES OF CARBAPENEMS

They are used for treatment of hospital-acquired infections – skin and soft-tissue, genitourinary, respiratory, abdominal infections, etc. Dose of carbapenems should be reduced in patients with renal failure.

Monobactams

Aztreonam is a β -lactam antibiotic with **only** one ring in its structure, hence the name monobactam. It also acts by inhibiting the bacterial cell wall synthesis. It is effective **only** against gram-negative bacteria, such as Enterobacteriaceae, *P. aeruginosa*, gonococci and *H. influenzae*, but has no activity against gram-positive bacteria and anaerobes. It is resistant to most β -lactamases. It is administered **only** parenterally (i.m., i.v.). The main advantage with aztreonam is lack of cross-reactivity with other β -lactam antibiotics (except with ceftazidime). It is useful for treatment of hospital-acquired gram-negative infections (genitourinary, intra-abdominal, etc.).

Aminoglycosides

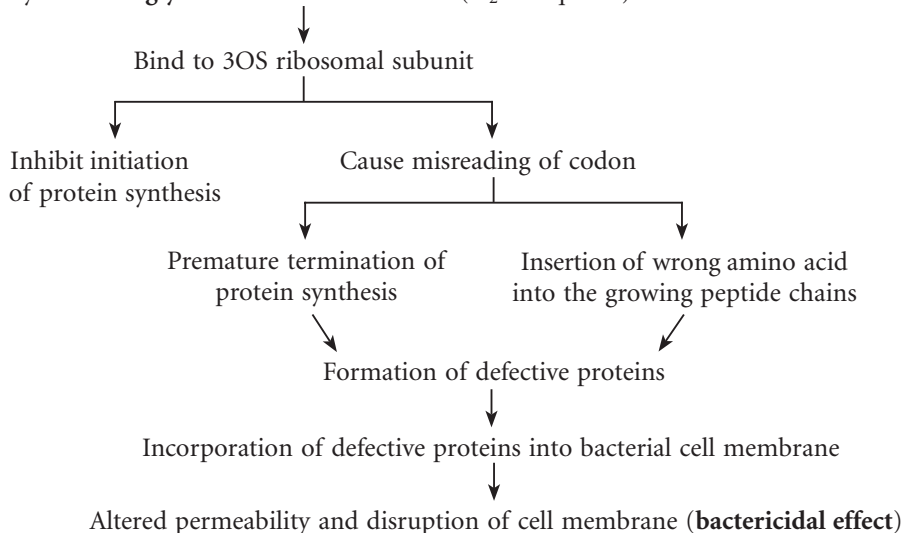
They include streptomycin, gentamicin, tobramycin, amikacin, kanamycin, sisomicin, neomycin, framycetin, netilmicin and paromomycin.

Common Properties of Aminoglycosides

1. They contain two or more *amino sugars* attached by glycosidic linkage to hexose ring.
2. They are highly polar compounds, hence *poorly absorbed* from the GI tract. They are administered by *parenteral* route (i.m./i.v.) for systemic effect.
3. They are mainly *distributed* into extracellular fluid and poorly penetrate into the CSF.
4. They are not *metabolized* in the body.
5. They are *excreted* unchanged in urine.
6. They have *bactericidal* action against gram-negative aerobes and are more active at alkaline pH.
7. They cause *ototoxicity* and *nephrotoxicity*.
8. They exhibit partial *cross-resistance* among them.
9. Transport of aminoglycosides into the bacterial cell requires oxygen; hence, *anaerobes are resistant* to aminoglycosides.

Mechanism of Action. Aminoglycosides are bactericidal agents – inhibit protein synthesis.

Entry of **aminoglycosides** into bacterial cell (O_2 is required)



Mechanisms of Bacterial Resistance. Bacterial resistance to aminoglycosides is due to (i) inactivation of the drug by bacterial enzymes, (ii) decreased entry of drug into bacterial cell and (iii) decreased affinity of the drug for the ribosomes.

Aminoglycosides Exhibit

1. A concentration-dependent killing effect – higher the plasma concentration, more of the bacteria killed rapidly.
2. A postantibiotic effect – bactericidal effect is present even when serum concentration falls below MIC. Therefore, once-daily dosing regimen is effective.

Dosing

1. Once-daily dosing regimen – total daily dose is given as a single injection. It is preferred because it:
 - Is as effective as multiple-dose regimen. Higher peak plasma concentration is achieved following single dose.
 - Is safer than multiple-dose regimen. The plasma trough concentration of aminoglycosides remains below threshold levels for toxicity for a long period of time.
 - Is convenient.
2. Multiple-daily dosing regimen – the total daily dose is administered in two or three equally divided doses.

Once-daily dosing regimen is not preferred in bacterial endocarditis, children and patients with renal impairment. Dose adjustment of aminoglycosides is done according to body weight and creatinine clearance.

Adverse Effects

1. **Ototoxicity:** Vestibular and cochlear dysfunctions can occur due to VIII cranial nerve damage. Aminoglycosides get concentrated in the perilymph and endolymph of the inner ear which can lead to progressive damage to vestibular and cochlear hair cells. Streptomycin and gentamicin mainly affect vestibular function. Vestibular dysfunction causes intense headache (earliest symptom), dizziness, nausea, vomiting, vertigo, nystagmus and ataxia. Amikacin and kanamycin affect auditory function, causing more cochlear damage. The manifestations of cochlear damage are tinnitus (reversible on discontinuation of the drug) and deafness (permanent).

The important risk factors for ototoxicity are the following:

- (a) Elderly patients
- (b) Repeated courses of aminoglycosides
- (c) Persistently increased concentration of the drug in plasma
- (d) Patients with preexisting auditory impairment
- (e) Concurrent use of other ototoxic drugs, such as vancomycin, minocycline and loop diuretics

2. **Nephrotoxicity:** Aminoglycosides get concentrated in renal cortex and produce nephrotoxicity, which is usually reversible on discontinuation of the drug. The incidence of nephrotoxicity is highest with neomycin and least with streptomycin. There is a decrease in urinary concentrating capacity, albuminuria, etc. The risk factors for nephrotoxicity are elderly patients, preexisting renal disease and concurrent use of other nephrotoxic drugs, such as AMB, vancomycin, cisplatin and cyclosporine.

3. **Neuromuscular blocking effect:** Apnoea and muscular paralysis have been reported. It may be reversed by administration of calcium salt. Aminoglycosides inhibit release of acetylcholine from motor nerve. Myasthenic patients are more susceptible to neuromuscular blocking effect of these drugs; hence, they should be avoided.

4. **Hypersensitivity reactions** are rare; occasionally skin rashes, drug fever and eosinophilia can occur. Cross-sensitivity between aminoglycosides may occur.
5. Use of aminoglycosides during pregnancy may cause ototoxicity in fetus.

STREPTOMYCIN

Streptomycin was the first aminoglycoside discovered in 1944. The common properties, mechanism of action and adverse effects are explained above.

Uses. Streptomycin is one of the first-line drugs for TB and is used in combination with other antitubercular drugs. The other uses include tularaemia, plague and brucellosis.

GENTAMICIN

It is the most commonly used aminoglycoside antibiotic for aerobic gram-negative bacillary infections due to *E. coli*, *Klebsiella*, *Proteus*, *Enterobacter* and *P. aeruginosa*. It is also effective against gram-positive infections – enterococci, *S. viridans* and staphylococci but not *M. tuberculosis*. It is available for parenteral and topical administration. Common properties, mechanism of action and adverse effects are discussed above.

NEOMYCIN

It is highly nephrotoxic, hence never used for systemic effect. It is used only for local effect. The common properties, mechanism of action and adverse effects are as for other aminoglycosides.

Uses of Neomycin

■ *Topically*

- (a) Infections of the skin and mucous membranes: Ulcers, wounds and burns.
- (b) Infections of the eye and external ear: Neomycin is often used in combination with bacitracin or polymyxin B.

■ *Orally (for local action)*

- (a) Neomycin sulphate is useful in combination with erythromycin base for preparation of bowel before abdominal surgery.
- (b) Hepatic encephalopathy: Neomycin, on oral administration, reduces blood ammonia level by destroying the colonic bacteria. Neomycin is highly toxic; hence, it has been replaced by oral lactulose, which is preferred for hepatic encephalopathy.

FRAMYCETIN (SOFRAMYCIN)

Like neomycin, framycetin is also highly nephrotoxic, hence not used for systemic administration. The common properties, mechanism of action and adverse effects are similar to those of other aminoglycosides. Framycetin is widely used topically for skin, eye and ear infections.

AMIKACIN

Among the aminoglycosides, it has the broadest spectrum of activity. It is resistant to aminoglycoside-inactivating enzymes. It is useful for the treatment of nosocomial gram-negative infections and tuberculosis.

TOBRAMYCIN

All features are similar to those of gentamicin. It is superior to gentamicin against *P. aeruginosa* – useful in the treatment of serious infection by this organism.

PAROMOMYCIN

It is an aminoglycoside with activity against protozoans. It can be used in intestinal amoebiasis, giardiasis, vaginal trichomoniasis, visceral leishmaniasis and hepatic encephalopathy.

NETILMICIN

It is resistant to aminoglycoside-inactivating enzymes, hence effective against most of the gentamicin-resistant bacteria.

THERAPEUTIC USES OF GENTAMICIN AND OTHER AMINOGLYCOSIDES

Among aminoglycosides, gentamicin is the most commonly used because it is cheap and effective against most of the aerobic gram-negative bacilli.

1. Severe aerobic gram-negative bacillary infections

■ Urinary tract infection with pyelonephritis ■ Pneumonia ■ Meningitis ■ Osteomyelitis ■ Septicaemia ■ Peritonitis ■ Infected burns	}	Due to <i>Pseudomonas</i>, <i>Klebsiella</i>, <i>E. coli</i>, <i>Proteus</i>, etc.
- Gentamicin, tobramycin, amikacin and netilmicin are effective against *P. aeruginosa*.
 - Amikacin and netilmicin are used for treatment of serious nosocomial infections due to gram-negative bacilli.
 - Aminoglycosides are often used in combination with penicillins/third-generation cephalosporins in these conditions.

2. Bacterial endocarditis due to *S. viridans* and *Enterococcus*: Gentamicin is used in combination with a penicillin or vancomycin. Combination broadens the spectrum of activity, produces synergistic effect and decreases emergence of resistance.

- Penicillin G + gentamicin for *S. viridans*.
- Ampicillin + gentamicin for *Enterococcus*.
- Vancomycin + gentamicin for *Enterococcus* (patients allergic to β -lactam antibiotics).
- Gentamicin and ampicillin combination is also used for the prophylaxis of endocarditis in high-risk patients before surgical procedures.

3. TB: Streptomycin, kanamycin and amikacin are used in the treatment of TB.

4. Other gram-negative infections

- **Plague:** Streptomycin/gentamicin is used intramuscularly.
- **Brucellosis:** Streptomycin/gentamicin is used in combination with doxycycline.
- **Tularaemia:** Streptomycin or gentamicin is the drug of choice. FQs and tetracyclines are also effective.

5. Gentamicin, tobramycin, neomycin, sisomicin, framycetin, etc., are used topically for gram-negative skin, eye and ear infections.

Broad-Spectrum Antibiotics

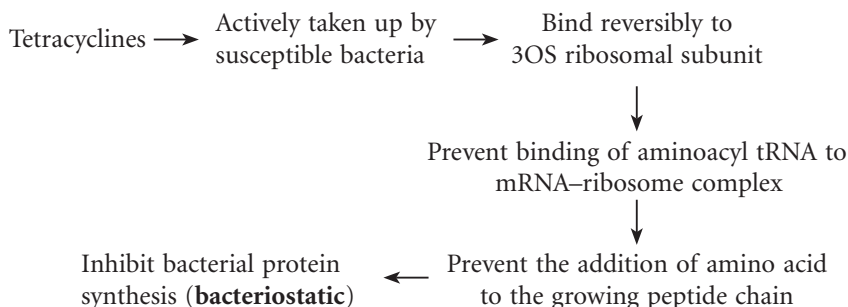
Tetracyclines and chloramphenicol are broad-spectrum antibiotics. They are so called because of their effectiveness against a wide range of microorganisms, such as:

- Gram-positive and gram-negative cocci – *S. aureus*, *S. pneumoniae*, *N. gonorrhoeae*
- Gram-negative bacilli – *V. cholerae*, *H. ducreyi*, *H. influenzae*, *H. pylori*, *Campylobacter*, *Yersinia pestis*
- Gram-positive bacilli – *B. anthracis*, *Listeria*, *Clostridia*, *Propionibacterium acnes*
- Others – *Rickettsiae*, *Mycoplasma*, *Chlamydia*, *Spirochetes*, *Actinomyces*, *Plasmodia*, *Entamoeba histolytica*

Tetracyclines

Tetracyclines have four cyclic rings in their structure (Fig. 11.8).

Mechanism of Action



Resistance. Bacterial resistance to tetracyclines is due to: (i) decreased influx or increased efflux of tetracyclines and (ii) inactivation of the drug by enzymes.

Pharmacokinetics. The older tetracyclines are incompletely absorbed after oral administration (Table 11.10), but that is adequate to produce antibacterial activity. Food interferes with the absorption of all tetracyclines; doxycycline and minocycline are less affected. Tetracyclines have chelating property, hence form stable insoluble and unabsorbable complexes with calcium, magnesium, iron and other metal ions. Therefore, the absorption of tetracyclines is reduced by simultaneous administration with dairy products, antacids, iron, sucralfate and zinc salts. Tetracyclines are widely distributed throughout the body, and get concentrated in liver, spleen, bone, dentine, enamel of unerupted teeth but concentration in CSF is relatively low. They cross placental barrier, and are metabolized in liver and excreted in urine. Doxycycline is excreted mainly in the faeces via bile. Therefore, doxycycline is safe for use in patients with renal insufficiency. Doxycycline undergoes enterohepatic cycling.

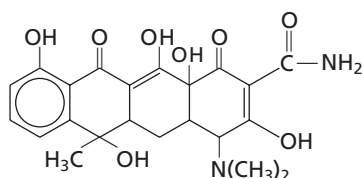


Fig. 11.8 Basic structure of tetracycline.

Table 11.10 ■ Important features of tetracyclines

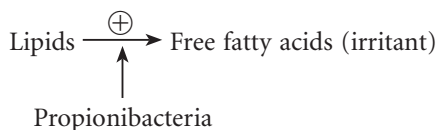
Drugs	Route of administration	Absorption from the gut	Half-life, $t_{1/2}$ (hours)	Dosage
Oxytetracycline Tetracycline	Oral, i.v., topical Oral, topical	Incomplete	6–12	250–500 mg q.i.d.
Demeclocycline	Oral	Incomplete	16–18	300–600 mg b.d.
Doxycycline Minocycline	Oral, i.v. Oral	High	18–24	100 mg b.d. or o.d.

Adverse Effects

- GI:** On oral administration, they can cause GI irritation manifested as nausea, vomiting, epigastric distress, abdominal discomfort and diarrhoea. Diarrhoea is more common with tetracycline and oxytetracycline as they are incompletely absorbed → cause alteration of normal flora. Risk of diarrhoea is low with doxycycline.
- Phototoxicity:** It is particularly seen with demeclocycline and doxycycline. They may also produce sunburn-like reaction in the skin on exposure to sunlight. They may also produce pigmentation of nails.
- Hepatotoxicity:** Acute hepatic necrosis with fatty changes is common in patients receiving high doses (>2 g/day) intravenously. It is more likely to occur in pregnant women.
- Renal toxicity:** Demeclocycline may produce nephrogenic diabetes insipidus by blocking the action of antidiuretic hormone (ADH) on collecting duct. This effect of demeclocycline has been used therapeutically in patients with syndrome of inappropriate secretion of antidiuretic hormone (SIADH).
Fanconi syndrome: Use of outdated tetracyclines may damage proximal renal tubules – the patient may present with nausea, vomiting, polyuria, proteinuria, acidosis, etc.
- Superinfection:** It is common with older tetracyclines because of their incomplete absorption in the gut; they cause alteration of the gut flora. Superinfection occurs with organisms like *Candida*, *Proteus*, *Pseudomonas* and *C. difficile*. Pseudomembranous colitis caused by *C. difficile* is a serious complication. It is characterized by severe diarrhoea, fever, abdominal pain and stool mixed with blood and mucus, which is treated with oral metronidazole.
- Effects on bones and teeth:** Tetracyclines have calcium chelating property and form tetracycline–calcium orthophosphate complex which is deposited in growing bone and teeth. Use of tetracyclines in children and during pregnancy can cause permanent brownish discolouration of deciduous teeth due to deposition of chelate in the teeth. There is increased incidence of caries in such teeth. Tetracyclines also affect the linear growth of bones. The incidence of hepatotoxicity is more in pregnant women. Therefore, tetracyclines are contraindicated during pregnancy in the interest of both fetus and mother. It is also contraindicated in children up to the age of 8 years.
- They may cause **increased intracranial pressure** (pseudotumour cerebri) in infants.
- Hypersensitivity reactions:** Skin rashes, fever, urticaria, exfoliative dermatitis, etc., may occur rarely. Cross-sensitivity among tetracyclines is common.

Therapeutic Uses

- 1. Rickettsial infections:** Tetracyclines are the first-choice drugs for the treatment of rickettsial infections – epidemic typhus, Rocky Mountain spotted fever, scrub typhus, rickettsial pox and Q fever. Doxycycline 100 mg b.d. is given orally or intravenously for 5–7 days.
- 2. *Mycoplasma pneumoniae* infections:** Doxycycline has good activity against *Mycoplasma* – used to shorten the duration of illness. It is a first choice drug in atypical pneumonia due to *M. pneumoniae*.
- 3. Chlamydial infections**
Lymphogranuloma venereum: It is a sexually transmitted infection caused by *C. trachomatis*. Doxycycline is the drug of choice. In complicated cases (i.e. pelvic inflammatory disease), doxycycline 100 mg b.d. should be continued for 21 days. Macrolides are also effective.
Chlamydial urethritis and granuloma inguinale: Doxycycline is highly effective and is the drug of choice.
Psittacosis: Doxycycline is the preferred agent; treatment should be continued for 2 weeks to prevent relapse.
- 4. Cholera:** Fluid and electrolyte replacement is the mainstay of therapy. Single dose of tetracycline 2 g or doxycycline 300 mg is effective in adults. It reduces the stool volume.
- 5. Brucellosis:** Treatment of choice is a combination of doxycycline with rifampin/gentamicin/streptomycin.
- 6. Plague:** Doxycycline is highly effective for treatment of plague.
- 7. As an alternative drug:** For treatment of leptospirosis (doxycycline is an alternative to penicillins), pneumonia due to *Chlamydia pneumoniae* (doxycycline alternative to azithromycin), tularaemia (alternative to streptomycin, gentamicin), etc.
- 8. Acne:** Low doses of tetracyclines are used.



Tetracyclines act by inhibiting propionibacteria, thereby prevent the formation of free fatty acids.

- 9. Malaria:** Doxycycline is used in combination with other antimalarial agents for treatment of chloroquine-resistant *P. falciparum* malaria. It is used alone for malarial chemoprophylaxis.
- 10. Amoebiasis:** See p. 452.
- 11. SIADH:** Demeclocycline has anti-ADH action; hence, it is used in SIADH to promote diuresis.
- 12. Leprosy:** It is one of the components in ROM (rifampin, ofloxacin and minocycline) regimen for single-lesion paucibacillary leprosy (PBL).
- 13. Filariasis:** Doxycycline is given orally in filarial infection.

Advantages of Doxycycline over Tetracycline

1. It can be administered orally as well as intravenously.
2. It is highly potent.
3. It is completely absorbed after oral administration.
4. Food does not interfere with its absorption.

5. It has a longer duration of action ($t_{1/2}$ – 24 hours); requires less frequent dosing subscript
6. Incidence of diarrhoea is rare as it does not affect the intestinal flora.
7. It can be safely given to patients with renal failure, as it is excreted primarily in bile.

Tigecycline

The spectrum of activity of tigecycline is similar to that of tetracyclines. It is also effective against organisms resistant to tetracyclines. Mycobacteria are also susceptible. Tigecycline has a long half-life. It is administered intravenously. Adverse effects include nausea and vomiting. It can cause brown discolouration of the teeth in children. It is useful in serious skin, soft-tissue and intra-abdominal infections.

Chloramphenicol

Chloramphenicol, a broad-spectrum antibiotic; was isolated from *Streptomyces venezuelae*. Even though chloramphenicol has a broad spectrum of antibacterial activity, its use is limited to only a few conditions because of its dangerous side effect – bone marrow suppression.

Mechanism of Action

Chloramphenicol $\rightleftharpoons$ Binds reversibly to 50S ribosomal subunit $\rightleftharpoons$ Prevents the formation of peptide bond $\rightleftharpoons$ Inhibits protein synthesis

Chloramphenicol is a bacteriostatic agent, but in high concentration, it can be bactericidal against *H. influenzae*, *N. meningitidis* and *S. pneumoniae*. It can also inhibit mitochondrial protein synthesis in mammalian cells by acting on 70S ribosomes.

Resistance to chloramphenicol is caused by:

1. Production of inactivating enzyme – acetyltransferase, e.g. *H. influenzae*, *S. typhi*, *S. aureus*
2. Decreased permeability of the microbial cell wall
3. Ribosomal mutation

Pharmacokinetics. Chloramphenicol is commonly given by oral route and is rapidly absorbed from the gut. It is also available for parenteral and topical administration. It has a bitter taste; to improve the taste, chloramphenicol palmitate suspension has been developed for paediatric use. It gets activated in the intestine by pancreatic lipase. Chloramphenicol is widely distributed to all tissues including CSF and brain. It also crosses placental barrier and is secreted in milk. It gets metabolized in liver by glucuronide conjugation and the metabolite is excreted mainly in urine.

Adverse Effects. Most of the adverse effects of chloramphenicol are due to inhibition of mammalian mitochondrial protein synthesis.

1. **Hypersensitivity reactions:** Skin rashes, drug fever and angioedema may occur rarely.
2. **Bone marrow suppression:** The most serious adverse effect of chloramphenicol is on bone marrow. It can occur in two ways:
 - (a) Dose-dependent reversible suppression of bone marrow, which manifests as anaemia, leucopenia and thrombocytopenia
 - (b) Idiosyncratic non-dose-related irreversible aplastic anaemia, which is often fatal

3. **GI effects:** These include nausea, vomiting and diarrhoea. Prolonged use may cause superinfection due to suppression of gut flora.
4. **Gray baby syndrome:** In neonates, especially in premature babies, chloramphenicol can cause a dose-related gray baby syndrome due to reduced degradation and detoxification of the drug in liver because of the deficiency of glucuronyl transferase enzyme. The manifestations are nausea, vomiting, abdominal distension, diarrhoea, refusal to suck, cyanosis, irritability and circulatory collapse. The skin appears ashen gray colour, hence the name 'gray baby' syndrome. Mortality is high. Therefore, chloramphenicol should be avoided in neonates.

Drug interactions: Like erythromycin, chloramphenicol increases plasma concentration of certain drugs, such as warfarin, phenytoin, rifabutin and antiretroviral protease inhibitors (PIs), by inhibiting hepatic cytochrome P450 isoenzymes.

Therapeutic Uses

1. **Typhoid fever:** Chloramphenicol was the first-choice drug for typhoid. Antibiotics useful in typhoid are third-generation cephalosporins, FQs, azithromycin, ampicillin, cotrimoxazole, etc. Now, FQs (ciprofloxacin, ofloxacin, levofloxacin, etc.) or third-generation cephalosporins (ceftriaxone, cefoperazone) are the drugs of choice for typhoid fever. The dose of ciprofloxacin is 750 mg 12 hourly for 10 days. It also eliminates carrier state. MDR cases are treated with ceftriaxone (2–4 g i.v. daily for 10 days) or azithromycin.
2. **Bacterial meningitis:** Third-generation cephalosporins are the preferred drugs for the treatment of bacterial meningitis caused by *H. influenzae*, *N. meningitidis* and *S. pneumoniae*. However, chloramphenicol can be used alone or in combination with ampicillin.
3. **Anaerobic infections:** Chloramphenicol is effective against most anaerobic bacteria including *B. fragilis*. It is often used in combination with metronidazole for the treatment of brain, lung, intra-abdominal or pelvic abscesses.
4. **Rickettsial infections:** Tetracyclines are the drugs of choice for the treatment of rickettsial diseases. Chloramphenicol can be used to treat rickettsial infections in children and pregnant women.
5. **Eye and ear infections:** Chloramphenicol is used topically for eye and ear infections due to susceptible organisms.
6. **Brucellosis:** Chloramphenicol can be used when tetracyclines are contraindicated.

Macrolides

Erythromycin was obtained from *Streptomyces erythreus*. Roxithromycin, clarithromycin and azithromycin are semisynthetic macrolides. Erythromycin is active against *S. pyogenes*, *S. pneumoniae*, *N. gonorrhoea*, *C. perfringens*, *C. diphtheriae*, *Listeria*, *Mycoplasma*, *Legionella*, *C. trachomatis*, *B. pertussis*, etc. It is not effective against *B. fragilis*.

Mechanism of Action. Erythromycin and other macrolides bind to bacterial 50S ribosomal subunit and inhibit protein synthesis. They are bacteriostatic, but at high concentrations, they can act as bactericidal agents. They are more active at alkaline pH.

Pharmacokinetics. Erythromycin is adequately absorbed from the upper GI tract. It is destroyed by gastric acid (acid labile), hence must be administered as Enteric-coated tablets to protect it from gastric acid. Food may delay the absorption of erythromycin. It is widely distributed in the body and reaches therapeutic concentration in prostatic secretions but does not cross BBB. It is partly metabolized in liver and excreted in bile.

Preparations of Erythromycin. They are erythromycin base, Erythromycin Estolate and erythromycin stearate.

Adverse Effects

1. The common side effects are related to the GI tract (Enteral toxicity): Nausea, vomiting, epigastric pain and diarrhoea. Erythromycin increases GI motility by stimulating motilin receptors in the gut.
2. Hypersensitivity reactions: Skin rashes, drug fever, eosinophilia and hepatitis with cholestatic jaundice, particularly with erythromycin estolate. Incidence of hepatotoxicity is more in pregnant women.

Erythromycin
Enteric-coated tablets
Erythromycin Estolate
Enteral toxicity mainly
Enzyme inhibitor

Drug Interactions. Erythromycin and clarithromycin are Enzyme inhibitors, hence increase the blood levels of a number of drugs, such as theophylline, carbamazepine, valproate, warfarin, digoxin and cyclosporine, and potentiate their effects. Erythromycin and clarithromycin can precipitate fatal ventricular arrhythmias when given with cisapride, astemizole, terfenadine, etc. – such interactions are not seen with azithromycin.

Drawbacks of Erythromycin

1. It has a narrow spectrum of antibacterial activity.
2. Its oral bioavailability is low.
3. It has a short duration of action.
4. Poor patient compliance due to GI side effects.

To overcome the above drawbacks, semisynthetic macrolides – roxithromycin, clarithromycin and azithromycin – have been developed (Table 11.11).

CLARITHROMYCIN (Table 11.11)

Mechanism of action and spectrum of activity is similar to that of erythromycin. It is administered orally. It achieves high concentration inside the cells. It is also used for the treatment of MAC, leprosy and *H. pylori* infection. The uses are mentioned on p. 404.

Table 11.11 ■ Comparative features of macrolides

	Erythromycin	Roxithromycin	Clarithromycin	Azithromycin
1. Source	Natural	Semisynthetic	Semisynthetic	Semisynthetic
2. Duration of action	Short-acting (6 hours)	Long-acting (12 hours)	Long-acting	Long-acting
3. GI absorption	Incomplete	Good	Good, but undergoes first-pass metabolism	Good
4. Acid labile/stable	Acid labile, hence administered as enteric-coated tablets	Acid stable	Acid stable	Acid stable

Continued

Table 11.11 ■ Comparative features of macrolides—cont'd

	Erythromycin	Roxithromycin	Clarithromycin	Azithromycin
5. Antibacterial spectrum and therapeutic uses	Narrow spectrum Uses (see below)	Almost similar to erythromycin	Expanded anti-bacterial spectrum – effective against <i>Myco-bacterium avium</i> complex (MAC), <i>Mycobacterium leprae</i> , <i>Helicobacter pylori</i> , <i>T. gondii</i> , etc., in addition to organisms sensitive to erythromycin	Expanded antibacterial spectrum – effective against MAC, <i>H. influenzae</i> , <i>Salmonella</i> , malaria, <i>T. gondii</i> , etc., in addition to organisms sensitive to erythromycin
6. Dosage and duration of therapy	250–500 mg oral q.i.d. for 7 days	150 mg b.d. half an hour before food for 7 days	250 mg b.d. for 1–2 weeks	500 mg o.d. 1 hour before or 2 hours after food for 3–5 days
7. Enzyme inhibitor	Causes various drug interactions	Drug interactions are rare	Yes; drug interactions are same as for erythromycin	Drug interactions are rare

GI, gastrointestinal.

AZITHROMYCIN (Table 11.11)

It can be administered orally and intravenously. Oral administration should be either 1 hour before or 2 hours after food. It does not cross BBB. Azithromycin is more active against *H. influenzae* than erythromycin and clarithromycin (Table 11.11). It is well absorbed, has wide tissue distribution and achieves high intracellular concentration than erythromycin. It is better tolerated and longer acting (single daily dose) than erythromycin.

Antibacterial Spectrum and Therapeutic Uses of Macrolides

1. As a drug of choice in the following conditions:

- (a) *M. pneumoniae* infections: Azithromycin and clarithromycin are often used for the treatment of community-acquired pneumonia. Erythromycin can also be used.
- (b) Legionnaires’ pneumonia: Macrolides, especially azithromycin, is the drug of choice because of high tissue concentration, excellent activity, better tolerability and single daily dosing.

- (c) Chlamydial infections: Azithromycin is the first choice drug in urethritis, lymphogranuloma venereum and chlamydial pneumonia. Macrolides are preferred for chlamydial infections in children and pregnant women.
 - (d) Diphtheria: Erythromycin is very effective for eliminating the carrier state and for the treatment of acute infection.
 - (e) Pertussis (whooping cough): Erythromycin is most effective for the treatment as well as for prophylaxis of close contacts. Clarithromycin and azithromycin are also effective.
 - (f) Chancroid: Azithromycin is effective as single dose in chancroid.
- 2. As an alternative drug in patients who are allergic to penicillins/cephalosporins**
- (a) Tetanus: Administration of human tetanus antitoxin, tetanus toxoid, anticonvulsant (e.g. diazepam) and debridement of wound are important therapeutic measures. A course of oral erythromycin for 10 days may be given to eradicate *C. tetani*.
 - (b) Streptococcal infections: Tonsillitis, pharyngitis, otitis media, cellulitis, pneumonia, etc., respond to azithromycin and erythromycin.
 - (c) MDR typhoid fever: It is an alternative to cephalosporins.
 - (d) Prophylactic uses
 - Before surgical procedures to prevent bacterial endocarditis in patients with valvular lesion – azithromycin or clarithromycin can be used.
 - For prophylaxis of recurrences of rheumatic fever.
- 3. Other Uses.** For treatment of MAC infections in AIDS patients, azithromycin/clarithromycin is used in combination with other drugs. Clarithromycin is also useful in the treatment of *H. pylori* infection and leprosy along with other drugs.

KETOLIDES

Ketolides (e.g. telithromycin) are semisynthetic derivatives of erythromycin.

- Spectrum of activity and site of action is similar to that of azithromycin. Also effective against some macrolide-resistant organisms.
- Used orally for community-acquired pneumonia.
- Hepatotoxicity is a serious adverse effect.

SPIRAMYCIN

It is a macrolide. Spectrum of activity is similar to that of erythromycin. It is used mainly to prevent transmission of *Toxoplasma gondii* from mother to fetus.

Miscellaneous Antibacterial Agents (see Table 11.12)

CLASSIFICATION

1. Lincosamides: Clindamycin
2. Streptogramins: Quinupristin/dalfopristin
3. Oxazolidinones: Linezolid
4. Glycopeptides: Vancomycin, teicoplanin
5. Aminocyclitols: Spectinomycin
6. Lipopeptides: Daptomycin
7. Others: Bacitracin, polymyxin B, colistin, mupirocin, fusidic acid

Table 11.12 ■ Miscellaneous antibacterial agents (see also Figs 11.9 and 11.10)

Drug with mechanism of action	Antibacterial spectrum	Pharmacokinetics	Uses	Adverse effects
Clindamycin (lincosamide) inhibits protein synthesis by binding to 50S subunit of bacterial ribosomes (bacteriostatic)	Gram-positive cocci, anaerobes (including <i>Bacteroides fragilis</i>), <i>P. jiroveci</i> , <i>T. gondii</i>	Administered by oral, i.m., i.v. and topically; widely distributed in the body including bones, poorly crosses BBB	1. Anaerobic infections due to <i>B. fragilis</i> (pelvic, abdominal and lung abscess) 2. In AIDS patients (a) For <i>P. jiroveci</i> pneumonia in combination with primaquine (b) For toxoplasmosis in combination with pyrimethamine 3. Acne vulgaris – topically or orally	Skin rashes Pseudomembranous colitis (superinfection) – diarrhoea with blood and mucus in the stools due to <i>Clostridium difficile</i> The drug should be stopped immediately. It is treated with metronidazole (drug of choice) or vancomycin
Quinupristin/dalfopristin (streptogramins): They inhibit protein synthesis by binding to 50S ribosomal subunit (synergistic combination) bactericidal – streptococci and staphylococci bacteriostatic – <i>E. faecium</i>	Gram-positive cocci including MRSA and some VRE	Administered only by i.v. infusion	1. Vancomycin-resistant enterococcal (<i>E. faecium</i>) infections (VRE) 2. Nosocomial pneumonia due to MRSA	Pain due to thrombophlebitis, arthralgias and myalgias. It is an enzyme inhibitor and may raise the plasma levels of coadministered drugs (macrolides, fosphenytoin, fluoxetine, haloperidol, etc.)
Linezolid: Inhibits protein synthesis by binding to 50S ribosomal subunit; bacteriostatic except against streptococci (bactericidal)	Gram-positive organisms – streptococci, staphylococci including MRSA, VRSA, VRE, <i>Listeria</i>	Administered by oral and i.v. infusion	Skin and soft-tissue infections, nosocomial (hospital-acquired) pneumonia, urinary tract infection, etc., caused by VRE, MRSA and VRSA	GI side effects – nausea, vomiting and diarrhoea, headache, bone marrow suppression with anaemia, leucopenia and pancytopenia occasionally

Tedizolid: Mechanism of action is similar to that of linezolid	Gram-positive organisms – streptococci, staphylococci including MRSA, VRE	Oral, i.v.	Skin and soft-tissue infections, nosocomial (hospital-acquired) pneumonia	Haematological adverse effects and neuropathy are less than in linezolid
Vancomycin: Inhibits bacterial cell wall synthesis (bactericidal)	Gram-positive cocci: <i>S. aureus</i> including MRSA, <i>S. epidermidis</i> , <i>S. pyogenes</i> , <i>S. pneumoniae</i> , <i>S. viridans</i> and <i>Enterococcus</i> . Gram-positive bacilli: diphtheroids and <i>Clostridium</i> spp.	Poorly absorbed after oral administration, hence used intravenously for systemic infections. Orally for antibiotic associated colitis (for local action)	1. MRSA infections: Pneumonia, endocarditis, osteomyelitis, etc. 2. Endocarditis due to <i>S. viridans</i> or enterococci: Vancomycin is used in combination with aminoglycoside in patients allergic to penicillin 3. It is used with ampicillin and third-generation cephalosporin for empirical treatment of bacterial meningitis 4. Orally for pseudomembranous colitis caused by <i>C. difficile</i> or staphylococci	Highly toxic, causes ototoxicity, nephrotoxicity and hypersensitivity reactions (skin rashes and anaphylaxis). Rapid i.v. infusion may cause shock-like state with flushing, fever, chills, tachycardia and hypotension – ‘red man’ syndrome due to release of histamine
Teicoplanin: Inhibits bacterial cell wall synthesis (bactericidal)	Similar to that of vancomycin	Administered by i.m. or i.v. route	MRSA and enterococcal infections; for severe infections, teicoplanin is used in combination with gentamicin	Skin rashes, drug fever and rarely hypersensitivity reactions may occur
Bacitracin: Inhibits bacterial cell wall synthesis (bactericidal)	Mainly against gram-positive cocci and bacilli	Highly nephrotoxic on parenteral administration, hence used only topically	Used topically for eye and skin infections – usually in combination with neomycin and/or polymyxin B	Rarely may cause hypersensitivity reactions

Continued

Table 11.12 ■ Miscellaneous antibacterial agents (see also Figs 11.9 and 11.10)—cont'd

Drug with mechanism of action	Antibacterial spectrum	Pharmacokinetics	Uses	Adverse effects
Spectinomycin: Inhibits protein synthesis by binding to 30S ribosomal subunit (bacteriostatic)	Gram-negative bacteria	Given intramuscularly 2 g as a single dose	1. For gonococcal infections in patients who are allergic to β-lactam antibiotics 2. Multidrug-resistant gonococcal infections 3. Can be used in pregnancy to treat gonococcal infections if patient is allergic to β-lactams	Skin rashes, fever and pain at injection site
Polymyxin B and colistin: Bind to membrane phospholipids of gram-negative bacteria $\rightarrow$ form pseudopores $\rightarrow$ leakage of cell contents $\rightarrow$ death of the bacilli (bactericidal)	Gram-negative bacteria	Administered topically	1. Used topically for skin, eye and ear infections due to gram-negative organism, often in combination with other AMAs (polymyxin B, bacitracin and neomycin) 2. Orally in diarrhoeas due to gram-negative organisms – <i>Salmonella</i>, <i>Shigella</i>, <i>E. coli</i>	GI symptoms on oral administration
Fusidic acid: Inhibits bacterial protein synthesis (bacteriostatic)	Gram-positive bacteria including <i>S. aureus</i>	Topically	Used topically for staphylococcal infections – boils, folliculitis, angular cheilitis, etc.	Skin rashes
Mupirocin: Inhibits bacterial protein synthesis (bacteriostatic)	Gram-positive bacteria including MRSA, <i>S. pyogenes</i>	Topically	Used for impetigo, burns, open wounds and ulcers	Irritation and burning

AMA, antimicrobial agent; BBB, blood–brain barrier; GI, gastrointestinal; MRSA, methicillin-resistant *S. aureus*; VRE, vancomycin-resistant *Enterococcus*; VRSA, vancomycin-resistant *S. aureus*.

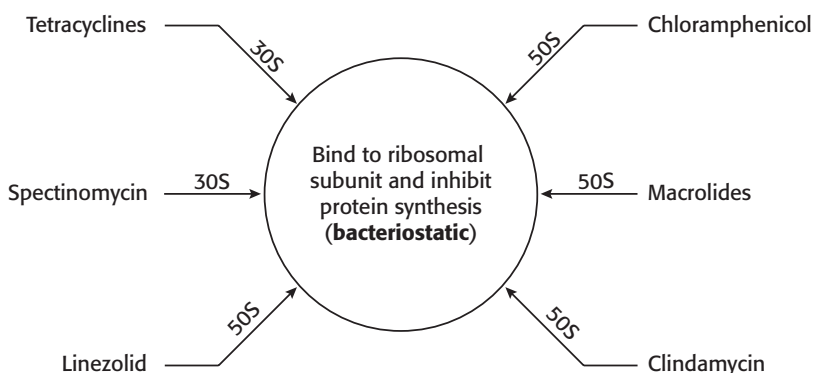


Fig. 11.9 AMAs inhibit protein synthesis by binding to either 50S or 30S ribosomal subunit.

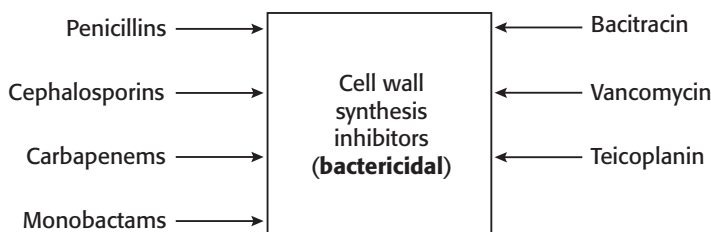


Fig. 11.10 AMAs that inhibit bacterial cell wall synthesis.

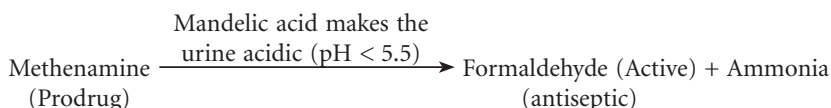
Urinary Antiseptics

PH1.48

Some AMAs on oral administration attain high concentration only in the urinary tract and exert antibacterial activity locally. They are used to treat infections of the urinary tract and are called urinary antiseptics. Common organisms involved in UTI are *E. coli*, *Proteus*, *Klebsiella* and *Pseudomonas*.

METHENAMINE

Methenamine is a prodrug. In acidic urine, it is hydrolyzed to ammonia and formaldehyde.



Formaldehyde inhibits both gram-positive and gram-negative organisms and produces bactericidal activity. It is ineffective against urea-splitting microorganisms (e.g. *Proteus* spp.) as it increases urinary pH. To prevent the release of formaldehyde in the stomach, methenamine is administered as enteric-coated tablets. It is useful mainly for chronic suppressive therapy in recurrent UTI particularly if the causative organism is *E. coli*. Methenamine is contraindicated in patients with hepatic insufficiency because of the release of ammonia. The adverse effects are nausea, vomiting, diarrhoea and even haematuria with high doses.

NITROFURANTOIN

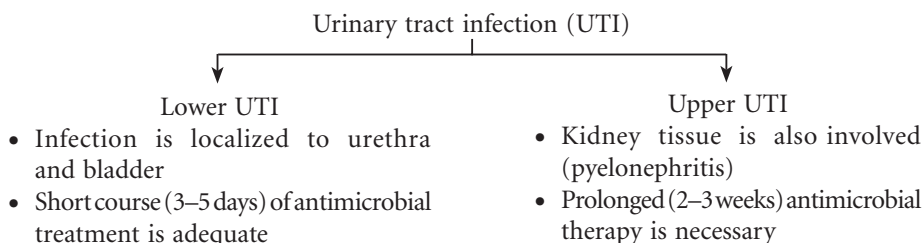
It is a bacteriostatic agent and is more active in acidic pH. It is effective for the prophylaxis of UTI due to *E. coli*. It stains the urine brown. The common adverse effects are nausea,

vomiting and diarrhoea. The hypersensitivity reactions include fever, leucopenia, anaemia, cholestatic jaundice, acute pneumonitis and rarely polyneuropathy.

PHENAZOPYRIDINE

It is not an AMA. It is a dye and has analgesic action in urinary tract. It relieves pain, burning, urgency and frequency of urination associated with cystitis. It makes the urine orange red, which is harmless. Occasionally, it may cause nausea and vomiting.

Treatment of Urinary Tract Infection



Treatment Schedules (Empirical Therapy)

Acute Cystitis

- Ciprofloxacin 250–500 mg b.d. oral for 3 days
- Norfloxacin 400 mg b.d. oral for 3 days
- Ofloxacin 200 mg b.d. oral for 3 days
- Cefpodoxime proxetil 200 mg b.d. for 3–5 days
- Cotrimoxazole DS b.d. oral for 3 days
- Nitrofurantoin 100 mg b.d. for 5 days

Acute Pyelonephritis

- Ampicillin 1 g q6h i.v. and gentamicin 1 mg/kg q8h i.v. for 3 weeks
- Ciprofloxacin 750 mg q12h oral for 3 weeks
- Ofloxacin 200 mg q12h oral for 3 weeks
- Cotrimoxazole DS q12h oral for 3 weeks

Chronic Pyelonephritis. Drug regimen is similar to that for acute pyelonephritis, but duration of treatment is 3–6 months.

Drugs Useful in the Treatment of Sexually Transmitted Diseases

PH1.48

The mechanism of action, pharmacokinetics and adverse effects of individual drugs are described in respective chapters. The important drug regimens are given in [Table 11.13](#).

Antipseudomonal Agents (Drugs Used in Pseudomonal Infections)

β-Lactam Antibiotics

- *Antipseudomonal penicillins* – carbenicillin, carbenicillin indanyl, ticarcillin, piperacillin, mezlocillin
- *Cephalosporins* – cefoperazone, ceftazidime, cefepime

Table 11.13 ■ Important treatment regimens for sexually transmitted diseases

Disease	Treatment schedule
Gonorrhoea	Ceftriaxone 125 mg i.m., single dose Or Cefixime 400 mg oral, single dose Or Azithromycin 1 g oral, single dose
Syphilis	Benzathine penicillin G 2.4 MU, i.m., single dose Or Doxycycline 100 mg oral, b.d. for 2 weeks Or Inj. ceftriaxone 1 g i.m. daily for 1 week
Lymphogranuloma venereum	Doxycycline 100 mg oral, b.d. for 3 weeks Or Azithromycin 1 g oral, once weekly for 3 weeks
Granuloma inguinale	Doxycycline 100 mg oral, b.d. for 3 weeks Or Azithromycin 1 g oral, once weekly for 3 weeks Or Ciprofloxacin 750 mg oral, b.d. for 3 weeks
Chancroid	Azithromycin 1 g oral, single dose Or Ceftriaxone 250 mg i.m., single dose Or Ciprofloxacin 500 mg oral, b.d. for 3 days

■ *Carbapenems* – imipenem, meropenem, doripenem

■ *Monobactams* – aztreonam

Aminoglycosides. Gentamicin, amikacin, tobramycin, netilmicin, sisomicin.

Fluoroquinolones. Ciprofloxacin, levofloxacin.

Sulphonamides. Silver sulfadiazine,* mafenide.*

Others. Polymyxin B,* colistin.*

Drugs Used in Anaerobic Infections

Nitroimidazoles. Metronidazole, tinidazole.

β-Lactam Antibiotics

■ Penicillins – piperacillin with tazobactam; ticarcillin with clavulanic acid

■ Cephalosporins – cefoxitin, cefotetan, ceftizoxime

■ Carbapenems – imipenem, ertapenem, meropenem, doripenem

Fluoroquinolones. Moxifloxacin.

Broad-Spectrum Antibiotics. Tigecycline, chloramphenicol.

Sulphonamides. Mafenide.*

Others. Vancomycin, clindamycin.

*Topical agents.

Drugs Used in Typhoid Fever

Third-generation cephalosporins: Ceftriaxone and cefoperazone are very effective for the treatment of MDR *Salmonella* infections. Injection ceftriaxone is injected intravenously in a dose of 2–4 g daily for 7–10 days. It is also effective to eliminate carrier state.

Fluoroquinolones: Ciprofloxacin (750 mg orally twice daily for 10 days) is the preferred drug for the treatment of typhoid. It causes rapid resolution of symptoms. Levofloxacin and ofloxacin can also be used. These agents are also effective in eliminating chronic carrier state of *S. typhi*, when therapy is continued for 4 weeks, as they attain effective concentration in bile and intestinal mucosa. FQs are contraindicated in children and pregnant women.

Azithromycin: It is used in cases of MDR typhoid fever. It is administered orally 500 mg daily for 7 days.

Chloramphenicol: It was the first choice drug for typhoid. It is no longer used now.

Cotrimoxazole: It is rarely used now.

Agents Used in Staphylococcal Infections

Penicillins: Penicillinase-resistant penicillins – methicillin, cloxacillin, dicloxacillin

Cephalosporins: Cefprozil, cefpodoxime proxetil, cefepime

Carbapenems: Imipenem, meropenem, faropenem, doripenem

Tigecycline

Aminoglycoside: Netilmicin

Rifampin

Miscellaneous antibiotics: Vancomycin, teicoplanin, clindamycin, streptogramins (quinupristin/dalfopristin), linezolid

Drugs for MRSA. Clindamycin, doxycycline, minocycline, tigecycline, linezolid, vancomycin, streptogramins, daptomycin, ceftaroline, teicoplanin.

Antituberculosis Drugs

PH1.44, PH1.45

Tuberculosis (TB) is a chronic infectious disease caused by *M. tuberculosis*.

Mycobacterial infections require prolonged treatment. Since TB is a chronic infection, it consists of excessive fibrous tissue with central necrosis. So vascularity of the lesion is poor; hence, the penetration of the drug into the lesion is decreased.

Classification

1. First-line antitubercular drugs (standard drugs): Isoniazid (H), rifampin (R), pyrazinamide (Z), ethambutol (E), streptomycin (S)

2. Second-line antitubercular drugs (reserve drugs): *para*-Aminosalicylic acid (PAS), thiacetazone, cycloserine, ethionamide, kanamycin, capreomycin, amikacin, levofloxacin, moxifloxacin, ofloxacin, clarithromycin, rifabutin, rifapentine

Another form of classification is shown in [Table 11.14](#).

First-Line Antituberculosis Drugs ([Table 11.15](#))

PH1.44

They are cheap, more effective, routinely used and less toxic.

Table 11.14 ■ Antituberculosis drugs

Groups	Drugs
First-line drugs (oral)	Isoniazid, rifampin, ethambutol, pyrazinamide
Parenterally (injections) administered drugs	Streptomycin, kanamycin, amikacin, capreomycin, viomycin
Fluoroquinolones	Ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin (Mfx)
Second-line drugs (oral)	Ethionamide, prothionamide, cycloserine, terizidone, <i>para</i> -aminosalicylic acid, rifabutin, rifapentine
Drugs with doubtful/unproven efficacy	Clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, imipenem/cilastatin, high-dose isoniazid (high-dose H), clarithromycin, bedaquiline

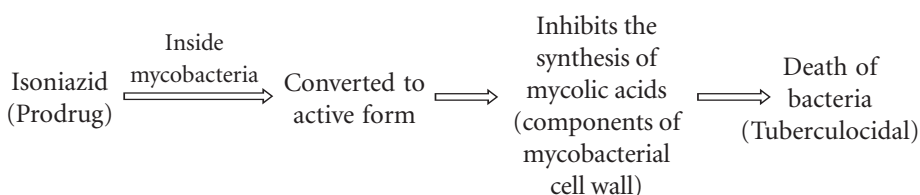
Note: Treatment of tuberculosis is based on WHO guidelines, 2008 and 2010.

Table 11.15 ■ First line antituberculosis drugs and their daily doses (WHO 2010 guidelines)

Drug	Daily dose (mg/kg)
Isoniazid (H)	5 (4–6)
Rifampin (R)	10 (8–12)
Pyrazinamide (Z)	25 (20–30)
Ethambutol (E)	15 (15–20)
Streptomycin (S)	15 (12–18)

Isoniazid (Isonicotinic Acid Hydrazide [INH]). Isoniazid is a highly effective and the most widely used antitubercular agent. It is orally effective, cheapest and has tuberculocidal activity. It is active against both intracellular and extracellular bacilli. It is a first-line drug for the treatment of TB. It is also used for chemoprophylaxis of TB (see p. 419).

Mechanism of Action. Isoniazid inhibits biosynthesis of mycolic acids, which are essential constituents of the mycobacterial cell wall.



Pharmacokinetics. INH is readily absorbed from the gut, distributed well all over the body, tubercular cavities and body fluids like CSF, and also crosses placental barrier. It is metabolized by acetylation and the metabolites are excreted in urine. The rate of acetylation of INH is under genetic control resulting in either rapid or slow acetylators.

Uses. Isoniazid (INH) is a first-line drug for the treatment of TB. It is also used for chemoprophylaxis of tuberculosis.

Adverse Effects and Drug Interactions

1. **Hepatotoxicity:** The risk of hepatic damage is more in chronic alcoholics, elderly patients and rapid acetylators. It is reversible on discontinuation of the drug. Patients receiving INH should be monitored for symptoms like anorexia, nausea, vomiting and jaundice.
2. **Peripheral neuritis:** It is a dose-related toxicity. Isoniazid is structurally similar to pyridoxine; hence, INH competitively interferes with utilization of pyridoxine. It also promotes the excretion of pyridoxine. Peripheral neuritis is more common in slow acetylators. Pyridoxine 10 mg/day is generally given along with INH to reduce the risk of peripheral neuritis in alcoholics, diabetic patients and HIV-positive patients receiving antitubercular therapy. It is also used for the treatment (100 mg/day) of INH-induced peripheral neuritis.
3. Other side effects are fever, skin rashes, arthralgia, anaemia, GI disturbances, psychosis and rarely convulsions.

Isoniazid inhibits the metabolism of phenytoin, carbamazepine, warfarin, etc. → increases plasma levels of these drugs → may result in toxicity.

Rifampin (Rifampicin). Rifampin is a derivative of rifamycin and is a first-line antitubercular drug. It rapidly kills intracellular and extracellular bacilli including spurters (those residing in caseous lesion). It is the only agent that can act on all types of bacillary subpopulations; hence, it is called sterilizing agent.

Mechanism of Action. Rifampin binds to bacterial DNA-dependent RNA polymerase and inhibits RNA synthesis. It has bactericidal effect against mycobacteria, *N. meningitidis*, *H. influenzae*, *S. aureus*, *E. coli*, *Pseudomonas*, etc.

Pharmacokinetics. It is given orally and is rapidly absorbed from the GI tract but presence of food reduces its absorption; it is distributed widely throughout the body and gets metabolized in liver. The active deacetylated form is excreted in bile and undergoes enterohepatic recycling. The rest of the drug is excreted in urine.

Uses

1. Tuberculosis: Rifampin is used along with INH and other antitubercular drugs for the treatment of TB. It is also used for chemoprophylaxis of tuberculosis.
2. Leprosy (see p. 420).
3. Prophylaxis of meningococcal and *H. influenzae* meningitis: Rifampin reaches high concentration in the nasopharynx and eradicates the carrier state in case of meningococcal and *H. influenzae* infections. It is given orally 600 mg every 12 hours for four doses in adults. In children, the dose of rifampin is 10 mg/kg every 12 hours for four doses.
4. Rifampin, in combination with β -lactam antibiotics, may be useful in staphylococcal infections, such as endocarditis and osteomyelitis.
5. Rifampin is used with doxycycline for the treatment of brucellosis.

Adverse Effects and Drug Interactions

1. Hepatitis is the main adverse effect – the risk of hepatotoxicity is more in alcoholics and elderly patients.
2. Flu-like syndrome with fever, chills, headache, muscle and joint pain.
3. GI disturbances, such as nausea, vomiting and abdominal discomfort.
4. Skin rashes, itching and flushing.

It stains various body fluids, such as urine, tears, saliva, sweat and sputum, orange red, which is harmless.

Rifampin is a potent microsomal enzyme inducer, hence reduces the plasma levels of a number of drugs, such as oral contraceptives (resulting in contraceptive failure), oral anticoagulants, oral antidiabetic drugs, HIV PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs). It also induces its own metabolism.

Pyrazinamide. Pyrazinamide is a synthetic analogue of nicotinamide. It is active in acidic pH – effective against intracellular bacilli (has sterilizing activity). It has tuberculocidal activity. Like INH, pyrazinamide inhibits mycobacterial mycolic acid biosynthesis but by a different mechanism. It is given orally, absorbed well from the GI tract and distributed widely throughout the body including CSF. It is metabolized in liver and excreted in urine. The most important adverse effect of pyrazinamide is dose-dependent hepatotoxicity. It impairs the excretion of urates resulting in hyperuricaemia and may also precipitate acute attacks of gout in susceptible individuals. The other side effects are anorexia, nausea, vomiting, fever and skin rashes.

Ethambutol. It is a first-line antitubercular drug. It inhibits arabinosyl transferases that are involved in mycobacterial cell wall synthesis. It is a bacteriostatic drug. It is used in combination with other antitubercular drugs to prevent emergence of resistance and for faster sputum conversion. There is no cross-resistance with other antitubercular drugs. Patients tolerate ethambutol well as it causes fewer adverse effects, and it is effective even in MAC infections.

Ethambutol is well absorbed after oral administration, is distributed widely in the body, is metabolized in liver, crosses BBB in meningitis and is excreted in urine. Optic neuritis is the main adverse effect seen with ethambutol, which is characterized by decreased visual acuity and colour vision defects (red–green). Hence, periodic eye examination is necessary when the patient is on ethambutol. The toxicity is reversible if the drug is discontinued early following onset of symptoms. It should be avoided in children younger than 6 years because they may not be able to report the disturbances in vision and it is also difficult to test visual acuity in children. Hyperuricaemia is due to decreased clearance of urates. Other side effects are nausea, vomiting, abdominal pain, skin rashes, itching and joint pain.

Streptomycin. Streptomycin is an aminoglycoside antibiotic. It is a bactericidal drug. It is active against extracellular bacilli in alkaline pH. Streptomycin is not effective orally; it must be injected intramuscularly. The adverse effects are ototoxicity, nephrotoxicity and neuromuscular blockade.

Second-Line Antituberculosis Agents

They are less effective, expensive and more toxic than the first-line drugs, hence are reserve drugs for TB.

Para-Aminosalicylic Acid. It is structurally similar to sulphonamides. Like sulphonamides, PAS also competitively inhibits folate synthetase enzyme and prevents the formation of tetrahydrofolic acid (THFA) which is necessary for growth and multiplication of bacteria. Thus, PAS produces tuberculostatic effect. PAS is rapidly absorbed after oral administration and distributed widely all over the body, but poorly penetrates the BBB. It is metabolized in liver by acetylation and excreted in urine. PAS inhibits the acetylation of INH, thus increasing the plasma levels of INH. At present, PAS is a reserve drug for the management of MDR-TB. The common adverse effects are GI

disturbances – anorexia, nausea, vomiting and abdominal discomfort – which can be minimized by giving the drug in divided doses on full stomach. The other side effects are hepatic damage, drug fever, skin rashes and thrombocytopenia.

Ethionamide. It is structurally similar to INH but is less efficacious. It inhibits synthesis of mycolic acids. It is a bacteriostatic drug and is effective against both extracellular and intracellular bacilli. It is absorbed well after oral administration, and is distributed widely all over the body including CSF. It is metabolized in liver and excreted in urine. The common adverse effects are nausea, vomiting and epigastric pain. Other side effects are hepatitis, headache, blurred vision and paraesthesia.

Cycloserine. It is a second-line antitubercular drug with bacteriostatic activity. It inhibits bacterial cell wall synthesis. It is distributed widely in the body including the CSF. The common side effects are related to CNS and include headache, tremor, psychosis and convulsions.

Terizidone. The mechanism of action is similar to that of cycloserine. It is effective in both pulmonary and extrapulmonary TB. It achieves good concentration in urine, hence useful in TB affecting urinary tract. It is better tolerated than cycloserine.

Other Antitubercular Agents

- *Fluoroquinolones:* Ciprofloxacin, ofloxacin, moxifloxacin and levofloxacin – bactericidal agents, given orally.
- *Aminoglycosides:* Amikacin and kanamycin – bactericidal agents, administered parenterally. Amikacin is less toxic than kanamycin.
- *Capreomycin (i.m.):* May cause nephrotoxicity and ototoxicity.
- *Macrolides:* Azithromycin and clarithromycin – given orally.
- *Rifamycins:* Rifampentine and rifabutin – bactericidal agents, given orally.

Rifabutin: It is a derivative of rifampin. Rifabutin is preferred to rifampin for the treatment of TB in HIV-infected patients on PIs as rifabutin is a less potent enzyme inducer. It is also used for the treatment of MAC infection in combination with clarithromycin and ethambutol.

Rifampentine: Analogue of rifampin is a potent enzyme inducer.

- *Bedaquiline:* It is a diarylquinoline. Bedaquiline inhibits production of energy in mycobacteria by inhibiting its ATP synthase. It is bactericidal and has a long half-life. It is administered orally. It is indicated for treatment of pulmonary MDR-TB in combination with other drugs. Bedaquiline should not be administered for more than 6 months. Patient should be monitored for response to treatment and adverse effects. It can cause hepatotoxicity and prolongation of QTc interval.

TREATMENT OF TUBERCULOSIS

PH1.55

The WHO recommends the use of MDT for all cases of TB. The objectives of MDT are as follows:

1. To make the patient noninfectious as early as possible and decrease transmission of disease
2. To prevent the development of drug-resistant bacilli
3. To prevent relapse
4. To reduce the total duration of effective therapy

The choice of standardized treatment regimens by each country – as recommended by the WHO – should be based on their efficacy, effectiveness and availability of financial resources.

All regimens for treatment of TB have two phases – an intensive phase followed by continuation phase.

- 1. **Intensive phase:** The patient receives intensive treatment with four to six drugs daily for a period of 2 months. The main objective of this phase is to rapidly kill the bacilli and render the patient noncontagious.
- 2. **Continuation phase:** The patient receives three to four drugs daily for a period of 4 months. This phase helps to eliminate the remaining bacilli and prevents relapse.

Guidelines for the Treatment of Tuberculosis

The regimen recommended for each patient depends on the diagnostic category for each patient. The Revised National Tuberculosis Control Programme (RNTCP) was launched in India in 1997. Under this programme, directly observed treatment, short-course (DOTS) treatment is being implemented. In DOTS, patient is administered drugs under the supervision of a health worker or other trained person to ensure that drugs are actually consumed. The therapy must be supervised and monitored by bacteriological examination. DOTS is the backbone of RNTCP. It is aimed at ensuring patient compliance, thus preventing the emergence of drug-resistant TB. The latest revision of RNTCP guidelines was in 2016.

Treatment of Drug-Sensitive Tuberculosis (Table 11.16)

They could be new or previously treated case.

New case: Those TB patients who have either never taken anti-TB drugs or taken them for less than a month.

Previously treated case: Those TB patients who have taken anti-TB drugs for 1 month or more. They include treatment of recurrent TB, loss to follow-up and treatment failure cases.

Table 11.16 ■ RNTCP 2016 guidelines for treatment regimens in drug-sensitive tuberculosis

Type of patient	Intensive phase (IP)	Continuation phase (CP)	
New patients	2 HRZE	4 HRE	6
Previously treated patients	2 HRZES + 1 HRZE	5 HRE	8

The prefix number before a regimen indicates the number of months of treatment. H, isoniazid; R, rifampin; Z, pyrazinamide; E, ethambutol; S, streptomycin; RNTCP, Revised National Tuberculosis Control Programme.

For treatment of drug-sensitive TB, oral first-line drugs are administered daily as fixed-dose combinations, whereas streptomycin is injected i.m. as per body weight bands.

Dose of fixed dose combinations (FDCs) of first-line antituberculosis drugs and streptomycin for adults

Body weight (kg)	Number of FDCs of HRZE ^a	Number of FDCs of HRE ^b	Streptomycin (g)
25–39	2	2	0.5
40–54	3	3	0.75
55–69	4	4	1
≥70	5	5	1

E, ethambutol; H, isoniazid; R, rifampin; Z, pyrazinamide.

^aTaken during intensive phase; FDC of HRZE contains 75/150/400/275 mg, respectively.

^bTaken during continuation phase; FDC of HRE contains 75/150/275 mg, respectively.

(Source: Technical and Operational Guidelines for TB Control in India 2016 (<https://tbcindia.gov.in/showfile.php?lid=3219>).

Drug Resistance

Monoresistance	The bacilli are resistant to only one first-line anti-TB drug
Polydrug resistance	The bacilli are resistant to more than one first-line anti-TB drug but not both INH and rifampin
MDR	The bacilli are resistant to both isoniazid and rifampin with or without resistance to any other first-line anti-TB drugs
XDR	A MDR-TB case with bacilli being additionally resistant to a fluoroquinolone or second-line injectable anti-TB drug (amikacin, kanamycin/capreomycin)

INH, isonicotinic acid hydrazide; MDR, multidrug resistance; TB, tuberculosis; XDR, extensive drug resistance. (Source: Technical and Operational Guidelines for TB Control in India 2016 (<https://tbcindia.gov.in/showfile.php?lid=3219>).)

Multidrug-Resistant Tuberculosis PH1.45

MDR-TB can be treated by either standard or individualized regimens. Drug sensitivity testing should be done for all patients. Patients with or highly likely to have MDR-TB should be treated with regimens containing at least four drugs to which organisms are known or presumed to be susceptible. Pyridoxine should also be administered to patients with MDR-TB to prevent neurotoxicity due to ethionamide, cycloserine, etc.

Standard treatment regimen for MDR-TB

Intensive phase (6–9 months)	Continuation phase (18 months)
Kanamycin, levofloxacin, ethionamide, cycloserine, pyrazinamide, ethambutol + pyridoxine 100 mg/day	Levofloxacin, ethionamide, ethambutol, cycloserine + pyridoxine 100 mg/day

(Source: Technical and Operational Guidelines for TB Control in India 2016; <https://tbcindia.gov.in/showfile.php?lid=3219>).

All drugs are administered daily under directly observed treatment.

To address the problem of MDR-TB, DOTS plus has been implemented. It is recommended in areas where DOTS is fully in place.

Extensive Drug-Resistant Tuberculosis (XDR-TB) PH1.45

Treatment is difficult and mortality rate is high.

Treatment of TB in HIV-Positive Patients

Generally, TB treatment is the same for HIV-infected as for non-HIV-infected TB patients. Short-course chemotherapy (daily regimen) must be started immediately once TB is diagnosed. Rifabutin is preferred to rifampin in HIV patients on antiretroviral drugs, such as PIs, as it does not interact with them.

Tuberculosis in Pregnancy

All first-line drugs (INH, rifampin, pyrazinamide and ethambutol) except streptomycin can be used in pregnancy.

Management of antitubercular drug-induced adverse drug reactions (WHO guidelines)

- Anorexia, nausea: Administer the drugs with small meals.
- Burning/numbness in the extremities: Administer pyridoxine.
- Joint pain (associated with pyrazinamide): Treat with NSAID.
- Flu-like syndrome (with intermittent dosing of rifampin): Switch to daily administration of rifampin.

- Jaundice/hepatitis: Major adverse effect associated with H, R and Z. All drugs have to be stopped till the reaction subsides. Then the drugs are reintroduced, one at a time. Rifampin is introduced first, followed by INH after 7 days. If both are tolerated, then Z should not be administered.
- Skin rash: Stop anti-TB drugs. The drugs are restarted one at a time at low doses which is then gradually increased. If reaction occurs following reintroduction of a particular drug, it should be stopped.
- Visual disturbances: Ethambutol should be discontinued.

Chemoprophylaxis of Tuberculosis

It is the prophylactic use of antitubercular drugs to prevent the development of active TB in patients who are at risk. INH 300 mg (10 mg/kg in children) is administered daily for 6 months.

Indications for Chemoprophylaxis

1. Newborn of a mother with active TB
2. Young children (younger than 6 years) with positive tuberculin test
3. Household contacts of patients with TB
4. Patients with positive tuberculin test with additional risk factors, such as diabetes mellitus, malignancy, silicosis and AIDS

Role of Glucocorticoids in Tuberculosis

TB is a relative contraindication for the use of glucocorticoids. However, in certain situations, glucocorticoids may be used under the cover of effective antitubercular therapy. They are as follows:

1. TB of serous membranes like pleura, pericardium and meninges to prevent fibrous tissue formation and its sequelae
2. To treat hypersensitivity reactions to antitubercular drugs
3. TB of the eye, larynx and genitourinary tract to prevent fibrosis and scar tissue formation

Prednisolone is the preferred agent except in meningitis (dexamethasone is preferred as it lacks mineralocorticoid activity). When the patient's general condition improves, the steroid should be gradually tapered to avoid HPA-axis suppression. Glucocorticoids are contraindicated in intestinal TB owing to the risk of perforation.

Drugs Used in the Treatment of *Mycobacterium avium* Complex infections

Clarithromycin/azithromycin, ethambutol, rifabutin. Other useful drugs are ciprofloxacin, levofloxacin and moxifloxacin. A combination of drugs is used. The duration of therapy required is 18–24 months. For prophylaxis, azithromycin/clarithromycin/rifabutin is used.

Antileprotic Drugs

PH1.46

Leprosy is a chronic infectious disease caused by *M. leprae*, which is an acid-fast bacillus.

TYPES OF LEPROSY

Lepromatous Leprosy

The cell-mediated immunity (CMI) is impaired against *lepra bacilli*; hence, the course of the disease progresses very rapidly. This is characterized by extensive bilateral skin lesions which contain numerous lepra bacilli. There is involvement of more than one nerve.

Tuberculoid Leprosy

The CMI is intact and is characterized by predominant peripheral nerve involvement with a single or few skin lesions. The bacilli are rarely seen in the lesions.

Plenty of lepra bacilli are seen in the skin lesions of borderline (BB), borderline lepromatous (BL) and lepromatous leprosy (LL); hence, these groups are called **multibacillary leprosy** (MBL).

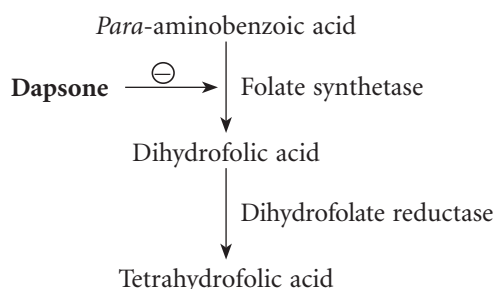
Borderline tuberculoid (BT), tuberculoid (TT) and indeterminate (I) leprosy are referred to as **PBL**.

Drugs Used for the Treatment of Leprosy. Dapsone or diaminodiphenylsulphone (DDS), clofazimine, rifampin, ethionamide, ofloxacin, moxifloxacin, minocycline and clarithromycin are the drugs used in leprosy.

Dapsone or Diaminodiphenylsulphone

Dapsone (Fig. 11.11), a sulphone, is the oldest, cheapest and most widely used agent for the treatment of leprosy even today.

Mechanism of Action. Sulphones are chemically related to sulphonamides and have the same mechanism of action. Lepra bacilli utilize PABA for the synthesis of folic acid, which, in turn, is necessary for its growth and multiplication. Dapsone is structurally similar to PABA, hence competitively inhibits folate synthetase enzyme and prevents the formation of THFA. Thus, dapsone produces leprostatic effect.



Pharmacokinetics. Dapsone is given orally and is almost completely absorbed from the gut; it is bound to plasma proteins, widely distributed in the body and concentrated mainly in the infected skin, muscle, liver, kidney, etc. It is partly secreted in bile and undergoes enterohepatic cycling. Dapsone is metabolized by acetylation and metabolites are excreted in urine.

Adverse Effects. The common adverse effects are dose-related haemolytic anaemia particularly in patients with G6PD deficiency. Other side effects are anorexia, nausea, vomiting, fever, headache, allergic dermatitis, itching and peripheral neuropathy. Methaemoglobinaemia can also occur.

Dapsone may cause exacerbation of lesions – ‘sulphone syndrome’, which is characterized by fever, dermatitis, pruritus, lymphadenopathy, methaemoglobinaemia, anaemia and hepatitis.

Rifampin

It is the most effective and rapidly acting bactericidal drug for lepra bacilli. It kills most of the lepra bacilli.

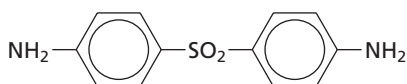


Fig. 11.11 Structure of dapsone.

Clofazimine

It is a phenazine dye and has leprostatic activity against lepra bacilli. It has anti-inflammatory effect, hence is also useful in the treatment of type 2 lepra reaction. Clofazimine binds to mycobacterial DNA to inhibit its template function. It also has activity against dapsone-resistant organism. It is given orally – fatty meal increases its absorption. It accumulates in tissues – $t_{1/2}$ is 70 days. It causes reddish-black discolouration of the skin on exposed parts. It can cause pigmentation of the conjunctiva and cornea, and discolouration of hair, tears, sweat, urine, etc. Nausea, vomiting, diarrhoea and abdominal pain are its other side effects. It is contraindicated in pregnancy.

Ethionamide

It is a second-line antitubercular drug and is also effective against lepra bacilli. Ethionamide can be used as an alternative drug when there is a contraindication for the use of clofazimine or if it is unacceptable. It may cause hepatotoxicity.

The other agents that are found to be effective against lepra bacilli are minocycline, clarithromycin, pefloxacin and ofloxacin.

Clarithromycin: It is a macrolide antibiotic and has bactericidal activity against *M. leprae*.

Minocycline: It is the only tetracycline that has antileprotic activity.

Ofloxacin: It has significant bactericidal activity against lepra bacilli.

Moxifloxacin: It has potent antileprotic activity.

CHEMOTHERAPY OF LEPROSY

The WHO recommends the use of MDT for all leprosy cases. The National Leprosy Eradication Programme (NLEP) has implemented the guidelines for treatment. The objectives and need for MDT are as follows:

1. To make the patient noncontagious as early as possible by killing the dividing bacilli
2. To prevent the development of drug-resistant bacilli
3. To prevent relapse
4. To shorten the duration of effective therapy

TREATMENT SCHEDULES OF LEPROSY

PH1.55

All drugs are administered orally.

1. For MBL (LL, BL and BB)

- Rifampin 600 mg once monthly (supervised) +
- Dapsone 100 mg daily (self-administered) +
- Clofazimine 300 mg once monthly (supervised) +
- Clofazimine 50 mg daily (self-administered)

The duration of treatment is 1 year.

2. For PBL (TT, BT and I)

- Rifampin 600 mg once monthly (supervised) +
- Dapsone 100 mg daily (self-administered)

The duration of treatment is 6 months.

3. Alternative regimens

- Clofazimine + any two newer drugs (minocycline, ofloxacin, clarithromycin, etc.) daily for 6 months followed by clofazimine + ofloxacin/minocycline daily for another 18 months

If clofazimine cannot be used for MBL, then minocycline or ofloxacin is used.

LEPROA REACTIONS

These are immunologically mediated reactions that occur during the course of the disease. The exact cause of such reactions is not clear and is usually precipitated by infection, trauma, mental stress, etc. There are two types of reactions:

- 1. **Reversal reaction:** It is a delayed type of hypersensitivity reaction seen in leprosy, both multibacillary and paucibacillary cases, e.g. BL and BT. There are signs of inflammation in the existing skin lesions – they become red, warm and swollen. New lesions may appear. Nerves are frequently affected. They are tender and painful. General symptoms are not common. They are treated with clofazimine or prednisolone.
- 2. **Erythema nodosum leprosum (ENL):** It occurs in cases of LL. It is a type III hypersensitivity reaction (Arthus-type) due to release of antigen from the dying lepra bacilli. There is erythema nodosum – red, painful, tender cutaneous and subcutaneous nodules. Nerves may be affected. Constitutional symptoms are present. Severe form of reaction is treated with thalidomide, but pregnancy is the absolute contraindication for its use. The other drugs used are aspirin, clofazimine, chloroquine and prednisolone.

Antifungal Agents

Most of the fungal infections (Table 11.17) are opportunistic; hence they are common in diabetes mellitus, cancer, AIDS and pregnancy, and in patients on broad-spectrum AMAs and on immunosuppressant therapy such as prolonged course of corticosteroids and anticancer drugs.

CLASSIFICATION

- 1. **Polyene antibiotics:** AMB, nystatin, hamycin
- 2. **Echinocandin antibiotics:** Caspofungin acetate, micafungin
- 3. **Heterocyclic compound:** Griseofulvin
- 4. **Azoles**
 - (a) Imidazoles: Ketoconazole (KTZ), miconazole, clotrimazole, econazole, oxiconazole
 - (b) Triazoles: Fluconazole, itraconazole, voriconazole, posaconazole
- 5. **Allylamine:** Terbinafine

Table 11.17 ■ Fungal infections/causative organisms

Superficial mycosis	Deep mycosis
1. Dermatophytes	1. <i>Aspergillus</i>
(a) <i>Epidermophyton</i>	2. <i>Blastomyces</i>
(b) <i>Trichophyton</i>	3. <i>Cryptococcus</i>
(c) <i>Microsporum</i>	4. <i>Coccidioides</i>
2. <i>Candida</i>	5. <i>Candida</i>
3. <i>Malassezia furfur</i>	6. <i>Histoplasma</i>
	7. <i>Mucormycetes</i>
	8. <i>Sporothrix schenckii</i>

6. Antimetabolite: Flucytosine

7. **Other topical antifungal agents:** Whitfield's ointment, tolnaftate, sodium thiosulphate, selenium sulphide, undecylenic acid, ciclopirox, butenafine

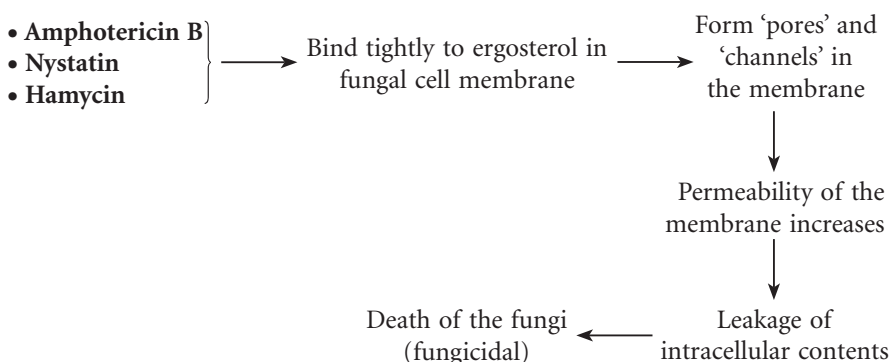
Polyene Antibiotics

AMB, nystatin and hamycin are polyene antibiotics; they have the same mechanism of action.

Amphotericin B. AMB is a broad-spectrum antifungal antibiotic. It is effective against *Cryptococcus*, *Coccidioides*, *Candida*, *Aspergillus*, *Blastomyces*, *Histoplasma*, *Sporothrix*, fungi causing mucormycosis, etc.

Pharmacokinetics. AMB is not absorbed from the gut, hence is not suitable orally for systemic infections. It is highly bound to plasma proteins and sterols in tissues, and widely distributed to various tissues but does not cross BBB. It is metabolized in liver and excreted slowly in urine and bile.

Mechanism of Action. Fungal cell membrane contains a sterol which resembles cholesterol and is called 'ergosterol'.



Adverse Effects. AMB is the most toxic of all antifungal agents.

The acute reactions are fever, chills, headache, dyspnoea, GI disturbances, phlebitis at the site of injection, etc. The drug should be continued. Coadministration of steroid can minimize the reaction.

Anaemia and electrolyte disturbances are commonly seen. Anaemia is less with lipid-based formulations.

Nephrotoxicity with azotaemia is seen in most of the patients on AMB therapy. Hepatotoxicity can occur occasionally. Headache and convulsions may occur on intrathecal administration.

Formulations of Amphotericin B. AMB is poorly water soluble; hence, intravenous preparation is made with deoxycholate – conventional amphotericin B (C-AMB).

AMB colloidal dispersion (ABCD), AMB–lipid complex (ABLC) and liposomal AMB (L-AMB) are the lipid-based new formulations of AMB. L-AMB provides targeted drug delivery and has less adverse effects like acute reaction, anaemia and nephrotoxicity than conventional preparation. It is expensive.

Uses. AMB is highly efficacious but highly toxic too; hence, azoles (fluconazole and itraconazole) have replaced AMB in the treatment of many fungal diseases.

1. It is effective in almost all systemic mycoses, e.g. mucormycosis, aspergillosis, cryptococcosis, sporotrichosis, histoplasmosis and blastomycosis.
2. It is useful topically for oral and cutaneous candidiasis.
3. Other uses: L-AMB is useful in leishmaniasis (as the drug reaches the reticuloendothelial cells) and febrile neutropenia.

Nystatin. Nystatin is poorly absorbed from skin and mucous membranes. It is highly toxic for systemic use. It is used only topically in *Candida* infections. It is available as suspension, ointment, cream, powder and tablet and also in combination with corticosteroids or antibacterial agents.

Uses. Nystatin is used:

1. Topically for oral, oropharyngeal, corneal, conjunctival and cutaneous candidiasis
2. As oral tablets for intestinal candidiasis and superinfection due to *Candida*
3. In vaginal candidiasis, as vaginal suppositories

Adverse Effects. They include nausea and bitter taste.

Hamycin. It was developed in India (Hindustan Antibiotics)

It is useful topically for oral, cutaneous and vaginal candidiasis. It is available as ointment and suspension for topical administration.

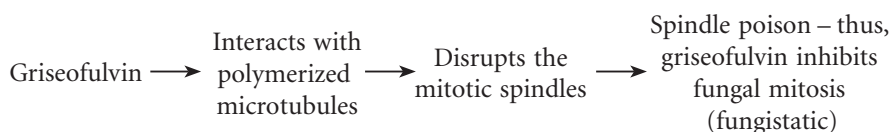
Echinocandins

Caspofungin Acetate. Caspofungin acetate is a semisynthetic antifungal agent effective against *Candida* and *Aspergillus*. It is an antifungal antibiotic that acts by inhibiting the synthesis of glucans in fungal cell wall. It is not effective orally and is administered by i.v. infusion, metabolized in liver, and metabolites are excreted in faeces and urine. It is used in the treatment of invasive aspergillosis and candidiasis, when patient is not responding to or intolerant to other antifungal agents. The adverse effects include nausea, vomiting, flushing, fever and phlebitis at the site of injection. It is expensive.

Micafungin. The mechanism of action is similar to that of caspofungin. It is administered for treatment of invasive candidiasis. It is also useful for prophylaxis of invasive candidiasis and in patients undergoing bone marrow transplantation.

Heterocyclic Compound – Griseofulvin. Griseofulvin, an antifungal antibiotic, is used orally for dermatophytic infections. It is not effective topically.

Mechanism of Action



Pharmacokinetics. Griseofulvin is administered orally. Its bioavailability is increased by taking with fatty food and by using ultrafine preparation. It gets concentrated in keratinized tissues, such as skin, hair and nails. It is an enzyme inducer, thus reduces the effectiveness of warfarin and oral contraceptives. It may produce disulfiram-like action, hence can cause intolerance to alcohol. It is metabolized in liver and excreted in urine.

Uses. Griseofulvin is used in the treatment of dermatophytic infections. The duration of treatment depends on the site of lesion and thickness of infected keratin layer. Treatment must be continued until infected tissue is completely replaced by normal skin, hair and nail. For tinea (ringworm) infections (tinea capitis, tinea barbae, tinea corporis, tinea pedis), 4–6 weeks of therapy is required. Ultrafine griseofulvin 250 mg q.i.d. for 4–6 weeks is given. In onychomycosis of fingernails, griseofulvin 250 mg q.i.d. for 6 months, and for toenails treatment up to 1 year, is required. Triazoles or terbinafine is preferred for onychomycosis.

Table 11.18 ■ Differences between amphotericin B and flucytosine

Amphotericin B	Flucytosine
Active drug	Prodrug
Has broad spectrum of activity	Has narrow spectrum of activity
Antifungal antibiotic	Antimetabolite
Fungicidal	Fungistatic
Not absorbed through the GI tract	Well absorbed from the GI tract
Highly bound to plasma proteins and sterols in tissues	Poorly bound to plasma proteins
Does not cross BBB	Freely crosses BBB and reaches high concentration in CSF
Metabolized in liver and excreted slowly in urine and bile	Excreted in urine mainly in unchanged form
Highly efficacious and highly toxic drug	Less effective and less toxic than AMB
Given intravenously, intrathecally and topically	Given orally

AMB, amphotericin B; BBB, blood–brain barrier; CSF, cerebrospinal fluid; GI, gastrointestinal.

Adverse Effects. They are headache, rashes, peripheral neuritis, confusion, fatigue, vertigo, blurred vision and GI effects, such as nausea, vomiting, diarrhoea and heartburn. The other side effects include leucopenia and rarely hepatotoxicity.

Antimetabolites

Flucytosine (Table 11.18). Flucytosine is a prodrug. It is taken up by susceptible fungal cells and converted into 5-fluorouracil (5-FU) that interferes with fungal DNA synthesis by inhibiting thymidylate synthase enzyme, thus producing fungistatic effect.



Flucytosine has narrow spectrum of activity and is effective against *Cryptococcus*, *Chromoblastomyces* and *Candida* spp.

Uses. Flucytosine is used in combination with AMB for cryptococcal meningitis. The advantages of this combination are as follows:

1. The entry of flucytosine into the fungal cells is facilitated because of increased permeability of membrane due to the action of AMB.
2. Reduced toxicity of AMB because of reduction in drug dosage.
3. Produces rapid culture conversion (culture becomes negative).
4. Reduced duration of therapy and less chance for emergence of resistance.

Adverse Effects. These include bone marrow suppression with anaemia, neutropenia and thrombocytopenia. The other side effects include nausea, vomiting, diarrhoea, alopecia, skin rashes, itching and rarely hepatitis.

Azoles

Azole antifungals are broadly divided into imidazoles and triazoles. Both of them are structurally related compounds, and have similar mechanism of action and antifungal spectrum (Table 11.19).

Table 11.19 ■ Antifungal drugs and their spectrum of activity

AMB	Flucytosine	KTZ	Fluconazole	Itraconazole	Voriconazole	Nystatin hamycin (topical)	Griseofulvin (oral)	Terbinafine	Caspofungin acetate
• Aspergillosis • Blastomycosis • Candidiasis • Cryptococcosis • Coccidioidomycosis • Histoplasmosis • Mucormycosis • Sporotrichosis	• Cryptococcosis • Candidiasis (some species) • Chromoblastomycosis	• Candidiasis • Dermatophytosis	• Cryptococcosis • Candidiasis • Coccidioidomycosis	• Candidiasis • Dermatophytosis • Blastomycosis • Histoplasmosis • Coccidioidomycosis • Aspergillosis • Sporotrichosis	• Aspergillosis • Candidiasis	Candidiasis only	Dermatophytosis only	• Candidiasis • Dermatophytosis	• Candidiasis • Aspergillosis

AMB, amphotericin B; KTZ, ketoconazole.

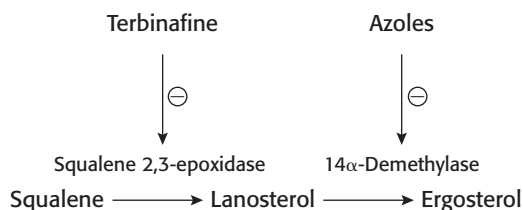


Fig. 11.12 Mechanism of action of azoles and terbinafine. ⊖, inhibition.

Mechanism of Action. Azoles impair ergosterol synthesis by inhibiting 14 α -demethylase enzyme (Fig. 11.12).

Miconazole and Clotrimazole. They are used topically for dermatophytic and *Candida* infections. They are available as cream, gel, lotion, solution, spray, vaginal pessary, etc. Clotrimazole troche is also available.

Uses

- 1. Dermatophytic infections:** Both are useful topically for *tinea pedis*, *tinea cruris*, *tinea corporis* and *tinea versicolor*.
- 2. Candida infections:** They are used topically for the treatment of oral, pharyngeal, vulvovaginal and cutaneous candidiasis.
- 3.** Miconazole is also useful in **otomycosis**.

Adverse Effects. These are local irritation, itching or burning. Miconazole is safe for use during pregnancy.

Ketoconazole. KTZ is a prototype drug among azoles. It is effective orally as well as topically for various fungal infections, such as candidiasis, dermatophytosis and deep mycosis (Table 11.19). It is the most toxic among azoles, hence used commonly by topical route for *Candida* and dermatophytic infections. For most of the systemic mycosis, it has been replaced by triazoles.

Pharmacokinetics. It is orally effective. Acidic environment favours the absorption of KTZ; hence, its bioavailability is reduced by drugs like H₂-blockers, proton pump inhibitors or antacids. It is highly bound to plasma proteins, metabolized in liver extensively and excreted mainly in faeces.

Adverse Effects. KTZ is the most toxic among azoles, but it is less toxic than AMB. Anorexia, nausea and vomiting are the most common side effects. KTZ reduces adrenal cortical steroids, testosterone and oestrogen synthesis – thus causes gynaecomastia, oligospermia, loss of libido and impotence in males, and menstrual irregularities and amenorrhoea in females. The other side effects are hepatotoxicity, hypersensitivity reactions like skin rashes and rarely itching.

Drug Interactions. KTZ is an enzyme inhibitor and increases the effect of the following drugs by inhibiting their metabolism:

- 1.** KTZ $\times$ Sulfonylureas $\Rightarrow$ Hypoglycaemia
- 2.** KTZ $\times$ Phenytoin $\Rightarrow$ Phenytoin toxicity
- 3.** KTZ $\times$ Cyclosporine $\Rightarrow$ Potentiates nephrotoxicity
- 4.** KTZ $\times$ Warfarin $\Rightarrow$ Increased risk of bleeding
- 5.** KTZ $\times$ Terfenadine $\Rightarrow$ Fatal ventricular arrhythmias

Uses

- 1. Dermatophytosis:** KTZ is used topically for *tinea pedis*, *tinea cruris*, *tinea corporis* and *tinea versicolor*.

2. **Candidiasis:** KTZ is very toxic for systemic use; hence, it has been replaced by triazoles.
3. Other uses include kala-azar, dermal leishmaniasis and Cushing syndrome.

Fluconazole. It is a triazole. It is available for oral and i.v. administration as well as for topical use in the eye. It has a broad spectrum of antifungal activity (Table 11.19). It is less toxic than KTZ.

Pharmacokinetics. It is well absorbed from the GI tract and has high bioavailability. Food or gastric pH does not affect its bioavailability. It is poorly bound to plasma proteins, widely distributed in the body, freely crosses the BBB and reaches high concentration in CSF. It is mainly excreted in urine in the unchanged form.

Adverse Effects. The common side effects are nausea, vomiting, diarrhoea and abdominal discomfort. The other side effects include headache, alopecia, skin rashes and hepatic necrosis. It is contraindicated during pregnancy because of teratogenic effect. Fluconazole is an enzyme inhibitor.

Uses

1. **Candidiasis:** Fluconazole is effective against oesophageal, oropharyngeal, vulvovaginal, cutaneous and invasive candidiasis.
 2. **Cryptococcal meningitis:** Intravenous fluconazole is the preferred drug in the treatment of cryptococcal meningitis.
 3. In *coccidioidal meningitis*, i.v. fluconazole is the drug of choice.
- It is not effective in aspergillosis.

Advantages Over Ketoconazole. It does not inhibit steroid synthesis, does not have antian-drogenic effect, has less drug interactions and absorption is not affected by gastric pH.

Itraconazole. It is a synthetic triazole. It is administered orally as well as by i.v. route. Gastric acidity favours the absorption of itraconazole. It is highly bound to plasma proteins, does not cross BBB and is metabolized in liver. It has a broad spectrum of activity against many fungi including *Aspergillus*.

Adverse Effects. These are nausea, vomiting, diarrhoea, headache, hepatotoxicity and hypokalaemia. Itraconazole inhibits CYP3A4 and can increase serum levels of drugs metabolized by this enzyme. Inhibition of steroid hormone synthesis is not seen with itraconazole.

Uses

1. Intravenous itraconazole is the drug of choice for histoplasmosis, blastomycosis and sporotrichosis.
2. Itraconazole is effective for oesophageal, oropharyngeal and vaginal candidiasis, but is not superior to fluconazole.
3. Dermatophytosis: It is useful in *tinea capitis*, *tinea corporis*, *tinea barbae* and *tinea versicolor*.
4. In onychomycosis, oral itraconazole is used.
5. Unlike fluconazole, it is also effective in aspergillosis.

Voriconazole. It is a triazole. It is used for the treatment of invasive aspergillosis and disseminated *Candida* infections. Voriconazole is administered orally or intravenously. Adverse effects of voriconazole include visual and auditory disturbances, prolongation of QT interval and skin rashes. It inhibits cytochrome enzymes. It is contraindicated in pregnancy.

Posaconazole. Posaconazole, an azole, has a broad spectrum of activity against many fungi including *Aspergillus* and agents causing mucormycosis. It is administered orally;

fatty food increases its bioavailability. Adverse effects include headache, sedation and GI disturbances.

Allylamine

Terbinafine. Terbinafine, an allylamine, inhibits squalene 2,3-epoxidase and blocks ergosterol synthesis (Fig. 11.12). It is available for topical as well as for oral administration (Fig. 11.13). It is well absorbed after oral administration and is concentrated in skin, nails and adipose tissue. It is highly bound to plasma proteins, poorly penetrates the BBB, is metabolized in liver and is excreted in urine. It is effective against dermatophytes and *Candida*. Terbinafine is a fungicidal agent.

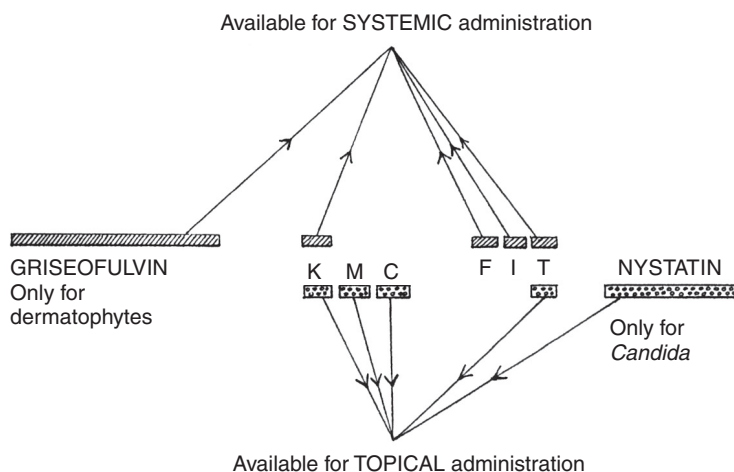
Adverse Effects. Terbinafine may cause side effects, such as nausea, diarrhoea, dyspepsia and rarely hepatitis. It may cause itching, rashes, local irritation on topical use.

Uses

1. **Dermatophytosis:** Terbinafine is very effective against dermatophytes. It is used topically or orally for *tinea pedis*, *tinea corporis* and *tinea cruris*. In onychomycosis of hands and feet, it is used orally and is more effective than itraconazole.
2. **Candidiasis:** Terbinafine is less effective in *Candida* infections.

Other Topical Agents

1. **Whitfield's ointment:** It contains 6% benzoic acid and 3% salicylic acid. Salicylic acid has keratolytic and benzoic acid has fungistatic effects. It is used in the treatment of *tinea pedis*.
2. **Undecylenic acid:** It is mainly a fungistatic drug. It is available as ointment, cream, powder, soap and liquid. It is used in the treatment of *tinea pedis*, *tinea cruris* and other dermatophytoses.
3. **Selenium sulphide:** It is useful for *tinea versicolor*.
4. **Tolnaftate:** It is useful in *tinea cruris* and *tinea corporis*.
5. **Ciclopirox:** It is useful against *tinea versicolor*.
6. **Butenafine:** Its mechanism of action and spectrum of activity is similar to that of terbinafine.



Mnemonic: KMC FIT

Fig. 11.13 Route of administration and spectrum of various antifungal agents. K, ketoconazole; M, miconazole; C, clotrimazole; F, fluconazole; I, itraconazole; T, terbinafine. KMC FI, have a wide spectrum of activity; terbinafine, for dermatophytes and *Candida*.

Antiviral Agents

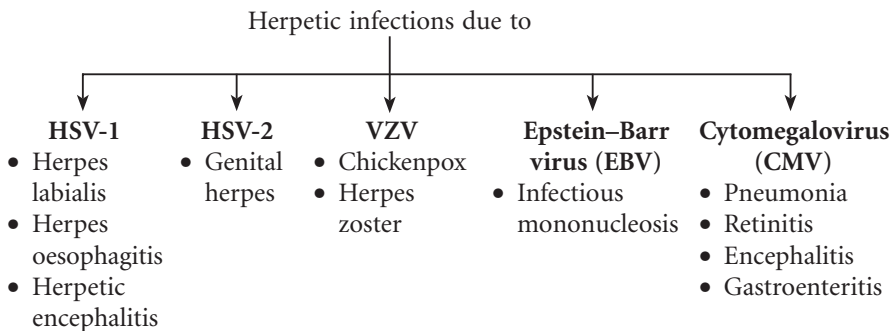
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Classification

1. **Drugs used against herpetic infection (antiherpes agents):** Acyclovir, valacyclovir, famciclovir, ganciclovir, valganciclovir, cidofovir, foscarnet, idoxuridine and trifluridine
2. **Drugs used against HIV infection (antiretroviral agents)**
 - (a) *Nucleoside reverse transcriptase inhibitors (NRTIs):* Zidovudine, stavudine, lamivudine, didanosine, zalcitabine, abacavir, emtricitabine, tenofovir
 - (b) *Non-nucleoside reverse transcriptase inhibitors (NNRTIs):* Nevirapine, delavirdine, efavirenz
 - (c) *Protease inhibitors (PIs):* Saquinavir, indinavir, ritonavir, lopinavir, nelfinavir, amprenavir
 - (d) *Fusion inhibitors:* Enfuvirtide, maraviroc
 - (e) *Integrase inhibitor:* Raltegravir, dolutegravir
3. **Anti-influenza agents:** Amantadine, rimantadine, oseltamivir, zanamivir, peramivir
4. **Other antiviral agents:** Lamivudine, tenofovir, adefovir dipivoxil (anti-hepatitis B) and interferons, ribavirin, sofosbuvir (anti-hepatitis C)

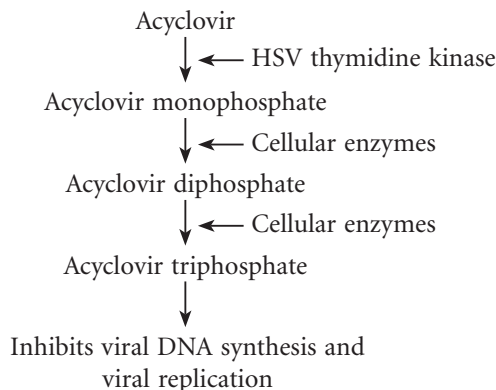
Antiherpes Agents

They are used for treatment of various herpetic infections.



Acyclovir. It is a synthetic, purine nucleoside analogue that has antiherpes activity. It is more effective against HSV-1 and HSV-2 than *varicella zoster virus* (VZV) infections.

Mechanism of Action



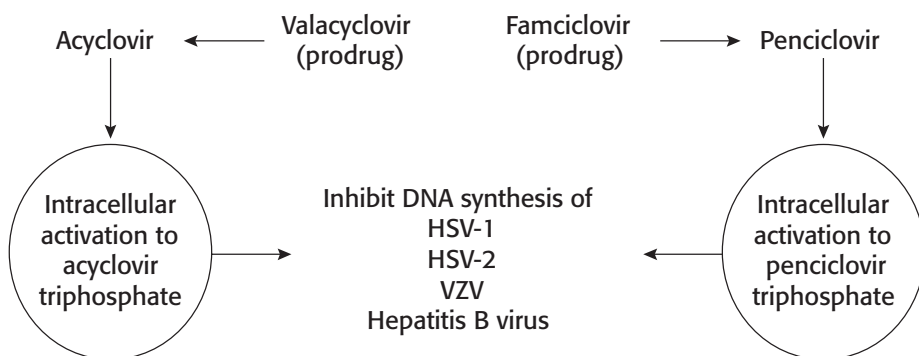
Acyclovir is selectively taken up by herpes virus–infected cells and activated to triphosphate derivative which inhibits viral DNA synthesis. It is available for oral, topical and i.v. administration. It is a highly potent antiherpes drug. It has high therapeutic index with low toxicity to host cells.

Its oral bioavailability is poor. It is poorly bound to plasma proteins, widely distributed in the body, freely crosses BBB and is excreted in urine.

Uses

1. **Genital herpes:** Oral/intravenous/topical acyclovir is effective in genital herpes simplex infections. It is used for primary and recurrent infections; high doses of acyclovir are needed for recurrent infections. It reduces the frequency and severity of herpetic lesions.
2. **Herpetic encephalitis:** Intravenous acyclovir is the drug of choice for encephalitis caused by HSV.
3. **Herpes simplex keratitis:** Acyclovir is used topically in herpetic keratoconjunctivitis.
4. **Mucocutaneous HSV:** Acyclovir is used orally or topically in the treatment of stomatitis, herpes labialis and ulcers in mouth. It is used intravenously in immunocompromised patients.
5. **Herpetic whitlow (nail-bed infection):** Oral acyclovir is useful for the prevention and treatment of whitlow.
6. **Chickenpox:** Acyclovir reduces the duration of illness if started early in patients at risk of severe illness and immunocompromised individuals.
7. **Herpes zoster:** Acyclovir (oral/topical/i.v.) and valacyclovir (oral) are effective.

Adverse Effects. Acyclovir is usually well tolerated. Nausea, vomiting, diarrhoea and headache are the other side effects. High doses may cause neurotoxicity with tremor, confusion, disorientation and convulsions. On topical use, it can cause irritation and burning.



Idoxuridine. Idoxuridine is a thymidine analogue that acts against DNA viruses. It inhibits viral replication. Idoxuridine is used topically for HSV keratoconjunctivitis. The adverse effects are local irritation, itching, pain and swelling of lids.

Valganciclovir. It is a prodrug of ganciclovir. It has better bioavailability than ganciclovir.

The important features of some of the antiherpetic agents are given in Table 11.20.

Anti-influenza Agents

Amantadine. It is an antiviral drug that has antiparkinsonian effect as well. It inhibits the uncoating and assembly of influenza A virus, thus prevents viral replication. It is administered orally, well absorbed from the GI tract and excreted unchanged in urine.

Table 11.20 ■ Important features of the antiherpetic agents

	Valacyclovir	Famciclovir	Ganciclovir	Foscarnet	Cidofovir
Active/ Prodrug	Prodrug	Prodrug	Active	Active	Prodrug
Route of admin- istration and oral bioavail- ability	Oral; better oral bio- availability than acy- clovir	Oral, well absorbed from the GI tract	Intravenous, oral	Intravenous	Intravenous
Uses	Genital herpes, orolabial herpes, herpes zoster	Genital herpes, orolabial herpes, herpes zoster	Prophylaxis and treatment of severe CMV infections – retinitis, pneumonia, gastroenteri- tis, etc., in immuno- compro- mised patients	Acyclovir resistant HSV and VZV in- fections	CMV retinitis
Adverse effects	Nausea, vomiting, skin rashes, CNS symptoms (in high doses)	Nausea, vomiting, diarrhoea, headache	Bone marrow suppression, nausea, vomiting, headache, hallucina- tions, con- vulsions, mutagenic, carcino- genic, em- bryotoxic	Nephrotox- icity, con- vulsions, head- ache, hallucina- tions, anaemia	Nausea, vomiting, hyper- sensitiv- ity, neph- rotoxicity, muta- genic, embryo- toxic

CNS, central nervous system; GI, gastrointestinal; VZV, varicella zoster virus.

Uses

- 1. Amantadine is used for the prophylaxis and treatment of influenza A virus infection.
- 2. For parkinsonism.

Adverse Effects. They include anorexia, nausea, epigastric discomfort, headache, insomnia, confusion, hallucinations and hypotension. It is contraindicated in pregnancy because of teratogenic effect.

Rimantadine. Its mechanism of action is similar to that of amantadine, but has a longer duration of action. It is administered orally, well absorbed through the GI tract, extensively metabolized and excreted in urine.

Oseltamivir. It selectively inhibits influenza A and B virus neuraminidases, thus interfering with the release of virus from infected cells. It is used orally in the treatment and

prevention of influenza A (avian influenza or bird flu and swine flu) and influenza B virus infections. Adverse effects are nausea, vomiting and abdominal discomfort. Dose: for prophylaxis, 75 mg o.d. for 7 days; for treatment, 75 mg b.d. for 5 days.

Zanamivir. The mechanism of action and uses are similar to those of oseltamivir. Oral bioavailability is low. It is administered by inhalation. Adverse effects are bronchospasm, headache and dizziness. It should be avoided in patients with airway disease.

Peramivir. It is active against influenza A and B, bird flu and swine flu virus. It is administered as a single i.v. dose in severe influenza. It is well tolerated.

Anti-Hepatitis Drugs

PH1.48

ANTI-HEPATITIS B DRUGS

The aim of treatment is viral suppression and prevention of complications like cirrhosis. Lamivudine, tenofovir, entecavir and adefovir dipivoxil inhibit hepatitis B virus DNA polymerase. Tenofovir is well tolerated and highly effective for chronic hepatitis B virus infections.

ANTI-HEPATITIS C DRUGS

Treatment is directed to suppress the virus. Drugs are expensive. They include ribavirin (inhibits RNA synthesis), sofosbuvir (inhibits viral RNA polymerase), interferon (inhibits viral protein synthesis), daclatasvir and ledipasvir (inhibit HCV replication).

Interferons. Interferons are proteins produced by virus-infected cells and also by recombinant DNA technology. There are mainly three types of interferons, namely α , β and γ . Antiviral activity of interferons is due to the inhibition of viral penetration, synthesis of mRNA, translation of viral proteins, assembly of viral particles and their release. They are administered by i.m. and s.c. routes or locally into the lesion.

Uses. Interferon- α is used for the treatment of venereal warts, herpetic infections in immunosuppressed individuals, chronic hepatitis B and C and Kaposi sarcoma in HIV patients.

Adverse Effects. These include fever, headache, myalgia, skin rashes, alopecia, bone marrow suppression, cardiotoxicity, neurotoxicity and thyroid dysfunction.

Ribavirin. It is a synthetic purine nucleoside analogue and has a wide range of anti-viral activity. Ribavirin monophosphate competitively inhibits cellular enzymes that are needed for the synthesis of guanosine triphosphate (GTP) and nucleic acid. Ribavirin triphosphate also competitively inhibits the viral mRNA synthesis. It is administered by oral, aerosol or i.v. routes. It is metabolized in liver and excreted in urine.

Ribavirin is effective against a wide range of RNA and DNA viruses. It is used to treat influenza, parainfluenza, measles, adenovirus and respiratory syncytial virus infections. Oral ribavirin is effective in the treatment of chronic hepatitis C infection.

Adverse Effects. These include nausea, tiredness, cough, dyspnoea, anaemia and insomnia. Conjunctival and respiratory irritation may occur on aerosol therapy. Ribavirin is contraindicated in pregnancy and child-bearing age group because of its teratogenic, mutagenic, embryotoxic and gonadotoxic effects.

Antiretroviral Drugs

PH1.48

Classification of antiretroviral drugs is shown on p. 430. NRTIs, PIs and integrase inhibitors are effective against both HIV-1 and HIV-2. NNRTIs and entry inhibitors are active against HIV-1.

Nucleoside Reverse Transcriptase Inhibitors

These drugs, after entering HIV-infected cells, are converted to their active triphosphate forms by cellular kinases and competitively inhibit HIV reverse transcriptase. They get incorporated into the growing viral DNA and cause termination of chain elongation of proviral DNA (Fig. 11.14).

Zidovudine (Azidothymidine [AZT]). Zidovudine, a thymidine analogue, was the first antiretroviral drug approved for the treatment of HIV infection. It is the prototype drug of NRTIs. Zidovudine is effective against HIV-1 and HIV-2. It protects the uninfected cells from HIV, but has no effect on HIV-infected cells. Zidovudine is orally effective. It is well absorbed from the GI tract, metabolized in liver by glucuronide conjugation and excreted in urine. It crosses placental and BBB and is also secreted in milk.

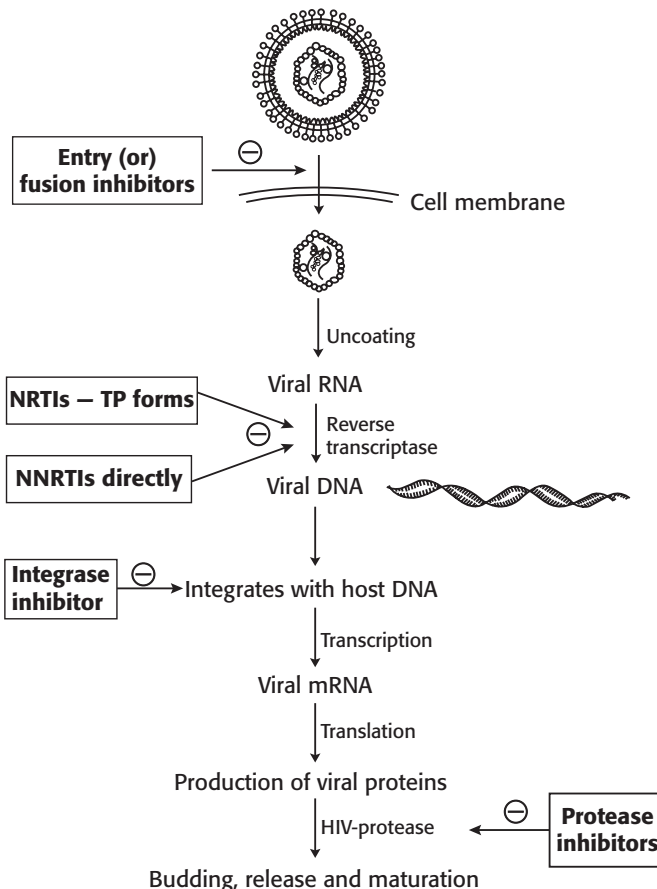
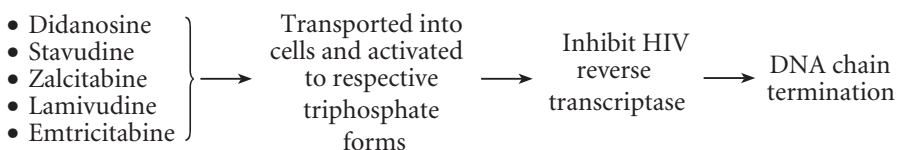


Fig. 11.14 Steps in the life cycle of HIV with sites of action of antiretroviral drugs. TP, triphosphate.

Adverse Effects and Drug Interactions. Bone marrow suppression, anaemia and neutropenia are the common side effects. Nausea, vomiting, abdominal discomfort, headache and insomnia are commonly seen during the initial stages of therapy. Long-term therapy may cause hepatotoxicity, myopathy with fatigue and lactic acidosis.

1. **Zidovudine** × paracetamol: Both are metabolized by glucuronide conjugation. Paracetamol competes and interferes with glucuronide conjugation of zidovudine. This leads to a rise in the plasma concentration of zidovudine and its toxicity.
2. **Azoles** × zidovudine: Azole antifungal agents are hepatic microsomal enzyme inhibitors. They inhibit the metabolism of zidovudine. This leads to an increase in plasma concentration of zidovudine resulting in its toxicity.
3. **Zidovudine and stavudine:** They should not be combined together because they compete for intracellular phosphorylation.

Zidovudine is used in combination with other antiretroviral drugs for the treatment of HIV-infected patients. It is also used for postexposure prophylaxis (PEP) and to prevent vertical transmission of HIV.

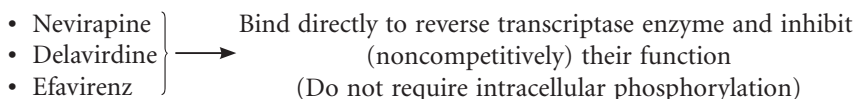


Didanosine, Stavudine, Zalcitabine, Lamivudine, Emtricitabine and Abacavir. They are effective orally. Lamivudine is a commonly used agent in antiretroviral therapy (ART) because of its low toxicity and efficacy. Emtricitabine is one of the least toxic antiretroviral agents. Stavudine and didanosine should not be combined because of increased risk of peripheral neuritis, pancreatitis and lactic acidosis. Abacavir can cause hypersensitivity reactions.

Tenofovir (Nucleotide Reverse Transcriptase Inhibitor). It is a nucleotide analogue of adenosine. It undergoes intracellular phosphorylation and inhibits viral reverse transcriptase enzyme resulting in termination of chain elongation of HIV DNA. Flatulence can occur with tenofovir. It should be cautiously used in patients with renal disease. It is used in combination with other antiretroviral agents for the treatment of AIDS. Tenofovir and lamivudine are also effective against hepatitis B virus.

Non-Nucleoside Reverse Transcriptase Inhibitors

NNRTIs are highly active against HIV-1 but have no effect on HIV-2. They directly and noncompetitively inhibit HIV reverse transcriptase enzyme. There is no cross-resistance with the NRTIs. They are used in combination with NRTIs in the treatment of AIDS. Adverse effects are skin rashes, fever, nausea, pruritus and CNS disturbances like headache, confusion, insomnia, bad dreams and amnesia.



Nevirapine. It is a highly lipid-soluble drug and is almost completely absorbed from the GI tract. It freely crosses the placental barrier and BBB. It is secreted in breast milk. Rashes are the frequent side effect of nevirapine. It can cause hepatotoxicity (risk is increased if the patient is also on antiTB drug, rifampin). It is extensively metabolized in liver and excreted mainly in urine.

Efavirenz. Efavirenz has a long duration of action and is administered once daily. It is taken on empty stomach. It mainly causes CNS side effects like headache and dizziness. Rashes also occur with efavirenz.

Protease Inhibitors

Examples are indinavir, nelfinavir, atazanavir, saquinavir, lopinavir, ritonavir, fosamprenavir and darunavir.

They competitively inhibit the HIV protease enzyme and prevent cleavage of viral polyproteins to the final functional, structural and enzymatic components of HIV → immature and noninfectious viral particles are produced and infection of other cells is prevented.

Cross-resistance is common among the PIs, but there is no cross-resistance with reverse transcriptase inhibitors. PIs are used orally with reverse transcriptase inhibitors in patients with AIDS. They are extensively metabolized in liver. Nausea, vomiting and diarrhoea are common side effects. They also produce skeletal muscle wasting, lipodystrophy, insulin resistance, diabetes, etc.

Indinavir. Nephrolithiasis and hyperbilirubinaemia are also seen. Good hydration can reduce the incidence of nephrolithiasis.

Nelfinavir. Diarrhoea is an important side effect.

Ritonavir. Ritonavir inhibits CYP3A4 and causes a number of drug interactions. It inhibits both HIV-1 and HIV-2 proteases. Low-dose ritonavir is used in combination with other PIs (saquinavir, lopinavir, indinavir and atazanavir) – **boosted PI regimen**. Ritonavir inhibits metabolism of coadministered PIs (by inhibiting CYP3A4), increases their bio-availability and half-life → dose and frequency of administration of coadministered PIs is reduced (number of tablets of PI to be taken is reduced). Nelfinavir is not combined with ritonavir as it is metabolized by a different enzyme.

Entry or Fusion Inhibitors

Enfuvirtide and Maraviroc. Enfuvirtide prevents fusion of HIV-1 membrane with host cell membrane → blocks viral entry into the cell. It is administered subcutaneously. Injection-site reactions like pain and erythema are the important adverse effects. It is given as an add-on drug in patients who are not responding to ongoing ART. It does not exhibit cross-resistance with reverse transcriptase inhibitors and PIs.

Maraviroc is a CCR5 chemokine receptor antagonist → blocks binding of CCR5 – tropic strains of HIV to host cell. It is given orally. It is generally well tolerated. Adverse effects like cough, myalgia, arthralgia, diarrhoea and hepatotoxicity may occur.

Integrase Inhibitors

Raltegravir and Dolutegravir. They inhibit integrase enzyme → prevent integration of viral DNA with host DNA. They are effective against both HIV-1 and HIV-2. Dolutegravir is better tolerated and is administered once daily. Myopathy can occur with raltegravir; dolutegravir can cause hepatotoxicity. There is a risk of neural tube defect with dolutegravir during its use in the first trimester. Hence, it should be avoided during periconception period. Rifampin induces metabolism of dolutegravir; hence, dose of dolutegravir must be doubled when coadministered with rifampin.

Treatment of HIV Infection

PH1.55

Retroviruses contain RNA-dependent DNA polymerase (reverse transcriptase) enzyme. They cause selective depletion of CD4 cells leading to a profound decrease in cell-mediated immunity. Hence, the infected person is prone to severe opportunistic infections, Kaposi sarcoma and lymphoid malignancies.

Objectives of Antiretroviral Therapy

1. To suppress HIV replication and improve immune status of the patient
2. To prevent the emergence of drug-resistant virus
3. To prevent opportunistic infections

Principles of Therapy. ART regimen is used to achieve the above objectives. In ART regimen, drugs with different mechanism of action should be used so that they produce synergistic effect. Use of drug combinations also prevents development of resistance. It usually consists of a combination of two NRTIs with a NNRTI/integrase inhibitor/PI.

Criteria for Anti-HIV Treatment. The National AIDS Control Organization (NACO) has adopted WHO 2016 guidelines for treatment of HIV infection. As per guidelines, ART should be started in all HIV-infected patients irrespective of CD4 count or clinical stage. Treatment is lifelong. A combination of antiretroviral drugs is used.

First-Line ART Regimen in Adults

Two NRTIs + one NNRTI/integrase inhibitor (INSTI)

The preferred regimen is the following:

- Tenofovir (TDF) + lamivudine (3TC) + efavirenz (EFV)
- Tenofovir (TDF) + emtricitabine (FTC) + efavirenz (EFV)
- Tenofovir (TDF) + lamivudine (3TC)/emtricitabine (FTC) + dolutegravir (DTG) is another first-line regimen which can be used.

Alternate regimens

- Zidovudine (AZT) + lamivudine (3TC) + efavirenz (EFV)
- Zidovudine (AZT) + lamivudine (3TC) + nevirapine (NVP)
- Tenofovir (TDF) + lamivudine (3TC)/emtricitabine (FTC) + nevirapine (NVP)

Fixed-dose combination once daily is preferred for initiation of treatment.

Monitoring of Therapy. Estimation of HIV viral load is preferred.

Second-Line ART Regimen in Adults. It should consist of 2NRTIs + boosted PI.

The NRTIs to be used are the following:

- Zidovudine (AZT) + lamivudine (3TC), if the first-line regimen was tenofovir based
- Tenofovir (TDF) + lamivudine (3TC), if the first-line regimen was zidovudine based
- Boosted PI:

Atazanavir/ritonavir (ATV/r) or lopinavir/ritonavir (LPV/r) is preferred.

Alternative boosted PI is darunavir/ritonavir (DRV/r).

Pregnant Women. ART should be started in all pregnant women with HIV irrespective of CD4 count and WHO clinical stage. A combination of tenofovir (300 mg) + lamivudine (300 mg) + efavirenz (600 mg) is recommended in HIV-positive pregnant women. Treatment is lifelong.

Prophylaxis in Infants. Infants of women on ART should receive nevirapine daily for 6 weeks.

Prophylaxis of HIV Infection

Pre-exposure prophylaxis (PrEP) is administration of antiretroviral drugs prior to exposure to HIV for preventing HIV infection. Those at high risk of HIV infection include heterosexual men, women, transgenders and i.v. drug abusers. A fixed-dose combination of tenofovir (300 mg) + emtricitabine (200 mg) daily is used.

Post-Exposure Prophylaxis (PEP). Use of antiretroviral drugs after exposure has occurred to prevent HIV infection is post-exposure prophylaxis. Individuals who have had exposure (e.g. sexual exposure, needle-prick injury, exposure to blood, breast milk, CSF, pleural, pericardial fluid) need PEP depending on the risk of HIV transmission and HIV status of the source. PEP should be initiated as early as possible, preferably within 72 hours of exposure.

Preferred regimen for adults and adolescents:

Tenofovir (300 mg) + emtricitabine (200 mg) + lopinavir/ritonavir (400/100 mg)
or

Tenofovir (300 mg) + emtricitabine (200 mg) + atazanavir/ritonavir (300/100 mg)

The drugs should be administered for 28 days.

PEP is not required if exposure is to tears, urine or sweat, or source is HIV negative.

ART in Adults with Tuberculosis

All TB patients with HIV should receive ART. Treatment with anti-TB drugs is started first. This is followed by administration of ART within 8 weeks of start of treatment with anti-TB drugs.

Antimalarial Drugs

PH1.47

Malaria is a protozoal infection caused by genus *Plasmodium* and transmitted to humans by the infected female *Anopheles* mosquito. The species of malarial parasites are *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, *P. falciparum* and *Plasmodium knowlesi*. The incidence of malaria is increasing due to the resistance of vectors to insecticides and drug-resistant parasites. In India, *P. vivax* and *P. falciparum* are common.

CLASSIFICATION

1. Chemical classification

- (a) *4-Aminoquinolines*: Chloroquine, amodiaquine, piperaquine
- (b) *8-Aminoquinolines*: Primaquine, tafenoquine
- (c) *Quinoline methanol*: Mefloquine
- (d) *Alkaloids*: Quinine, quinidine
- (e) *Antifolates*: Pyrimethamine, sulphadoxine, dapsone, proguanil
- (f) *Antibiotics*: Doxycycline, clindamycin
- (g) *Hydroxynaphthoquinone*: Atovaquone
- (h) *Artemisinin*: Artemisinin, artemether, artesunate, arteether, arterolane, dihydroartemisinin
- (i) *Aryl alcohol*: Lumefantrine

2. Clinical classification

- (a) This classification is based on the stage of the parasite they affect ([Table 11.21](#) and [Fig. 11.15](#)).
 - (i) *Tissue schizontocidal agents*: These act on primary (pre-erythrocytic) and latent (hypnozoites) tissue forms in the liver, e.g. primaquine, and are effective against both forms; atovaquone and proguanil act on primary form.
 - (ii) *Blood schizontocidal agents*: These act on erythrocytic stage of *Plasmodium* and, thereby, terminate the clinical attack.
 - *Rapid acting and high-efficacy agents*, e.g. chloroquine, artemisinin derivatives, quinine, mefloquine, atovaquone, amodiaquine and lumefantrine.
 - *Slow-acting and low-efficacy agents*, e.g. proguanil, pyrimethamine + sulphadoxine and clindamycin; used always in combination with rapid-acting agents.

Table 11.21 ■ Antimalarial drugs effective against various stages of life cycle of malarial parasite

Stages of malarial parasite	Hepatic stages		Blood stages	
	Primary tissue forms	Latent tissue forms (hypnozoites)	Asexual forms	Sexual forms
Drugs	• Sulfadoxine + Pyrimethamine • Proguanil/atovaquone • Primaquine	• Primaquine • Tafenoquine	• Chloroquine • Mefloquine • Quinine • Artemisinins • Sulfadoxine + pyrimethamine • Proguanil/atovaquone • Antibiotics • Tafenoquine	• Chloroquine • Quinine • Primaquine • Artemisinins • Quinghaosu

Note: Points to remember

1. None of the agents available are effective against sporozoites.
2. Most of the antimalarials are effective against asexual blood stages except primaquine.
3. Only primaquine and tafenoquine are effective against hypnozoites (latent tissue forms).
4. All agents with 'quinine' (primaquine, chloroquine and quinine) are effective against gametocytes except mefloquine and tafenoquine.
5. Primaquine, proguanil and pyrimethamine are effective against hepatic primary tissue forms.

- (iii) *Gametocidal agents*: These kill gametocytes of plasmodia in blood, e.g. artemisinin and primaquine (active against all species); chloroquine and quinine (*vivax*). They reduce transmission to mosquitoes.
- (b) Based on clinical indication for use (clinical utility)
- (i) *Drugs used for causal prophylaxis*, i.e. pre-erythrocytic stage of *Plasmodium* in liver, e.g. proguanil and primaquine. Primaquine is effective against all species but not used due to its toxic potential. Proguanil is effective mainly for *P. falciparum*.
 - (ii) *Drugs for suppressive prophylaxis*: Suppress erythrocytic phase, thus clinical attack of malaria is prevented – clinical disease is not manifested, e.g. chloroquine, mefloquine and doxycycline.
 - (iii) *Drugs used for clinical cure*: These agents act on erythrocytic stages of malarial parasite to terminate the clinical attack. They are rapid-acting and slow-acting blood schizontocidal agents.
 - (iv) *Drugs used to prevent relapse*: These drugs act on the latent tissue forms (hypnozoites) of *P. vivax* and *P. ovale* which cause relapse, e.g. primaquine and tafenoquine.

Radical cure of *P. vivax* and *P. ovale* is achieved with the use of a blood schizontocidal agent along with primaquine which acts on latent tissue forms (hypnozoites) to prevent relapse.

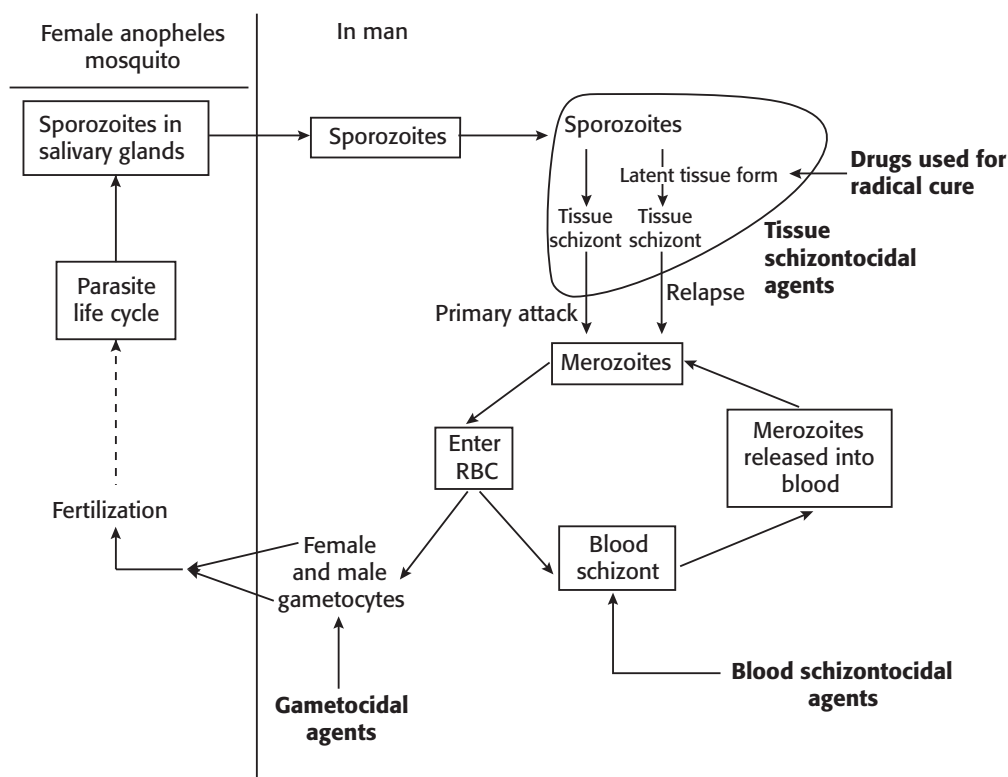


Fig. 11.15 The life cycle of malarial parasite and the site of action of antimalarial drugs.

- (v) Drugs used to prevent the transmission of infection to *Anopheles* mosquito (gametocidal agents): Primaquine has gametocidal effect against all species of plasmodia that infect humans.

4-Aminoquinolines

Chloroquine. Chloroquine is a 4-aminoquinoline. It is very effective and rapidly acting blood schizonticide against *P. vivax*, *P. ovale*, *P. malariae*, chloroquine-sensitive strains of *P. falciparum* and *P. knowlesi*. It has no activity against liver forms (pre-erythrocytic and hypnozoites).

Mechanism of Action. Chloroquine is a basic drug, which is taken up by the acidic food vacuoles of susceptible plasmodia and inhibits the conversion of haeme to haemozoin. The 'drug-haeme' complex is toxic and kills the parasite. Resistance to chloroquine is common with *P. falciparum*.

In the acidic vacuole of plasmodia:

- Haemoglobin $\rightleftharpoons$ Haeme (toxic) $\rightleftharpoons$ Haemozoin (nontoxic)
- Chloroquine (weak base) $\rightleftharpoons$ Concentrated in acidic vacuole of parasite $\rightleftharpoons$ binds to haeme



Damages plasmodial membrane $\rightleftharpoons$ Drug-haeme complex
(prevents formation of haemozoin)

Pharmacokinetics. Chloroquine is commonly administered by oral route. It is well absorbed after oral and parenteral administration. It has strong affinity for melanin-containing tissues. It gets rapidly distributed to tissues (extensive tissue binding); therefore, to achieve

an effective therapeutic plasma concentration, a loading dose is used during treatment of malaria. It gets concentrated in liver, spleen, kidney, lungs, skin, etc. Chloroquine is metabolized in the liver and slowly excreted in urine.

Adverse Effects and Contraindications. Chloroquine in antimalarial doses may cause nausea, vomiting, skin rashes, itching, headache and visual disturbances. Parenteral administration can cause hypotension, confusion, cardiac arrhythmias, convulsions and even cardiac arrest. Prolonged administration in large doses, as in rheumatoid arthritis, may cause irreversible retinopathy and ototoxicity. It can also cause myopathy, cardiomyopathy, neuropathy and rarely psychiatric disturbances. Long-term therapy requires ophthalmological examination once in 3–6 months. It should be avoided in patients with epilepsy. It should not be given with mefloquine (can precipitate seizures). It is safe for use in pregnancy.

Uses

1. Malaria

- (a) Chloroquine is the drug of choice for the treatment of **acute attack** of malaria caused by *P. vivax*, *P. ovale*, *P. malariae*, chloroquine-sensitive *P. falciparum* and *P. knowlesi* (Table 11.22). Fever resolves within 24–48 hours; blood smear becomes negative within 2–3 days.
- (b) For malaria due to *P. vivax* and *P. ovale*, primaquine is also administered in addition to chloroquine (for **radical cure**).
- (c) Chloroquine is a very effective **chemoprophylactic** agent for all types of malaria (Table 11.23) except that caused by the resistant strains of *P. falciparum*.

Table 11.22 ■ Regimens for treatment of malaria

PH1.55

1. Treatment of uncomplicated malaria

(a) For acute attack of malaria due to *P. vivax*, *P. ovale*, *P. malariae*

Oral chloroquine is the drug of choice.

Chloroquine 600 mg base (10 mg/kg) stat, followed by

600 mg base (10 mg/kg) – second day

300 mg base (5 mg/kg) – third day

(b) For radical cure of *P. vivax* and *P. ovale*

Chloroquine (as above)

+

Primaquine 15 mg base orally, from day 4 daily for 14 days

(Primaquine destroys the hypnozoites in liver and prevents relapse in *P. vivax* and *P. ovale* infections)

(c) For acute attack of malaria due to *P. falciparum*

- (i) **ACT regimen + Primaquine (on Day 2), single dose 0.75 mg/kg body weight (for gametocidal action)**

ACT regimens

- Artesunate (4 mg/kg) 100 mg BD × 3 days

+

Sulphadoxine and Pyrimethamine (S/P) 1500 mg/75 mg as a single dose – day 1 (recommended in India except north eastern states)

- Artemether + Lumefantrine (AL) – (FDC – 20 mg + 120 mg) 4 tablets BD × 3 days (for those with body weight > 35 kg) -preferably administered with fatty meal to increase absorption (recommended in north eastern states)

Continued

Table 11.22 ■ Regimens for treatment of malaria—cont'd

- Artesunate 100 mg BD × 3 days
+
Mefloquine 750 mg (15 mg/kg) – 2nd day
and 500 mg (10 mg/kg) – 3rd day
(Mefloquine is given in divided doses to minimize nausea and vomiting)
 - Artesunate 4 mg/kg/day + Amodiaquine 10 mg/kg/day OD × 3 days
- (ii) **Alternative to ACT regimens**
- Quinine sulphate 8 mg base/kg orally TDS for 7 days with either
Doxycycline or clindamycin

2. For severe or complicated *P. falciparum* malaria (cerebral malaria)

Parenteral antimalarials should be administered for at least 24 hours once started
Then complete the treatment with full course of oral ACT once the patient is able to
take orally

Artesunate:

Dose: 2.4 mg/kg at 0 hour (i.v./i.m.); repeat at 12 and 24 hours

Then, once a day till patient is able to take oral medication

If patient is able to take orally after 24 hours, switch over to full course of 3-day
oral ACT^a

Alternatives

- **Quinine dihydrochloride** 600 mg (20 mg/kg) is diluted in 500 mL of 5% dextrose and infused intravenously slowly over 3–4 hours; 10 mg/kg is repeated as i.v. infusion over 4 hours every 8 hours till the patient can take orally. Then oral quinine sulphate 600 mg t.d.s. should be substituted to complete 1-week therapy along with doxycycline 100 mg o.d. × 7 days. Blood pressure, blood glucose and electrocardiogram (ECG) should be monitored during quinine therapy. Infusion rate should not exceed 5 mg salt/kg/h
 - **Artemether**
On admission – 3.2 mg/kg i.m.
Then once a day – 1.6 mg/kg i.m. till patient can take orally – then switch over to full course of 3-day **oral ACT**
 - **α/β Arteether**
150 mg i.m. daily for 3 days; then switch over to 3-day **oral ACT** when the patient can take orally
- ^a**Oral ACT:** see treatment of uncomplicated falciparum malaria. ACT containing mefloquine should be avoided in cerebral malaria because of risk of neuropsychiatric complications.

Supportive measures

- Tepid sponging for fever
- Sodium bicarbonate to correct acidosis
- Intravenous diazepam to control convulsions
- 10% dextrose to combat hypoglycaemia
- Blood transfusion to correct anaemia

ACT, artemisinin-based combination therapy.

NVBDCP guidelines for diagnosis and treatment of malaria 2014

Table 11.23 ■ Regimens for chemoprophylaxis of malaria

- (a) **For travel to areas with chloroquine-sensitive *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale* malaria**
 Chloroquine phosphate is given orally. Chloroquine phosphate 500 mg (chloroquine 300 mg base) once weekly; start 1 week before entering the endemic area; continue during the stay there, and for 4 weeks after leaving that area
- (b) **In areas with chloroquine-resistant *P. falciparum* malaria**
 Mefloquine 250 mg salt (228 mg base) orally, once weekly; start 1 week before entering the endemic area; continue once weekly there, and for 4 weeks after leaving that area
 Or
 Doxycycline 100 mg orally daily, start 1 day before entering the endemic area; continue daily during the stay there, and daily for 4 weeks after leaving that area. Doxycycline is contraindicated in pregnancy and in children
 Or
 Atovaquone 250 mg + proguanil 100 mg, fixed-dose combination tablet is available for oral administration. One tablet of FDC daily; start 1 day before entering the endemic area; continue daily during the stay there and daily for 1 week after leaving that area
- (c) **For terminal prophylaxis (for *P. vivax* and *P. ovale* malaria – to prevent relapse)**
 Primaquine 30 mg daily is started shortly before or after the person leaves the endemic area, and continued for 2 weeks

2. Other uses are the following:

Malaria.

Amoebiasis – hepatic, as it is highly concentrated in the liver.

Lepra reaction – anti-inflammatory effect is useful.

Rheumatoid arthritis – it scavenges-free radicals and stabilizes lysosomal membrane.

Infectious mononucleosis.

Autoimmune disorder – discoid lupus erythematosus.

Note: Uses of chloroquine: Mnemonic – **MALARIA**.

Tablet chloroquine phosphate 500 mg = 300 mg chloroquine base

Tablet chloroquine phosphate 250 mg = 150 mg chloroquine base

Amodiaquine. It is a congener of chloroquine. The mechanism of action is similar to that of chloroquine. It is an erythrocytic schizontocide used in combination with artesunate for the treatment of chloroquine-resistant *falciparum* malaria. It is not used for prophylaxis of malaria owing to its toxicities – agranulocytosis and hepatotoxicity.

Piperaquine. It is structurally related to chloroquine. It acts on blood stages of parasite. It has a long duration of action. Piperaquine is approved for use in combination with dihydroartemisinin for treatment of chloroquine-resistant *falciparum* malaria. It is also used in combination with arterolane.

Alkaloids

Quinine and Quinidine. Cinchona bark contains several alkaloids, of which quinine and quinidine are important.

Mechanism of Action. It is similar to that of chloroquine.

Pharmacological Effects

- 1. Antimalarial actions:** Quinine is a highly effective blood schizonticide against all the four species of plasmodia. It has gametocidal activity against *P. vivax*. It has no activity on hepatic forms (i.e. pre-erythrocytic and latent tissue forms).
- 2. Other actions**
 - (a) *GIT*: Being bitter, quinine reflexly increases gastric acid secretion.
 - (b) *CVS*: Quinine directly depresses the myocardium and can cause hypotension. But this effect may not be seen with oral antimalarial doses.
 - (c) *Skeletal muscle*: Quinine directly depresses the skeletal muscle contraction. Response to ACh is also diminished – symptoms of myasthenia gravis are exaggerated, while symptoms of myotonia congenita are relieved.
 - (d) *CNS*: In therapeutic doses, quinine often causes disturbances of hearing and vision. It also has mild analgesic and antipyretic effects.
- 3. Local action:** Quinine has local anaesthetic effect, but there is invariably an initial irritation. Orally, it causes GI irritation with nausea, vomiting and abdominal discomfort. Intramuscularly, it causes local pain and necrosis. Intravenously, it can cause thrombophlebitis.

Pharmacokinetics. Quinine is readily absorbed from the gut or i.m. site, well distributed in the body, extensively metabolized in liver and excreted mainly in urine.

Adverse Effects. Quinine causes dose-dependent toxicities. They are cinchonism, hypoglycaemia and hypotension. Cinchonism comprises tinnitus, deafness, visual disturbances like blurred vision and colour defects, headache, nausea and vomiting. These symptoms are reversible on stoppage of therapy. Hypoglycaemia is common with i.v. quinine which is due to release of insulin – it is treated with intravenous glucose. Hypotension is also seen with intravenous administration of cinchona alkaloids. Quinine in large doses can cause hypotension, cardiac arrhythmias and A–V block. Quinidine is more cardiotoxic than quinine.

‘Blackwater fever’, a hypersensitivity reaction to quinine, is characterized by haemolysis, haemoglobinaemia and haemoglobinuria leading to renal failure.

Quinine/quinidine should not be used concurrently with mefloquine because of risk of serious cardiac toxicity. Quinine can be used in pregnancy.

Uses

- 1. Malaria:** Quinine is effective for treatment of acute attack of chloroquine-resistant *P. falciparum* malaria. Combination of clindamycin or tetracycline with quinine enhances the antimalarial efficacy of quinine. In severe malaria, quinine or quinidine is administered intravenously.
- 2. Nocturnal leg cramps:** Quinine may be effective in some cases. Quinine is not used for chemoprophylaxis of malaria because of its toxicity.

Quinoline Methanol

Mefloquine. It is a synthetic quinoline methanol. Like quinine, it is a highly effective blood schizonticide and has no effect on hepatic forms, i.e. pre-erythrocytic stages and hypnozoites of *P. vivax*. It has no gametocidal activity.

Mechanism of Action. It is similar to that of chloroquine and quinine. It binds to heme and causes damage to membrane of Plasmodium.

Pharmacokinetics. Mefloquine is administered orally and is not suitable for parenteral use because of its local irritant action. It is well absorbed, widely distributed, highly bound to plasma proteins, secreted in bile and undergoes extensive enterohepatic cycling. It is slowly excreted in the faeces with a terminal half-life of about 3 weeks.

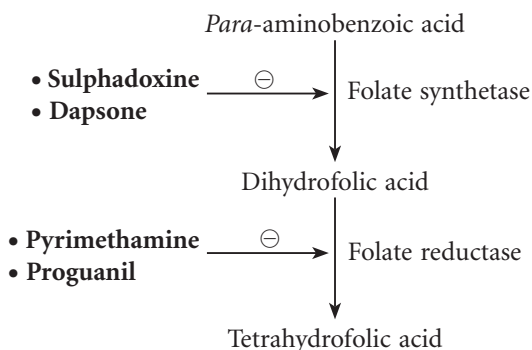
Uses. Mefloquine is used for prophylaxis of chloroquine-resistant *P. falciparum* and *P. vivax* malaria. It is used in combination with artesunate for the treatment of chloroquine-resistant *P. falciparum* malaria.

Adverse Effects. The common side effects include nausea, vomiting, diarrhoea and dizziness. Nausea and vomiting can be minimized by dividing the dose. Neuropsychiatric symptoms and seizures can occur. Mefloquine is contraindicated in patients with conduction defects, epilepsy and psychiatric disorders. It is safe for use in young children.

Antifolates

They are pyrimethamine, sulphadoxine, sulphones (dapsone) and proguanil. They are not used as single agents in malaria owing to rapid development of resistance.

Mechanism of Action. Plasmodia utilize PABA for the synthesis of folic acid which, in turn, is necessary for DNA synthesis. Sulphadoxine and dapsone inhibit folate synthetase, whereas pyrimethamine and proguanil inhibit DHF reductase enzyme of the parasite. Sulfadoxine has a long half-life like pyrimethamine. Combination of these drugs (pyrimethamine + sulphadoxine/dapsone) inhibits two successive steps (**sequential blockade**) in the folate pathway, acts faster and produces enhanced antimalarial action (**supra-additive effect**).



Pyrimethamine. Pyrimethamine is a slow-acting blood schizontocide and has a greater affinity for plasmodial DHF reductase. The combination of pyrimethamine with sulphadoxine along with artesunate is used in the treatment of chloroquine-resistant *P. falciparum* malaria. Pyrimethamine–sulphadiazine combination is the treatment of choice for toxoplasmosis in immunocompromised patients.

Preparations

Pyrimethamine 25 mg + sulphadoxine 500 mg

Pyrimethamine 25 mg + dapsone 100 mg

Pyrimethamine is completely absorbed after oral administration, binds to plasma proteins, and accumulates in liver, kidney, lungs and spleen. It has a long plasma half-life (80–90 hours) and is excreted slowly in urine. Adverse effects are skin rashes, urticaria, megaloblastic anaemia and teratogenic effect.

Proguanil (Chloroguanide). Proguanil is a prodrug. It has a wide margin of safety. It is a slow-acting blood schizonticide for all the four species of plasmodia. It also has activity against primary hepatic stages of *P. falciparum*. It is absorbed slowly after oral administration, metabolized in liver and excreted in urine. It rarely causes side effects, such as nausea, vomiting, diarrhoea, abdominal pain, haematuria and skin rashes.

Hydroxynaphthoquinone

Atovaquone. Atovaquone is a rapidly acting blood schizonticide and is also effective against liver stages (pre-erythrocytic forms) of *P. falciparum*. It is administered orally. It is highly bound to plasma proteins and excreted unchanged in faeces via bile.

Atovaquone is used with proguanil (Malarone) for prophylaxis of chloroquine-resistant *P. falciparum* malaria. It is also effective in the treatment of opportunistic infections with *P. jiroveci* and *T. gondii* in immunocompromised patients. The common adverse effects include nausea, vomiting, diarrhoea, abdominal pain, skin rashes and headache. It should be avoided in pregnant women.

8-Aminoquinoline

Primaquine. It is a synthetic 8-aminoquinoline. It is effective against hepatic stages, i.e. primary and latent tissue forms of *Plasmodia* species that infect humans. It also has marked gametocidal activity but is ineffective against erythrocytic forms of malarial parasite. The exact mechanism of action of primaquine is unknown. It probably acts by generating reactive oxygen radicals and interfering with the mitochondrial electron transport in the parasite.

It is almost completely absorbed after oral administration, widely distributed, metabolized in liver and excreted slowly in urine.

Primaquine is used for radical cure and terminal prophylaxis of *P. vivax* and *P. ovale* as it has strong activity against hypnozoites. For terminal prophylaxis, primaquine 15 mg daily is started shortly before or after return from an endemic area. For radical cure of relapsing malaria (*P. vivax* and *P. ovale*), a 2-week course of primaquine is given concurrently with chloroquine or after the treatment of acute attack.

Adverse Effects. These include nausea, vomiting and epigastric distress – can be minimized by taking it with food. The important side effect with primaquine is haemolytic anaemia in people with G6PD deficiency. Methaemoglobinaemia can also occur with primaquine. Primaquine is contraindicated in pregnancy.

(Tablet primaquine phosphate 26 mg contains 15 mg base of primaquine base.)

Tafenoquine. It is an 8-aminoquinoline. It is very effective against latent tissue forms (hypnozoites) of *P. vivax*, and also has blood schizontocidal activity. It has a longer duration of action ($t_{1/2}$ is 15–19 days), hence used as a single-dose antirelapse agent. It can cause hemolysis in G6PD deficient individuals.

Artemisinin and its Derivatives (Qinghaosu Compounds). Artemisinin is derived from the plant *Artemisia annua*. The semisynthetic derivatives of artemisinin are dihydroartemisinin, artemether and artesunate. Another compound, arteether, was developed in India.

They are highly effective against erythrocytic stages of all plasmodia. They also have gametocidal action – reduce transmission of malarial parasite. They have no effect on hepatic stages of the parasite.

Mechanism of Action

In the acid vacuole of parasite, cleavage of endoperoxide bridge of artemisinin compounds by haeme iron



Free radicals generated



Damage to proteins and lipid peroxidation



Death of parasite

Pharmacokinetics

- Dihydroartemisinin: Oral
- Artesunate: Oral, i.m., i.v., rectal
- Artemether: Oral, i.m.
- Arteether: i.m.

Artesunate and artemether are metabolized to the active metabolite, dihydroartemisinin.

Artesunate can enhance its own metabolism (autoinduction). The half-life of dihydroartemisinin is about 2 hours. Arteether has a longer half-life.

Adverse Effects. They are generally well tolerated. Artemisinins can cause mild GI disturbances, neutropenia and prolongation of QT interval.

Arterolane. It is a synthetic derivative of artemisinin which acts on erythrocytic stages of the parasite. It is potent and has a rapid onset and short duration of action. A combination of arterolane with piperazine has been found to be effective and well tolerated for the treatment of *P. falciparum* malaria.

Uses of Artemisinins. Artemisinins are used in the treatment of uncomplicated chloroquine-resistant falciparum malaria and severe malaria.

Artemisinins have a short half-life and are not used for chemoprophylaxis. They should not be used as monotherapy because of risk of development of resistance. They are used in combination with other antimalarials – **artemisinin-based combination therapy (ACT)**. They are more potent, faster acting, better tolerated and affect various erythrocytic forms of the parasite as compared to chloroquine. The use of ACT improves treatment efficacy, provides faster clinical cure and rapid parasite clearance, and prevents recrudescence and development of resistance. Artemisinin derivatives (short $t_{1/2}$) can be combined with slowly eliminated antimalarials (long $t_{1/2}$), e.g. mefloquine, lumefantrine and amodiaquine, for the treatment of chloroquine-resistant *falciparum* malaria – duration of therapy is 3 days. Artemisinins rapidly kill 90%–95% of parasites; the remaining parasites are killed by the other drug.

Artemisinin derivatives can also be combined with doxycycline, tetracycline and clindamycin – duration of therapy is 7 days.

Recommended ACT regimens for treatment of uncomplicated *P. falciparum* malaria are shown in Table 11.22.

Severe malaria: It is a medical emergency. Patient with severe *P. falciparum* malaria may present with one or more of the following features: impaired consciousness, convulsions, prostration, respiratory distress, circulatory collapse, shock, jaundice, pulmonary oedema, spontaneous bleeding, haemoglobinuria, hypoglycaemia, metabolic acidosis, renal failure and hyperparasitaemia. (For treatment, see Table 11.22, p. 442).

The main aim of treatment is to prevent mortality. Treatment should be started as early as possible. Artesunate is preferred to quinine for treatment of severe malaria because:

- Risk of death is lower.
- It causes rapid parasite clearance.
- It is safe and well tolerated.
- It does not require cardiac monitoring.
- It does not require rate-controlled infusion.
- Risk of hypoglycaemia is lower.
- No cross-resistance with other antimalarial agents.

Lumefantrine

It is active against erythrocytic stages of all species of malarial parasite. Fatty meal increases its absorption. It can cause GI disturbances. It does not significantly prolong QT interval. It is used in the treatment of *P. falciparum* malaria in combination with artemether.

Antibiotics

Tetracyclines and Clindamycin. Tetracycline, doxycycline and clindamycin are slow-acting blood schizontocides for all species of plasmodia that infect humans. They do not affect hepatic stages. They are used in combination with quinine or artesunate for the treatment of *P. falciparum* malaria. Doxycycline can also be used alone as a chemoprophylactic agent for MDR strains of malaria. Tetracyclines should not be used in pregnancy and young children (younger than 8 years); clindamycin can be used safely in such cases.

Treatment of Malaria during Pregnancy: *P. vivax* malaria is treated with chloroquine. For *P. falciparum* malaria, quinine with clindamycin is administered in first trimester; ACT in 2nd and 3rd trimesters. Doxycycline and primaquine are contraindicated in pregnancy.

Treatment of Mixed Infection due to both *P. falciparum* and *P. vivax*: It should be treated as *P. falciparum* malaria with ACT regimen (except ACT regimen of artesunate + sulfadoxine-pyrimethamine as it is not effective against *P. vivax*). A 14 day course of primaquine is also added.

Antiamoebic Drugs

PH1.47

Amoebiasis is a protozoal infection caused by *E. histolytica*, which is transmitted through faeco-oral route.

Classification (According to their Site of Action)

1. **Luminal amoebicides:** They are poorly absorbed after oral administration, hence attain high concentration in the bowel. They act on trophozoites in the gut lumen and kill them.
 - (a) **Amides:** Diloxanide furoate and nitazoxanide
 - (b) **8-Hydroxyquinolines:** Iodoquinol, iodochlorhydroxyquin
 - (c) **Antibiotics:** Tetracyclines, paromomycin
2. **Tissue amoebicides:** They attain high concentration in blood and tissues following oral or parenteral administration.
 - (a) **Nitroimidazoles:** Metronidazole, tinidazole, secnidazole, ornidazole, satranidazole

(b) **Alkaloids:** Emetine, dehydroemetine (DHE)

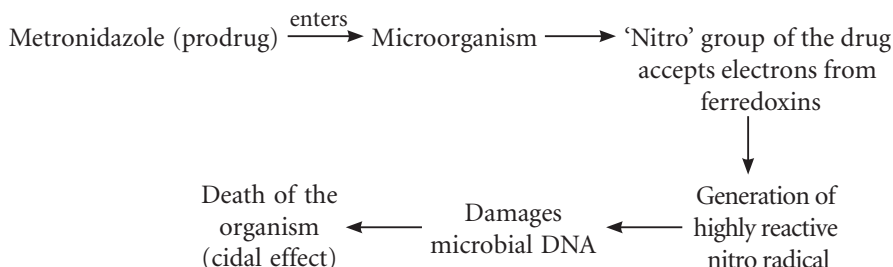
(c) **4-Aminoquinoline:** Chloroquine

Among tissue amoebicides, nitroimidazoles and alkaloids are used for intestinal and extraintestinal amoebiasis. Chloroquine is used for extraintestinal amebiasis.

Nitroimidazoles

Metronidazole. Metronidazole is a nitroimidazole derivative which is highly effective against most anaerobic bacteria and several protozoa, such as *E. histolytica*, *Giardia lamblia* and *Trichomonas vaginalis*. It helps in the extraction of guinea worm (*Dracunculus medinensis*).

Mechanism of Action



In the presence of oxygen (aerobes), highly reactive nitro radical cannot be generated; hence, it is **ineffective against aerobes**.

Pharmacokinetics. Metronidazole is available for oral, i.v. and topical administration. It is usually well absorbed in the small intestine after oral administration and poorly bound to plasma proteins. It diffuses well into the tissues including brain; therapeutic levels are achieved in various body fluids – saliva, semen, vaginal secretion, bile, breast milk and CSF. Metronidazole is metabolized in liver and the metabolites are excreted mainly in urine.

Adverse Effects. Adverse effects are rarely severe to necessitate the discontinuation of the drug.

1. **GIT:** Anorexia, nausea, metallic taste, dry mouth, epigastric distress, abdominal cramps and occasionally vomiting.
2. **Allergic reactions:** These include skin rashes, urticaria, itching and flushing.
3. **CNS:** Dizziness, vertigo, confusion, irritability, headache, rarely convulsions and ataxia may occur. Polyneuropathy may occur on prolonged therapy.
4. Disulfiram-like reaction (nausea, vomiting, abdominal cramps, headache, flushing, etc.) may occur if taken with alcohol; hence, the patient should be warned to avoid alcohol during treatment with metronidazole.

Teratogenic effect is seen in experimental animals; hence, metronidazole should be avoided in pregnant women.

Drug Interactions

1. Metronidazole potentiates the anticoagulant effect of warfarin and other oral coumarins by inhibiting their metabolism. There is prolongation of prothrombin time; hence, reduction of warfarin dose may be needed.
2. Metronidazole may potentiate lithium toxicity by decreasing the renal clearance of lithium.

Table 11.24 ■ Treatment of amoebiasis

I. For asymptomatic carriers (luminal amoebicide is used)	
Diloxanide furoate or paromomycin or iodoquinol	
Tab. diloxanide furoate 500 mg t.d.s. for 10 days	
II. For intestinal amoebiasis (amoebic dysentery or diarrhoea)	
Metronidazole/tinidazole + luminal agent	
Tab. metronidazole 400 mg t.d.s.	} for 7–10 days
+	
Tab. diloxanide furoate 500 mg t.d.s.	
III. For severe amoebic dysentery and extraintestinal amoebiasis	
Similar to intestinal amoebiasis (metronidazole + luminal agent) or metronidazole	
500 mg i.v. infusion q6h till patient can take oral therapy (total duration is 10 days)	
IV. Hepatic amoebiasis	
Similar to severe amoebic dysentery (metronidazole + luminal agent). Chloroquine may	
be used if patient is not responding to above therapy (Tab. chloroquine phosphate	
500 mg b.d. for 2 days, later 500 mg o.d. for 3 weeks)	

Uses (Table 11.24)

- 1. **Amoebiasis:** Metronidazole (400–800 mg t.d.s. for 7–10 days) is the first-line agent for the treatment of both intestinal and extraintestinal amoebiasis except in asymptomatic carriers (Table 11.24). As the metronidazole is almost completely absorbed in the small intestine, it is not effective as a luminal amebicide.
- 2. **Trichomonas vaginitis:** Metronidazole (400 mg t.d.s. orally for 7 days) is the drug of choice. Both sexual partners should be treated simultaneously.
- 3. **Giardiasis:** Metronidazole is very effective and is given orally (200 mg t.d.s. for 7 days).
- 4. **Anaerobic infections:** Metronidazole is highly effective in most of the anaerobic infections – pelvic inflammatory disease, lung abscess, intra-abdominal infection, etc., caused by *B. fragilis*, *Clostridium* and other anaerobic organisms.
 - (a) In anaerobic brain abscess, metronidazole is often used in combination with a third-generation cephalosporin.
 - (b) In antibiotic-associated pseudomembranous colitis, metronidazole is effective. It is cheaper and less toxic than vancomycin.
 - (c) Vincent’s angina: Metronidazole is combined usually with amoxicillin for treatment of Vincent’s angina (ulcerative gingival infection produced by anaerobes).
 - (d) In the treatment of *H. pylori* infection, metronidazole is useful in combination with clarithromycin or amoxicillin and a proton pump inhibitor.
 - (e) It is used for prophylaxis of colorectal surgery.
- 5. **Others:** It is used for treatment of bacterial vaginosis, extraction of guinea worm and Crohn’s disease. Other nitroimidazoles are shown in Table 11.25.

Emetine Group

Emetine and Dehydroemetine (DHE). Emetine is an alkaloid and DHE is a semisynthetic derivative. They are irritants, bitter in taste and nauseating, hence cannot be administered orally. They are administered through i.m. route. They kill tissue trophozoites and have no effect on cysts. They are highly toxic and are used only when metronidazole is

Table 11.25 ■ Other nitroimidazoles with their important features

Drug	Route of administration	Uses	Advantages and other features
1. Tinidazole	Oral, i.v. infusion	- Amoebiasis: 2 g once daily orally for 3 days or 600 mg twice daily for a week - Trichomoniasis and giardiasis: 2 g stat or 600 mg once daily for a week - Anaerobic infections: It can be used for <i>H. pylori</i> infection and prophylaxis of colorectal surgery	Longer duration of action and better tolerability than metronidazole
2. Secnidazole	Oral	Single oral dose of 2 g is effective in mild intestinal amoebiasis, giardiasis and trichomoniasis	- Single-dose therapy in mild intestinal amebiasis - The spectrum, side effects and mechanism of action are similar to those of metronidazole
3. Ornidazole	Oral and i.v. infusion Oral	- Amoebiasis - Trichomoniasis and giardiasis - Anaerobic infections	Longer duration of action and better tolerability than metronidazole
4. Satranidazole	Oral	- Amoebiasis - Trichomoniasis and giardiasis - Anaerobic infections	Satranidazole does not have interaction with alcohol (disulfiram-like reaction), better tolerability than metronidazole

contraindicated or if the patient is not responding to metronidazole. DHE is less toxic than emetine, hence preferred to emetine. It is administered in a dose of 60 mg once daily for 5 days. The duration of treatment should not exceed 10 days.

Adverse Effects (Mnemonic: EMETINE)

1. Emesis (vomiting) – due to the stimulation of chemoreceptor trigger zone (CTZ).
2. Muscle weakness and stiffness.
3. ECG changes – T-wave inversion and prolongation of PR interval.
4. Tachycardia, hypotension and cardiac arrhythmias.
5. Itching and skin rashes.
6. Nausea.
7. Eczematoid lesions may occur at the injection site.

Note: Patient should be hospitalized and advised to take bed rest during DHE therapy.

4-Aminoquinoline

Chloroquine. Chloroquine is effective in hepatic amebiasis. It is administered orally. It is completely absorbed from the upper GI tract and gets concentrated in liver. Chloroquine is not effective in intestinal amoebiasis because it attains low concentration in the gut wall and lumen. A luminal amoebicide has to be added to it when used for hepatic amoebiasis.

Amides

Diloxanide Furoate. Diloxanide furoate is a synthetic compound. The trophozoites in gut lumen which form cysts are killed by diloxanide furoate (luminal amoebicide). It is not effective against tissue trophozoites. After oral administration, diloxanide furoate in the gut is split into diloxanide and furoic acid. The diloxanide moiety is partly absorbed; the unabsorbed portion in the gut exerts antiamoebic activity. It is the drug of choice for asymptomatic amoebic carriers. In intestinal and extraintestinal amoebiasis, diloxanide furoate is given along with a tissue amoebicide for complete eradication of the organism (i.e. both trophozoites and cysts). Diloxanide furoate is administered in a dose of 500 mg t.d.s. for about 7–10 days. It is well tolerated and rarely causes side effects, such as flatulence, nausea and skin rashes.

Nitazoxanide. Nitazoxanide is a luminal amoebicide. It is converted to active metabolite (tizoxanide). It is useful orally in amoebiasis and giardiasis. Adverse effects are headache and GI disturbances.

8-Hydroxyquinolines

Hydroxyquinolines were widely used as luminal amoebicides in the past for amoebiasis. They have been banned in various countries because of their toxicity, subacute myelo-optic neuropathy (SMON).

Antibiotics

Tetracyclines. They are luminal amoebicides. The unabsorbed portion of older tetracyclines reaches colon and inhibits the bacterial flora, which are required for survival of *E. histolytica*.

Paromomycin. Paromomycin, an aminoglycoside, is a luminal amoebicide. It is not absorbed from the GI tract following oral administration. It alters the intestinal flora. Adverse effects like nausea, vomiting and abdominal pain can occur. Oral paromomycin is safe for use in pregnancy. It is also useful in kala-azar.

Treatment of Other Protozoal Infections PH1.47, PH1.55

Some of the protozoal infections with their clinical features, the preferred drug in those conditions with regimen and alternative drugs are mentioned in [Table 11.26](#).

Table 11.26 ■ Treatment of other protozoal infections

Disease and causative organism	Clinical features	Preferred drug, route and dose	Alternative drugs
Giardiasis: <i>Giardia lamblia</i>	Diarrhoea and flatulence	Metronidazole oral 200 mg t.d.s. for 7 days	• Tinidazole • Nitazoxanide • Furazolidone • Paromomycin

Table 11.26 ■ Treatment of other protozoal infections—cont'd

Disease and causative organism	Clinical features	Preferred drug, route and dose	Alternative drugs
Trichomoniasis: <i>Trichomonas vaginalis</i>	Itching and frothy discharge from vagina	Metronidazole oral 400 mg t.d.s. for 7 days. Both sex partners should be treated simultaneously	Tinidazole
*Leishmaniasis: (i) Visceral leishmaniasis (kala-azar): <i>L. donovani</i>	Fever, splenomegaly, hepatomegaly, lymphadenopathy, epistaxis and bleeding gums	• Liposomal Amphotericin B: single dose 10 mg/kg i.v. infusion • Inj paromomycin with miltefosine for 10 days	• Miltefosine (oral) - 28 days • Amphotericin B deoxycholate • Sodium stibogluconate if organism is sensitive
(ii) Cutaneous leishmaniasis	Papule, ulcers, depressed scar especially on face and hands	Liposomal Amphotericin B: 5 mg/kg/day i.v. infusion twice a week for 3 weeks (total dose 30 mg/kg)	• Miltefosine, oral • Amphotericin B deoxycholate
Toxoplasmosis: <i>T. gondii</i>	Congenital – fever, jaundice, diarrhoea, cataract, glaucoma, pneumonitis, myocarditis, hepatosplenomegaly	Pyrimethamine and sulphadiazine + folic acid orally	• Clindamycin • Pyrimethamine + azithromycin/clarithromycin/atovaquone • Spiramycin (pregnancy)
African trypanosomiasis or sleeping sickness – <i>Trypanosoma brucei</i>	Fever, lymphadenopathy, splenomegaly – later involvement of CNS and classical symptoms of sleeping sickness	• Suramin • Melarsoprol	Pentamidine

CNS, central nervous system.
*Treatment as per National kala azar elimination Program; WHO Technical Advisory board 2010.

Miltefosine (Oral). The exact mechanism of action in kala-azar is unknown. It interacts with lipids in the cell membrane of the parasite.

Sodium Stibogluconate (i.m./i.v.). It is a pentavalent antimonial compound. The mechanism of action in kala-azar is unknown. It is converted to a toxic compound which kills amastigotes within macrophages. Resistance has developed to this drug.

Pentamidine (i.v., i.m. and aerosol). It probably acts by inhibiting various enzymes, DNA and RNA synthesis in *Leishmania*. It is also effective against *P. jiroveci*.

Anthelmintics

PH1.47

Anthelmintics are drugs used in the treatment of infestation with helminths in the intestinal tract or tissues of the body (Table 11.27). Anthelmintics that kill worms are called *vermicides* and those that help to expel the worms are called *vermifuges*.

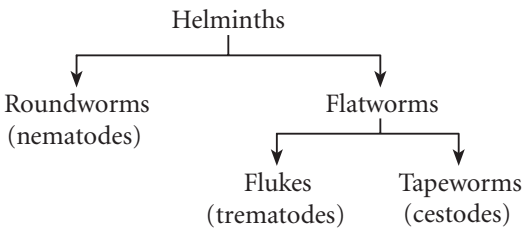


Table 11.27 ■ Drugs for the treatment of helminthiasis

Infestation and parasite	Drugs
1. Nematodes	
(a) Roundworm (<i>Ascaris lumbricoides</i>)	• Albendazole • Mebendazole • Pyrantel pamoate
(b) Hookworm (<i>Ancylostoma duodenale</i> , <i>Necator americanus</i>)	
(c) Pinworm (<i>Enterobius vermicularis</i>)	
(d) Whipworm (<i>Trichuris trichiura</i>)	• Albendazole • Mebendazole • Oxantel pamoate
(e) Threadworm (<i>Strongyloides stercoralis</i>)	• Ivermectin • Albendazole
(f) Mixed worm infestation	• Albendazole • Mebendazole • Pyrantel pamoate
(g) Filariasis (<i>Wuchereria bancrofti</i> , <i>Brugia malayi</i>), onchocerciasis (<i>Onchocerca volvulus</i>)	• Diethylcarbamazine (DEC) + albandazole • Ivermectin + albendazole
(h) Guinea worm (<i>Dracunculus medinensis</i>)	• Metronidazole
2. Trematodes	
(a) Blood flukes (schistosomes)	Praziquantel
(b) Intestinal flukes	
(c) Liver flukes	
(d) Lung flukes	
3. Cestodes	
(a) <i>Taenia saginata</i> (beef tapeworm)	• Praziquantel • Niclosamide
(b) <i>Taenia solium</i> (pork tapeworm)	
(c) <i>Diphyllobothrium latum</i> (fish tapeworm)	• Albendazole • Praziquantel
(d) <i>Hymenolepis nana</i> (dwarf tapeworm)	
(e) Neurocysticercosis (caused by <i>T. solium</i>)	
(f) Hydatid disease (<i>Echinococcus granulosus</i>)	• Albendazole • Mebendazole

DRUGS

■ Mebendazole	■ Albendazole ^a
■ Albendazole	■ Levamisole
■ Niclosamide	■ Praziquantel
■ Ivermectin	■ Diethylcarbamazine citrate
■ Pyrantel pamoate	

Note: Mnemonic – MANIPAL PD.

Mebendazole. Mebendazole is a benzimidazole and has a broad spectrum of anthelmintic activity. It binds to β -tubulin and inhibits microtubule polymerization. It also blocks glucose transport into the parasite. As a result, intestinal parasites are immobilized or die slowly.

Pharmacokinetics. Mebendazole is administered orally, poorly absorbed from the GI tract, highly bound to plasma proteins and metabolized in liver. Most of the oral dose is excreted in faeces.

Adverse Effects. Systemic toxicity of mebendazole is low because of its poor absorption. It is well tolerated and rarely causes GI side effects – anorexia, nausea, vomiting, diarrhoea and abdominal discomfort. Occasionally, it may cause skin rashes, itching, drug fever, etc. It is contraindicated in pregnancy and children younger than 1 year.

Uses. Mebendazole is highly effective against intestinal nematodes – roundworm, hookworm, whipworm, pinworm and mixed worm infestations. It is more effective than albendazole in trichuriasis.

Dose and Administration. Mebendazole 100 mg orally b.d. for 3 days. It does not require fasting or purging, is well tolerated and is relatively cheap.

Albendazole. It is also a benzimidazole and has a broad spectrum of anthelmintic activity. The mechanism of action is similar to that of mebendazole.

Pharmacokinetics. Albendazole is given orally. It is erratically absorbed – fatty food increases its absorption; it is metabolized in liver. It produces an active metabolite, albendazole sulphoxide, which is widely distributed into various tissues including hydatid cyst. Hence, albendazole is preferred to mebendazole in the treatment of hydatid disease.

Adverse Effects. Albendazole is very well tolerated. The side effects are rare, but can cause nausea, vomiting, diarrhoea and epigastric distress. During long-term therapy, it may cause hepatic dysfunction, headache, dizziness, fever, weakness, loss of hair and neutropenia.

Dose and Administration. It can be taken as a single oral dose of 400 mg for adults and children older than 2 years, and as 200 mg single dose for children between 1 and 2 years of age. It is taken at any time of the day, does not require fasting or purging and side effects are rare.

Uses

- 1. Nematodes:** Albendazole is highly effective against intestinal nematodes – roundworm, hookworm, whipworm, pinworm and threadworm – and also in mixed worm infestations. It is more effective than mebendazole in trichinosis.
- 2. Neurocysticercosis:** Both albendazole and praziquantel are highly effective in neurocysticercosis. But albendazole is preferred to praziquantel because of the following reasons:
 - (a) It is cheaper.
 - (b) Duration of treatment is shorter.

^aAlbendazole is highly active against many helminths, hence worth noting again.

- (c) It reaches high concentration in brain and CSF.
- (d) It is less toxic and better tolerated.
- (e) Glucocorticoids increase plasma levels of albendazole sulphoxide but decrease plasma praziquantel levels.

High doses of glucocorticoids are usually given with albendazole or praziquantel to minimize the inflammatory reactions to dying parasites. Drug treatment is contraindicated in ocular cysticercosis – blindness can occur due to inflammatory reaction.

3. Hydatid disease: In hydatid cyst, surgical resection is the treatment of choice, but albendazole is the drug of choice for medical therapy.

4. Filariasis: Single dose of (400 mg) albendazole is given with diethylcarbamazine citrate (DEC) or ivermectin in the treatment of lymphatic filariasis. Albendazole has adjuvant value.

Albendazole is also effective in cutaneous larva migrans.

Thiabendazole. A benzimidazole, thiabendazole has a broad spectrum of anthelmintic activity and is effective against most of the nematodes. The mechanism of action is similar to that of mebendazole and albendazole. It is rarely used because of high incidence of toxicity.

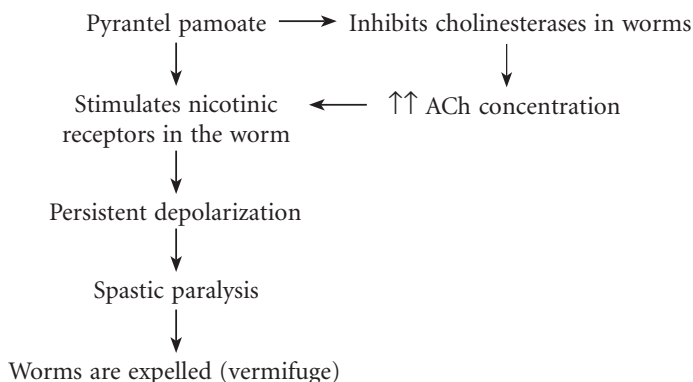
Piperazine. It is effective against roundworm and pinworm. It causes flaccid paralysis of worms that are later expelled by peristaltic movements. It is partly absorbed and most of the drug is excreted unchanged in urine.

Adverse Effects. The adverse effects include nausea, vomiting, abdominal pain, skin rashes and dizziness. It occasionally produces convulsions and is contraindicated in patients with epilepsy. It is safe for use during pregnancy.

Levamisole. It is effective against roundworm and hookworm infestations. It is an immunomodulator. It is also used as an adjunct in rheumatoid arthritis and cancer chemotherapy.

Pyrantel Pamoate. It is highly effective for the treatment of roundworm, pinworm and hookworm infestations. Oxantel pamoate is effective in trichuriasis.

Mechanism of Action



Pharmacokinetics. Pyrantel pamoate is given orally but absorbed poorly; about 80%–90% of oral dose is excreted in faeces.

Dose and Administration. It can be taken as a single oral dose of 11 mg/kg, does not require fasting or purging, is well tolerated and is relatively cheap.

Adverse Effects. These include nausea, vomiting, diarrhoea, headache, dizziness, skin rashes and fever. It is contraindicated in infants.

Diethylcarbamazine Citrate. Diethylcarbamazine is the most effective drug used in the treatment of filariasis and tropical eosinophilia caused by *W. bancrofti* and *B. malayi*. DEC is available as citrate salt. It acts mainly on microfilariae but the adult worms are killed slowly only on long-term treatment. DEC damages the microfilarial membrane structure so that they are destroyed by host defences.

Pharmacokinetics. It is well absorbed from the GI tract, widely distributed in the body, metabolized in liver and excreted in urine. DEC is safe for use during pregnancy.

Adverse Effects

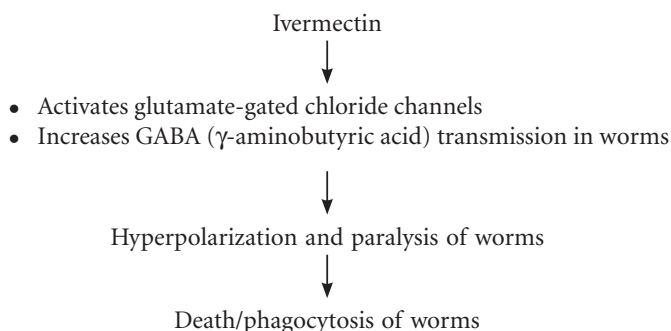
1. **Drug-induced effects:** These include anorexia, nausea, vomiting, headache and dizziness.
2. **Parasite-induced reactions:** These are due to the release of proteins from dying parasites. In *onchocerciasis*, DEC produces a severe reaction, which is termed 'Mazzotti' reaction. It is characterized by severe itching, fever, skin rashes, nausea, vomiting, headache, joint pain, lymphadenitis, keratitis and uveitis. Hence, DEC is not recommended in onchocerciasis. In *W. bancrofti*, the reaction is usually mild. This can be minimized by administering H₁-blockers. The reaction is treated with H₁-blockers and glucocorticoids.

Uses

1. **Filariasis:** Diethylcarbamazine is the drug of choice for the treatment of filariasis due to *W. bancrofti* and *B. malayi*. It is administered orally, 6 mg/kg/day in three divided doses for 3 weeks. (DEC 100 mg three times daily is taken after food for 3 weeks.) Addition of single dose of albendazole 400 mg to DEC produces sustained microfilaricidal effect. Diethylcarbamazine (300 mg) with albendazole (400 mg) is used to reduce transmission of filariasis.
2. **Tropical eosinophilia:** It is treated with DEC, 100 mg t.d.s. for 3 weeks. Antihistaminics and glucocorticoids may be required to control allergic reactions.

Ivermectin. It is the drug of choice in onchocerciasis and strongyloidiasis. It is effective against microfilaria of *W. bancrofti* and *B. malayi*.

Mechanism of Action



Pharmacokinetics. It is given orally, rapidly absorbed, widely distributed to various tissues, metabolized in liver and excreted mainly in faeces.

Uses

1. Ivermectin is the drug of choice for onchocerciasis. It kills microfilariae but has little effect on adult worms. It relieves pruritus and skin disease.
2. It is also very effective in strongyloidiasis, ascariasis and cutaneous larva migrans.
3. It is used orally in the treatment of scabies and pediculosis.
4. It is useful for mass chemotherapy of filariasis as single annual dose along with albendazole.

Adverse Effects. They are itching, skin rashes, oedema, headache, fever, muscle and joint pain. It can cause 'Mazzotti' reaction during treatment of filariasis. It is contraindicated in pregnancy and children.

Praziquantel. Praziquantel is effective in the treatment of trematodes and cestodes but not for nematodes.

Mechanism of Action

Praziquantel $\Rightarrow$ $\uparrow\uparrow$ influx of Ca^{2+} into the tegument $\Rightarrow$ increased muscular contraction and spastic paralysis

At higher concentration $\Rightarrow$ damages tegument $\Rightarrow$ death of the parasite

Pharmacokinetics. Praziquantel is readily absorbed after oral administration, undergoes extensive first-pass metabolism in liver, is highly bound to plasma proteins, crosses the BBB and is excreted mainly in urine.

Adverse Effects. The most common side effect is dizziness. Other side effects are nausea, vomiting, abdominal discomfort, headache, drowsiness, skin rashes, itching, muscle and joint pain.

Uses

1. **Schistosomiasis:** Praziquantel is the drug of choice for all species of schistosomes. Praziquantel 40 mg/kg, single oral dose usually produces a high cure rate. It is well tolerated and reasonably cheap.
2. **Tapeworm infestation:** A single oral dose of praziquantel gives a very high cure rate in all tapeworm infestations.
3. **Neurocysticercosis** (see under "Albendazole"): It is an alternative agent for neurocysticercosis.

Praziquantel is contraindicated in pregnancy and ocular cysticercosis.

Niclosamide. It is the second drug of choice for *T. saginata*, *D. latum* and *H. nana*. It is poorly absorbed from the GI tract. It inhibits oxidative phosphorylation in the mitochondria of the parasite and rapidly kills adult worms but not the ova. It is given orally in the form of chewable tablets.

Adverse Effects. Niclosamide produces few minor side effects. They are nausea, vomiting, diarrhoea, headache, skin rashes, itching and abdominal discomfort.

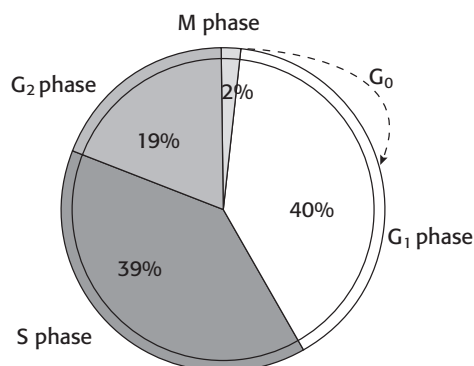


Fig. 11.16 Cell cycle kinetics.

Anticancer Drugs

PH1.49

Cancer is a disease of cells characterized by **Progressive, Persistent, Purposeless** and uncontrolled **Proliferation** of tissues.

Both normal and cancerous cells must pass through the following phases of cell cycle (Fig. 11.16):

1. **G₁ phase (presynthetic phase):** Synthesis of enzymes and other cellular components needed for DNA synthesis.
2. **Synthetic phase (S phase):** DNA synthesis takes place.
3. **G₂ phase (premitotic phase):** Synthesis of cellular components for mitosis (proteins and RNA synthesis).
4. **Mitotic phase (M phase):** Mitotic cell division takes place.
5. **G₀ phase (resting phase):** Cells stop dividing temporarily or permanently.

Cell cycle-specific (CCS) or phase-specific drugs

Antimetabolites: Methotrexate, 6-mercaptopurine (6-MP)
Antibiotic: Bleomycin
Taxane: Paclitaxel
Epipodophyllotoxins: Etoposide, teniposide
Vinca alkaloids: Vinblastine, vincristine



CCS drugs act mainly on dividing cells

Cell cycle-nonspecific (CCNS) or phase-nonspecific drugs

Alkylating agents: Cyclophosphamide, busulphan, mechlorethamine, melphalan
Anticancer antibiotics: Doxorubicin, daunorubicin, mitomycin, actinomycin D
Metal complexes: Cisplatin, carboplatin



CCNS drugs act on dividing as well as resting cells

CLASSIFICATION OF ANTICANCER DRUGS

Major groups of anticancer drugs

1. Alkylating agents

- (a) Nitrogen mustards: Mechlorethamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil
- (b) Alkyl sulphonate: Busulphan
- (c) Nitrosoureas: Carmustine, lomustine
- (d) Triazene: Dacarbazine

2. Platinum-containing compounds: Cisplatin, carboplatin, oxaliplatin.

3. Antimetabolites

- (a) Folate antagonist: Methotrexate
- (b) Purine antagonists: 6-Mercaptopurine (6-MP), 6-thioguanine (6-TG), azathioprine
- (c) Pyrimidine antagonists: 5-FU, cytarabine, capecitabine, gemcitabine.

4. Vinca alkaloids: Vinblastine, vincristine

5. Taxanes: Paclitaxel, docetaxel

6. Epipodophyllotoxins: Etoposide, teniposide

7. Camptothecins: Topotecan, irinotecan

8. Antibiotics: Actinomycin D, bleomycin, mitomycin C, doxorubicin, daunorubicin

9. Enzyme: L-Asparaginase

10. Miscellaneous agents: Hydroxyurea, imatinib

11. Hormones and antagonists

- (a) Oestrogens: Ethinyl estradiol, fosfestrol
- (b) Selective oestrogen receptor modulators (SERMs): Tamoxifen
- (c) Selective oestrogen receptor downregulators (SERDs): Fulvestrant
- (d) Aromatase inhibitors: Anastrozole, letrozole
- (e) Progestins: Hydroxyprogesterone caproate, medroxyprogesterone acetate
- (f) Antiandrogen: Flutamide
- (g) 5 α -Reductase inhibitor: Finasteride
- (h) GnRH analogues: Buserelin, goserelin, nafarelin
- (i) Corticosteroids: Prednisolone and others

(Natural products: Vincristine, vinblastine, paclitaxel (from plants), doxorubicin, daunorubicin, mitomycin, L-asparaginase from micro-organisms)

- | |
|----------------------------------|
| 1. Alkylating agents |
| 2. Platinum-containing compounds |
| 3. Antimetabolites |
| 4. Natural products |
| • Vinca alkaloids |
| • Epipodophyllotoxins |
| • Taxanes |
| • Antibiotics |
| • Camptothecins |
| • Enzymes |
| 5. Miscellaneous agents |
| • Hydroxyurea |
| • Imatinib |
| 6. Hormones and antagonists |

TOXICITY OF ANTICANCER DRUGS (CYTOTOXIC DRUGS)

While destroying cancer cells, anticancer drugs also affect rapidly proliferating normal cells. Bone marrow, skin, hair, GI mucosa, reticuloendothelial system, gonads, fetus, etc., are most severely affected.

1. General toxicity

- (a) **Bone marrow suppression:** It manifests as leucopenia, agranulocytosis, thrombocytopenia and aplastic anaemia. In such patients, infection and bleeding are common.

It is ameliorated/reduced by:

- (i) Platelet transfusion
- (ii) Granulocyte colony-stimulating factor (G-CSF)

- (iii) Erythropoietin
- (iv) Bone marrow transplantation
- (v) Using bone marrow-sparing drugs if possible (e.g. L-asparaginase, bleomycin, cisplatin and vincristine)
- (b) **Immunosuppression:** Decreased lymphocytes result in immunosuppression. Such patients are prone to opportunistic infections with fungi, bacteria, viruses and parasites (*P. jiroveci*, *Candida*, cytomegalovirus, etc.).
- (c) **GIT:** Nausea and vomiting are due to central action (stimulation of CTZ) and peripheral action in the GI tract. Most of the cytotoxic drugs cause vomiting. Cisplatin has the most emetogenic potential. 5-HT₃ antagonists, such as ondansetron and granisetron, are the commonly used antiemetics. The other antiemetics are metoclopramide and dexamethasone. Stomatitis, oral mucositis, diarrhoea, GI bleeding and ulcers are due to necrosis of rapidly dividing epithelial cells of gut mucosa.
- (d) **Skin and hair:** Alopecia (loss of hair) is due to the damage to hair follicles. It is usually reversible on stoppage of therapy. Dermatitis and skin rashes too can occur.
- (e) **Gonads:** Cytotoxic drugs also affect gonadal cells and cause oligozoospermia and infertility in males, and amenorrhoea and infertility in females.
- (f) **Fetus:** Administration of cytotoxic drugs during pregnancy usually causes abortion or teratogenic effects.
- (g) **Hyperuricaemia:** Gout and urate stones in the urinary tract are due to excessive cell destruction. They are prevented by good hydration, allopurinol and corticosteroids.
- (h) **Hypercalcaemia:** It may be due to either the malignancy or certain anticancer drugs. It is treated with adequate hydration, bisphosphonates, corticosteroids, etc.
- (i) **Carcinogenicity (secondary malignancy):** These drugs may rarely cause secondary cancers in some patients, e.g. development of leukaemia in patients with prolonged use of alkylating agents.
- (j) **Mutagenicity.**
- 2. **Specific toxicity**
 - (a) **Haemorrhagic cystitis** with cyclophosphamide: Ameliorated by administering mesna systemically and acetylcysteine locally.
 - (b) **Megaloblastic anaemia** with methotrexate: Ameliorated by folinic acid/leucovorin/citrovorum factor.
 - (c) **Nephrotoxicity** with cisplatin: Saline infusion and mannitol reduce the incidence of nephrotoxicity.
 - (d) **Neuropathy** with vincristine and paclitaxel.
 - (e) **Pulmonary** fibrosis and pigmentation of skin with busulphan and bleomycin.
 - (f) **Cardiotoxicity** with doxorubicin and daunorubicin. An iron chelating agent, dexrazoxane, is useful in reducing the toxicity.

Alkylating Agents

All alkylating agents have alkyl group(s) and are capable of introducing these groups into nucleophilic sites on DNA bases through the formation of covalent bonds. Alkylating agents are CCNS drugs. They also have radiomimetic effect.

Mechanism of Action

Alkylating agents (except platinum containing compounds)



Form highly reactive carbonium ion



Transfer of 'alkyl' group(s) to various sites on DNA



Results in



- Cross-linkage (inhibits DNA replication)
- Abnormal base pairing (alkylated guanine base pairs with thymine rather than with cytosine and results in production of defective protein)
- Break in the DNA strands



Cell death

Alkylating agents can also bind to proteins and damage them.

Nitrogen Mustards

Cyclophosphamide. Cyclophosphamide is a prodrug and is activated in liver (Fig. 11.17). The final active metabolites derived from cyclophosphamide are phosphoramidate mustard and acrolein. Phosphoramidate mustard produces cytotoxic effect and acrolein is responsible for haemorrhagic cystitis.

Cyclophosphamide is administered orally or intravenously. The metabolites are excreted mainly in urine.

Adverse Effects. Cyclophosphamide can cause general toxicity (see p. 460). The specific toxicity of cyclophosphamide is severe haemorrhagic cystitis. It is associated with dysuria and haematuria due to irritation of bladder mucosa by acrolein. It is a

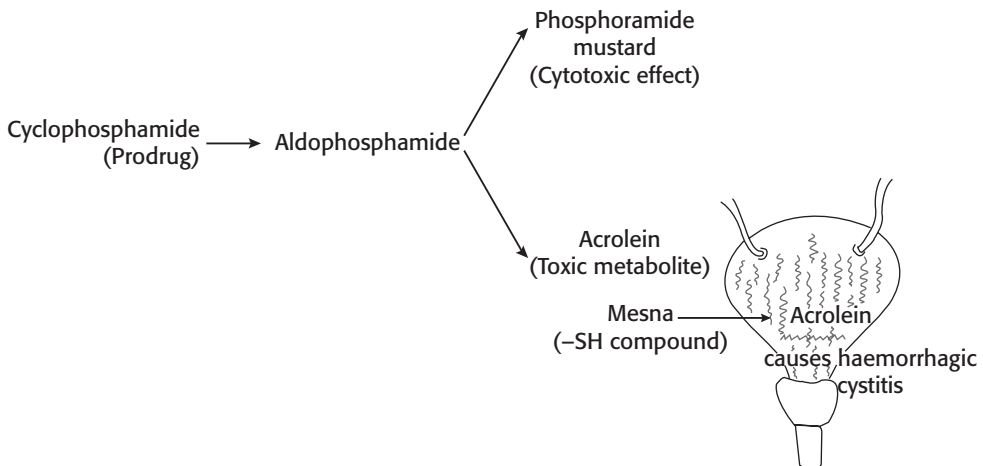


Fig. 11.17 Cyclophosphamide and haemorrhagic cystitis.

dose-limiting toxicity and can be reduced by adequate hydration and coadministration of i.v. mesna (2-mercaptoethane sulphonate). Mesna is also excreted in urine where it binds and inactivates acrolein, thus prevents haemorrhagic cystitis.

Uses. Cyclophosphamide is used in combination with other anticancer agents in the treatment of lymphomas, chronic lymphocytic leukaemia (CLL), breast cancer, etc. It also has a powerful immunosuppressant effect, hence is useful in rheumatoid arthritis, nephrotic syndrome and to prevent as well as to treat graft rejection during organ transplantation.

Ifosfamide is a congener of cyclophosphamide and is administered intravenously. It is useful in the treatment of testicular cancer and sarcomas.

Mechlorethamine. It is one of the components of MOPP (nitrogen mustard, Oncovin, prednisone and procarbazine) regimen for Hodgkin disease. It is a highly irritant drug so care should be taken to avoid extravasation during i.v. administration.

Chlorambucil. It is a slow-acting nitrogen mustard. Its main action is on lymphoid series and it produces marked lympholytic effect. It is given orally and was the standard treatment for CLL.

Melphalan. It is highly effective in multiple myeloma and is used in combination with other agents.

Alkyl Sulphonates

Busulphan. It depresses bone marrow with selective action on myeloid series. It was the preferred drug for chronic myeloid leukaemia (CML). The common side effects are pigmentation of the skin, interstitial pulmonary fibrosis and hyperuricaemia.

Nitrosoureas

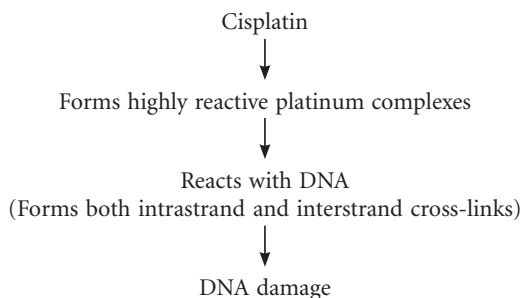
Carmustine and lomustine are highly lipid soluble drugs, hence reach high concentration in the CSF. Nitrosoureas are mainly used in brain tumours.

Procarbazine. It is an alkylating agent. It damages DNA and is a component of MOPP regimen for Hodgkin disease.

Platinum-Containing Compounds

Cisplatin. It is a heavy-metal complex with a highly effective antineoplastic activity. It is a CCNS drug and acts on both dividing and resting cells. Cisplatin is administered intravenously. It is highly bound to plasma proteins and gets concentrated in kidney, liver, intestine and testes. It poorly penetrates BBB and is slowly excreted in urine.

Mechanism of Action. Inside the cell:



Cisplatin is highly effective in the treatment of testicular, ovarian, endometrial and bladder cancer. It is also used in lung and oesophageal cancer.

Adverse Effects. Cisplatin is the most emetogenic anticancer drug. Nausea and vomiting can be controlled by 5-HT₃ antagonists, such as ondansetron or granisetron.

Nephrotoxicity: It can be minimized by proper hydration.

Ototoxicity with hearing loss can occur and is severe with repeated doses.

Electrolyte disturbances: Hypokalaemia, hypocalcaemia and hypomagnesaemia are common. Neuropathy is commonly seen with higher doses. Anaphylactic shock may rarely occur. Cisplatin has mutagenic, teratogenic and carcinogenic properties.

Carboplatin. The mechanism of action is similar to that of cisplatin. It is better tolerated than cisplatin. It causes less nausea, ototoxicity and nephrotoxicity than cisplatin.

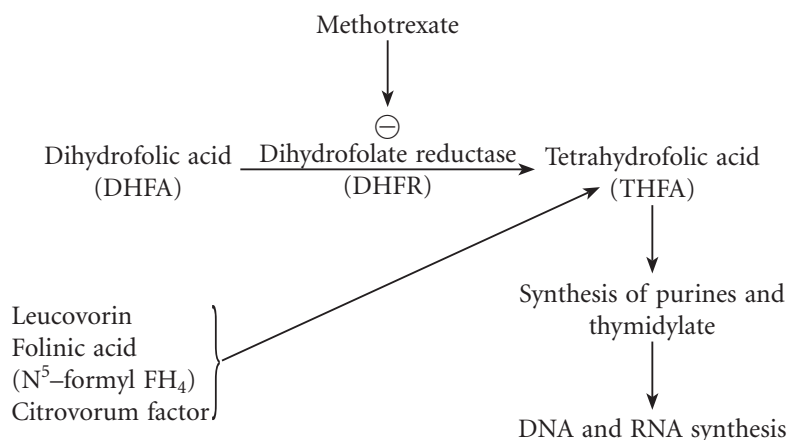
Oxaliplatin. It is effective in colorectal and gastric cancer. Peripheral neuropathy is an important adverse effect.

ANTIMETABOLITES

Folate Antagonist

Methotrexate. MTX is one of the most commonly used anticancer drugs. It is a CCS drug and acts during S phase of the cell cycle. It has antineoplastic, immunosuppressant and anti-inflammatory effects.

Mechanism of Action



MTX structurally resembles folic acid. It competitively inhibits dihydrofolate reductase enzyme and prevents the conversion of dihydrofolic acid (DHFA) to THFA, thus depletes the intracellular THFA. THFA is necessary for the synthesis of purines and thymidylate which, in turn, are necessary for DNA and RNA synthesis.

MTX is well absorbed after oral administration; it can also be given i.m., i.v. or intrathecally. It is bound to plasma proteins; it poorly crosses the BBB and most of the drug is excreted unchanged in urine.

MTX is the drug of choice for choriocarcinoma. It is also used in acute leukaemias, Burkitt lymphoma and breast cancer.

Low-dose MTX 7.5–25 mg once weekly is used for rheumatoid arthritis. It prevents joint erosion. It has anti-inflammatory and immunosuppressant effects. It is also used in psoriasis, inflammatory bowel disease and organ transplantation.

Adverse Effects. See general toxicity (p. 460). Other adverse effects are megaloblastic anaemia, pancytopenia, hepatic fibrosis, etc.

Drug Interactions. Salicylates/sulphonamides/tetracyclines $\times$ MTX: These drugs displace MTX bound to plasma proteins and increase its free form in plasma leading to its toxicity.

NSAIDs and sulphonamides potentiate MTX toxicity by interfering with its excretion.

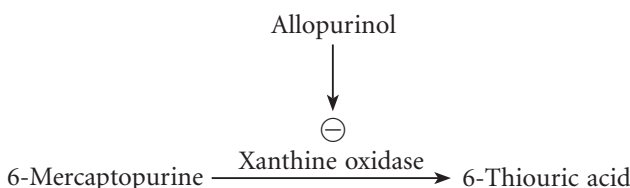
Folinic Acid Rescue/Leucovorin Rescue. The toxic effects of MTX on normal cells can be minimized by giving folinic acid. Availability of folinic acid has helped the use of very high doses of MTX for a better antineoplastic effect. After a few hours of MTX therapy, leucovorin is given. Folinic acid is the active coenzyme form. It bypasses the block produced by MTX and rapidly reverses the toxicity. This method is called leucovorin rescue/folinic acid rescue.

Pemetrexed: It affects thymidylate synthase more than dihydrofolate reductase. Hand-foot syndrome can occur.

Purine Antagonists: 6-Mercaptopurine and 6-Thioguanine

6-MP and 6-TG are activated to their ribonucleotides which inhibits purine ring biosynthesis and nucleotide interconversion. They are CCS drugs and act in S phase of cell cycle. 6-MP also has immunosuppressant action.

6-MP is administered orally and has poor penetration through BBB. It is metabolized by xanthine oxidase and its metabolite is excreted in urine.



Allopurinol interferes with the metabolism of 6-MP by inhibiting the enzyme xanthine oxidase and increases the antineoplastic effect of 6-MP. Therefore, allopurinol is frequently used in cancer patients receiving chemotherapy to prevent hyperuricaemia and to reduce the dose of 6-MP, thus reducing its toxicity. 6-MP is used mainly in acute lymphocytic leukaemia. Bone marrow depression is the major adverse effect of 6-MP.

Pyrimidine Antagonists

Fluorouracil (5-FU). 5-FU is activated to fluorodeoxyuridine monophosphate (FdUMP) (Fig. 11.18). This interferes with DNA synthesis and functions by inhibiting thymidylate synthetase enzyme.

It is used in colorectal, upper GIT, breast and ovarian carcinomas.

Capecitabine. It is a prodrug of 5-FU. It is useful in metastatic breast and colorectal cancer. Hand-foot syndrome is an important adverse effect.

Cytarabine. It inhibits DNA synthesis. It is used in leukaemias and lymphoma.

Plant Products

Vinca Alkaloids. Vinblastine and vincristine are derived from the periwinkle plant. They are CCS agents and act during M phase of cell cycle. Vinblastine and vincristine have the same mechanism of action but differ in antitumour spectrum and toxicity (Table 11.28).

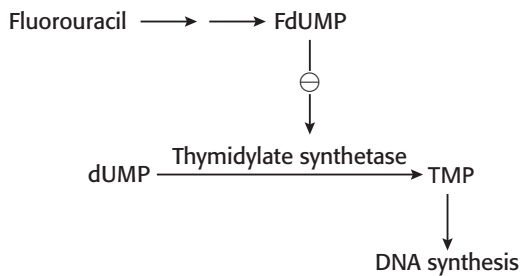
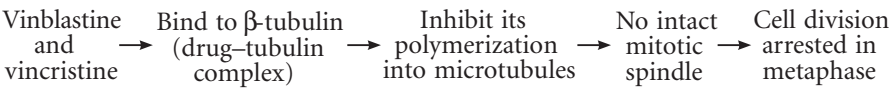


Fig. 11.18 Mechanism of action of fluorouracil.

Table 11.28 ■ Uses and adverse effects of vinca alkaloids

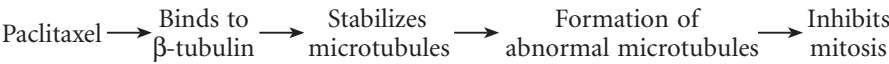
Vinblastine	Vincristine
Uses: Hodgkin disease Carcinoma of Breast Testicular tumours	Uses: Childhood leukaemias Childhood tumours – Wilms tumour, neuroblastoma Hodgkin disease
Toxicity: Bone marrow suppression, anorexia, nausea, vomiting and diarrhoea	Toxicity: Peripheral neuritis with paraesthesia, constipation. Vincristine has minimal myelosuppressive action

Mechanism of Action



Taxanes. Paclitaxel is a taxane derived from the bark of the western yew tree. Docetaxel is a newer taxane.

Mechanism of Action



Paclitaxel is administered by i.v. infusion. It is useful in advanced breast, ovarian, lung, oesophageal and bladder cancer. The unwanted effects are bone marrow suppression, peripheral neuropathy, myalgia and hypersensitivity reactions.

Camptothecins

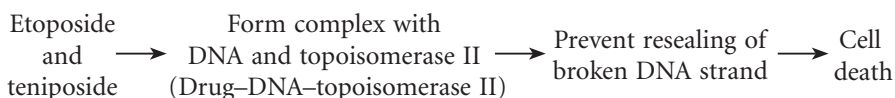
Topotecan and irinotecan are camptothecin analogues.

Mechanism of Action. Camptothecins bind to and stabilize DNA–topoisomerase I complex and inhibit the resealing function (the strand-breaking action is not affected), thus producing cell death. They are used in advanced ovarian, lung and colorectal cancer. The common side effects are bone marrow suppression and GI disturbances.

Epipodophyllotoxins

They act in S–G₂ phases of cell cycle.

Mechanism of Action



Etoposide is used in testicular and lung cancers in combination with other cytotoxic drugs. It is also effective in non-Hodgkin lymphoma and AIDS-related Kaposi sarcoma. The side effects are bone marrow suppression and GI side effects such as nausea, vomiting and diarrhoea. Hepatotoxicity is seen with high doses.

Anticancer Antibiotics

Mechanism of Action. Anticancer antibiotics have a direct action on DNA. Dactinomycin, doxorubicin and daunorubicin bind to DNA through intercalation between adjoining nucleotide pairs on the same strand of DNA and block transcription of DNA. Bleomycin binds to DNA and produces free radicals which cause DNA damage.

Actinomycin D. It is administered intravenously. It is mainly used in the treatment of Wilms tumour, Ewing sarcoma and choriocarcinoma. Bone marrow suppression and GI side effects are prominent.

Mitomycin C. It is converted to a compound which acts as an alkylating agent. It is used in the treatment of GI tumours, cervix and bladder cancer. It produces mainly bone marrow suppression, GI side effects and nephrotoxicity.

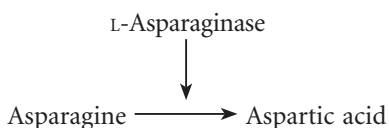
Bleomycin. It can be administered through s.c., i.m. and i.v. routes. It is used in the treatment of testicular and ovarian tumours and in Hodgkin lymphoma (ABVD* regimen). Its main side effects are hyperpigmentation of the skin and pulmonary fibrosis. There is very little bone marrow suppression (sparing bone marrow).

Doxorubicin and Daunorubicin. Daunorubicin is effective in acute leukaemias; doxorubicin is active against solid tumours. The side effects are bone marrow suppression, GI disturbances and cardiomyopathy with CCF, hypotension or arrhythmias.

Mithramycin. It is an anticancer antibiotic that reduces serum calcium levels by inhibiting osteoclasts. It is used in the treatment of hypercalcaemia with bone metastasis.

Enzyme

L-Asparaginase. It is an enzyme that is isolated from bacteria, *E. coli*. Asparagine is an amino acid which is necessary for protein synthesis. Normal cells can synthesize asparagine because they contain asparagine synthetase enzyme. Cancer cells lack this enzyme, so they depend on exogenous source – plasma.



*Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine

L-Asparaginase degrades asparagine (in plasma) to aspartic acid. Hence, neoplastic cells are deprived of asparagine, resulting in cell death. It is used in the treatment of acute lymphoblastic leukaemia (ALL).

Toxicity

- 1. Hypersensitivity reaction with skin rashes; itching, urticaria, etc.
- 2. Hyperglycaemia: Due to insulin deficiency
- 3. Headache, Hallucinations, confusion and coma
- 4. Haemorrhage: Due to inhibition of synthesis of clotting factors
- 5. Pancreatitis

Miscellaneous Agents

Hydroxyurea. Hydroxyurea acts in the S phase of cell cycle (CCS drug).

Mechanism of Action. Hydroxyurea interferes with the conversion of ribonucleotide to deoxyribonucleotide by inhibiting ribonucleoside diphosphate reductase. This results in inhibition of DNA synthesis. It is used mainly in CML, polycythaemia vera and psoriasis. The common side effects are bone marrow suppression with leucopenia, anaemia and thrombocytopenia.

Other anticancer drugs are shown in [Table 11.29](#).

Table 11.29 ■ Targeted drugs for cancer

Drug	Use	Adverse effects
<i>Tyrosine kinase inhibitor</i> Imatinib: (–) Tyr kinase of chronic myeloid leukaemia (CML) cells	CML	Vomiting, abdominal pain
<i>Angiogenesis inhibitor</i> • Bevacizumab (vascular endothelium growth factor inhibitor): binds to VEGF and blocks its binding to receptor • Sorafenib (VEGF inhibitor)	• Renal cell cancer • Lung cancer • Breast cancer Hepatocellular carcinoma	Hypertension, thrombo-embolism, bleeding Anorexia, hypertension
<i>Epidermal growth factor receptor inhibitor</i> Gefitinib: (–) cellular growth and proloiferation	Non-small cell lung cancer	Rash, diarrhoea
<i>Proteasome inhibitor</i> Bortezomib: Binds proteasome ↓ (–) proteolytic activity ↓ (–) cell proliferation (+) apoptosis	Multiple myeloma	Peripheral neuropathy
<i>Monoclonal antibodies</i> Rituximab: Binds to antigen on surface of B lymphocytes and B cell lymphoma	B cell lymphoma	Infusion reaction

CML, chronic myeloid leukaemia.

Hormones and Hormone Antagonists

1. **Glucocorticoids:** Because of their marked lympholytic action, they are used in acute leukaemias and lymphomas. Apart from this effect, glucocorticoids:
 - (a) Have anti-inflammatory effect, decrease oedema associated with the tumour
 - (b) Produce feeling of well-being
 - (c) Suppress hypersensitivity reaction due to certain anticancer drugs
 - (d) Control hypercalcaemia
 - (e) Increase the antiemetic effect of ondansetron/granisetron/metoclopramideBecause of the above effects, glucocorticoids are useful in the treatment of various cancers.
2. **Oestrogens:** The oestrogens are physiological antagonists of androgens. Hence, they are used to antagonize the effects of androgens in androgen-dependent prostatic tumours. Fosfestrol is a prodrug which is activated to stilboestrol in prostatic tissue. It achieves high concentration in prostatic tissue, therefore is preferred in carcinoma of prostate.
3. **Tamoxifen:** This is an antioestrogen mainly used in the palliative treatment of hormone-dependent breast carcinoma.
4. **Progestins:** The progestins are useful in endometrial carcinoma.
5. **Antiandrogens:** Flutamide is a nonsteroidal agent that blocks the action of androgen at the receptor level.
6. **Finasteride:** This blocks the conversion of testosterone to dihydrotestosterone by inhibiting 5α -reductase.

Both flutamide and finasteride are useful for the palliative treatment of advanced carcinoma of prostate. Finasteride is also effective in BPH.
7. **Aromatase inhibitors:** They are used in hormone-dependent breast cancer in postmenopausal women.
8. **GnRH agonists:** The pulsatile administration of these agents (buserelin, goserelin, leuprolide, etc.) produces a rise in follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Continuous administration, however, suppresses the pituitary gonadotropins by downregulating GnRH receptors. These agents produce palliative effects in advanced prostatic and breast cancers.

Miscellaneous Drugs

Chelating Agents

PH1.53

Chelating agents combine with metallic ions to form ring structures that are water-soluble complexes and are rapidly excreted from the body. These agents are used in heavy metal poisoning. Various chelating agents are (Table 12.1):

- Dimercaprol (British anti-Lewisite [BAL]).
- Disodium edetate (Na_2EDTA).
- Calcium disodium edetate (CaNa_2EDTA).
- Desferrioxamine
- Deferiprone
- Deferasirox
- D-Penicillamine

An **ideal chelating agent** should (a) be highly water soluble, (b) neither metabolized nor stored in the body, (c) be readily excreted in urine and (d) have low affinity for calcium.

Table 12.1 ■ Summary of chelating agents

Drug	ROA	Uses	Other points
British anti-Lewisite – BAL (Dimercaprol)	i.m.	Bi, As, Pb (Lead), Hg (mercury) , Au, Cu poisoning	Contraindications: Iron and cadmium poisoning
Disodium edetate	i.v.	Hypercalcaemia, as an anticoagulant <i>in vitro</i>	—
Calcium disodium edetate	i.v. infusion	Lead, Zn, Mn, Cu poisoning	Not suitable for mercury poisoning
Desferrioxamine	i.v., i.m.	Chronic iron (Fe) poisoning (i.m.), acute iron poisoning (i.v.)	Low affinity for calcium. Contraindications: Pregnancy, renal insufficiency
Deferiprone	Oral	Transfusion siderosis in thalassaemia, acute iron poisoning	—
Deferasirox	Oral	Chronic iron overload	—
D-Penicillamine	Oral	Cu, Hg, Zn, lead poisoning Other uses: Wilson's disease, scleroderma, cystinuria and rheumatoid arthritis	—

ROA, route of administration.

DIMERCAPROL

It was developed as an antidote for arsenic containing war gases, such as lewisite during World War II. The sulphhydryl (SH) groups of dimercaprol (BAL) react with metals to form a complex. It is administered intramuscularly. It is used in arsenic, mercury, gold and bismuth poisoning; also used as an adjuvant in copper and lead poisoning.

Adverse Effects. Nausea, vomiting, headache, fever, salivation, rise in BP, tachycardia and pain at the site of injection.

Succimer (2,3-dimercaptosuccinic acid, DMSA) and unithiol (DMPS) are analogues of dimercaprol. They are effective orally, less toxic and are used in the treatment of arsenic, mercury and lead poisoning.

DISODIUM EDETATE

On intravenous (i.v.) administration, it chelates calcium and causes hypocalcaemic tetany. It can be used in the treatment of hypercalcaemia and as an anticoagulant in vitro.

CALCIUM DISODIUM EDETATE

It is preferred in the treatment of lead poisoning, as it does not deplete calcium. Calcium in the chelating agent is exchanged with heavy metal. It can also be used in zinc, copper and manganese poisoning. It is infused intravenously.

Adverse Effects. Calcium EDTA is toxic to kidney. The other side effects are fatigue, fever, myalgia, headache, nausea, vomiting, etc.

DEFERRIOXAMINE (DEFEROXAMINE)

It is an iron-chelating agent. It is not effective orally as it is poorly absorbed from gastrointestinal tract (GIT). It is administered parenterally (i.m./i.v.). It chelates iron from haemosiderin and ferritin, but does not affect iron in haemoglobin or cytochrome. Affinity for calcium is low. Intravenous desferrioxamine is the drug of choice for acute iron poisoning. It can be used intravenously to chelate aluminium during dialysis. It is used intramuscularly for chronic iron poisoning (thalassaemia).

Adverse Effects. It includes various allergic reactions, such as skin rashes, itching, flushing and anaphylaxis. Other adverse effects are diarrhoea, dyspnoea, dysuria, hypotension and tachycardia. It can cause neurotoxicity on long-term use. It is contraindicated in pregnancy and renal insufficiency.

DEFERIPRONE

It is an orally effective iron-chelating agent. It is used in the treatment of transfusion siderosis in thalassaemia and acute iron poisoning (less effective than desferrioxamine).

Adverse Effects. Anorexia, nausea, vomiting, joint pain and rarely agranulocytosis.

DEFERASIROX

It is administered orally in chronic iron overload. Nausea, rash and epigastric distress are some of its adverse effects.

D-PENICILLAMINE

It is a degradation product of penicillin, hence it may have cross-reactivity with penicillins. It is effective in copper, mercury, zinc and lead poisoning. Other uses are Wilson disease, scleroderma, cystinuria and rheumatoid arthritis.

Wilson's disease is characterized by the accumulation of copper in many tissues and organs due to a decrease in serum ceruloplasmin. D-Penicillamine is used in Wilson's disease as it chelates copper and promotes its excretion. Life-long therapy is required.

Adverse Effects. Skin rashes, pruritus, urticaria, pemphigoid lesions, pyrexia, etc.

Immunosuppressants and Immunostimulants

PH1.50

IMMUNOSUPPRESSANTS

They are drugs that suppress the immune response; they inhibit cell-mediated/humoral immunity or both. Their main therapeutic application is in autoimmune diseases and organ transplantation.

Classification (Table 12.2)

1. *Calcineurin inhibitors*: Cyclosporine and tacrolimus
2. *Antiproliferative and cytotoxic agents*: Azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil
3. *mTOR (mammalian target of rapamycin) inhibitor*: Sirolimus, temsirolimus, everolimus
4. *Glucocorticoids*: Prednisolone, methylprednisolone
5. *Biologics*
 - a. TNF- α inhibitors: Etanercept, infliximab
 - b. Interleukin (IL-1) inhibitors: Anakinra
 - c. Antibodies: Muromonab-CD3, daclizumab, basiliximab, antithymocyte antibody and Rho (D) immunoglobulin

Details of some of the immunosuppressants are given in Table 12.2.

Drug Interactions

- Cyclosporine $\times$ aminoglycosides/amphotericin B/vancomycin/NSAIDs: Nephrotoxicity is enhanced.
- Cyclosporine $\times$ rifampicin/phenobarbitone/phenytoin: The blood level of cyclosporine is reduced due to induction of its metabolism.
- Cyclosporine $\times$ erythromycin: The plasma level of cyclosporine is increased as its metabolism is inhibited by erythromycin.
- Cyclosporine $\times$ potassium sparing diuretics: Severe hyperkalaemia can occur.

Tacrolimus: Drug interactions are similar to cyclosporine.

IMMUNOSTIMULANTS

They are drugs that enhance the immune response. Some of the immunostimulants and their uses are given in Table 12.3.

Thalidomide. It has immunomodulatory and anti-inflammatory properties. It enhances cell-mediated immunity (CMI) and IL production; decreases TNF- α and inhibits angiogenesis. It is useful to treat lepra reaction (erythema nodosum leprosum), multiple myeloma, Crohn disease, graft versus host disease, etc. Peripheral neuropathy is an important adverse effect. It is teratogenic.

Lenalidomide is an analogue of thalidomide. It is used in multiple myeloma.

Table 12.2 ■ Immunosuppressive agents

Immunosuppressant	MOA	ROA	Uses	Adverse effects
1. Calcineurin inhibitors				
Cyclosporine It is a polypeptide Source: <i>Beauveria nivea</i>	Enters target cells → binds to cyclophilin (intracellular protein) → cyclosporine-cyclophilin complex → inhibits calcineurin (phosphatase) → blocks activation of T cells by antigen; decreased production of IL-2 and other cytokines → ↓ cell-mediated immunity	Oral, i.v., i.v. infusion	To prevent and treat rejection episodes in organ transplantation: kidney, bone marrow, liver, etc. Autoimmune diseases: myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, etc.	Nephrotoxicity, hepatotoxicity, hypertrophy of gums, hypertension, hyperglycaemia, hyperlipidaemia, hirsutism, increased susceptibility to infections. Bone marrow toxicity is minimal (Note: 'h')
Tacrolimus	Binds to a different intracellular protein but mechanism similar to cyclosporine	Oral, parenteral, topical	Same as cyclosporine	Same as cyclosporine
2. Antiproliferative and cytotoxic agents				
Azathioprine	• Taken up into immune cells → activated to 6-MP → inhibits purine synthesis • Suppresses cell-mediated and humoral immune responses	Oral, i.v.	Used in combination with glucocorticoids or cyclosporine for prevention of rejection episodes in organ transplantation, rheumatoid arthritis, Crohn disease, etc.	Bone marrow suppression, hepatotoxicity, alopecia and gastrointestinal side effects
Methotrexate	• Decreases cytokine production and cell-mediated immunity • Has marked immunosuppressant and anti-inflammatory actions	Oral, parenteral	Autoimmune diseases: rheumatoid arthritis, myasthenia gravis, psoriasis, pemphigus, etc.	Mucositis, megaloblastic anaemia, hepatotoxicity

Continued

Table 12.2 ■ Immunosuppressive agents—cont'd

Immunosuppressant	MOA	ROA	Uses	Adverse effects
Cyclophosphamide	Has more effect on B cells and suppresses humoral immunity	Oral, i.v.	Autoimmune disorders: multiple sclerosis, autoimmune haemolytic anaemia and rarely in organ transplantation	Alopecia, cystitis
Mycophenolate mofetil	Prodrug, is converted to mycophenolic acid (active) - Lymphocyte proliferation and its functions are inhibited - Both CMI and humoral immunity are suppressed	Oral	In renal transplantation along with glucocorticoids and cyclosporine	Leucopenia, diarrhoea, vomiting, infections (CMV), etc.
3. mTOR (Mammalian target of rapamycin) inhibitor				
Sirolimus, Everolimus	Bind to intracellular protein → complex formed → inhibits interleukin (IL)-mediated T-cell proliferation	Oral	To prevent and treat graft rejection reactions	Bone marrow suppression, hepatotoxicity; does not cause nephrotoxicity
4. Glucocorticoids				
Prednisolone, methylprednisolone and others	Inhibit proliferation of T-lymphocytes and decrease ILs. Cell-mediated immunity (CMI) is mainly depressed. Have marked immunosuppressant and anti-inflammatory actions.	Oral, parenteral	To prevent and treat rejection episodes during organ transplantation; autoimmune diseases	Cushing habitus, osteoporosis, infections, hyperglycaemia, etc.

5. Biologics

Infliximab, Etanercept, Adalimumab	TNF- α inhibitors	i.v. s.c. s.c.	Rheumatoid arthritis, psoriatic arthritis, juvenile arthritis	Opportunistic infections
Anakinra	IL-1 receptor antagonist	s.c.	Refractory rheumatoid arthritis	Opportunistic infections
Muromonab CD3: Monoclonal antibody against CD3 molecules on T lymphocytes	Blocks the function of T cells	i.v.	In transplant rejection reactions	Fever, headache, vomiting, myalgia, arthralgia, etc.
Antithymocyte globulin (ATG)	Destroys T cells	i.v.	In acute renal transplant rejection	Anaphylaxis and serum sickness
Rituximab	B lymphocyte depletor	i.v. infusion	Used with methotrexate in re- sistant cases of rheumatoid arthritis, multiple sclerosis	Infusion reactions – fever, chills, rigour
Basaliximab Daclizumab	Block IL-2 receptor on T cell	i.v. s.c.	To prevent and treat rejection episodes during organ transplantation	Opportunistic infections
Rho(D) immunoglobulin	It is human IgG; antibodies are directed against Rho(D) antigen on RBCs	i.m., i.v.	To Rh negative mother within 24–72 hours of childbirth or after abortion in Rh incompatibility to prevent occurrence of haemolytic disease in subsequent fetuses	Pain and redness at injection site, nausea

MOA, mechanism of action; ROA, route of administration.

Table 12.3 ■ Immunostimulants and their uses

Drug	Uses
Levamisole	As an adjuvant in colon cancer
Thalidomide	Rheumatoid arthritis, lepra reaction (erythema nodosum leprosum) and multiple myeloma
BCG vaccine	Carcinoma <i>in situ</i> of urinary bladder
Interferons	Hairy cell leukaemia, malignant melanoma, AIDS-related Kaposi sarcoma

Antiseptics and Disinfectants

PH1.62

1. **Sterilization:** It is the destruction of all microorganisms including spores.
2. **Germicide:** It is an agent used to kill microorganisms but not spores. It includes disinfectants and antiseptics.
3. **Disinfectant:** It is an agent used to eliminate microorganisms on inanimate objects.
4. **Antiseptic:** It is an agent used to eliminate microorganisms on living tissues.

AN IDEAL ANTISEPTIC

- Should be effective against all pathogens
- Should be effective in the presence of organic matter like blood, pus and excreta
- Should be stable
- Should not cause irritation on topical application

Classification

1. Phenols and related agents: Phenol, cresol, resorcinol, chloroxylenol
2. Alcohols: Ethyl alcohol, isopropyl alcohol
3. Aldehydes: Formaldehyde, glutaraldehyde
4. Oxidizing agents: Hydrogen peroxide, potassium permanganate
5. Halogens and halogen-releasing agents: Chlorine, sodium hypochlorite, iodine, iodophores
6. Acids: Benzoic acid, boric acid
7. Metallic salts: Silver nitrate, zinc sulphate
8. Dyes: Gentian violet, brilliant green, methylene blue
9. Surface active agents (detergents): Common soaps, cetrimide, benzalkonium chloride, cetylpyridinium chloride
10. Gases: Ethylene oxide, β -propiolactone
11. Miscellaneous: Nitrofurazone

Phenols
Halogens
Alcohols, Aldehydes
SuRface active agents
Metallic salts, Miscellaneous
Acids
Gases
Oxidizing agents
Dyes

Note: Mnemonic for classification: 'PHARMA GOD'.

1. Phenols and Related Agents

They are protoplasmic poisons. They disrupt the cell wall.

Phenol (carbolic acid)

- Rarely used as antiseptic as it is corrosive and can penetrate intact skin.
- Used to disinfect sputum, pus and discarded cultures.

- Accidental or suicidal ingestion can cause corrosion of GIT, convulsions, hypothermia and collapse. Treatment is symptomatic.

Cresol (methylphenol)

- More active and safer than phenol.
- Used to disinfect utensils, excreta and infected glassware.

Chloroxylenol

- Active ingredient of Dettol.
- Less toxic than phenol.
- Used to disinfect surgical instruments and as an antiseptic for skin before any surgery.

Resorcinol

- Nonstaining and less toxic.
- It has keratolytic and antipruritic properties, hence used in eczema, ringworm and seborrhoeic dermatitis.

Hexachlorophene

- Chlorinated phenol.
- Greater than 2% solution is not used.
- Used as an antiseptic for skin before surgery, furunculosis and seborrhoeic dermatitis.

2. Chlorhexidine

- Used as a mouthwash and as an antiseptic for skin prior to surgery.
- Chlorhexidine mouthwash is used as an antiplaque and antigingivitis agent.
- Taste alteration and staining of oral cavity are the common side effects.

3. Alcohols

They act by denaturing bacterial proteins and precipitating them.

Ethyl alcohol

- 70% Ethyl alcohol is used as an antiseptic on skin before giving injections and surgical procedures. Its antiseptic efficacy decreases above 90%.
- It should not be used on open wounds, mucosa and ulcers as it is highly irritant.
- Not useful for disinfecting instruments as it promotes rusting.

Isopropyl alcohol

- More potent.
- 68%–72% Isopropyl alcohol is used as an antiseptic.
- Can be used to disinfect clinical thermometers.

4. Aldehydes

They act by denaturing the proteins. They are protoplasmic poisons.

Formaldehyde

- 40% Formaldehyde solution is called formalin.
- Formaldehyde solution is used for removal of warts on palms and soles, disinfection of sputum, preservation of anatomical and pathological specimens.
- Formaldehyde gas is used for fumigation of wards and operation theatres; rarely, for sterilization of heat-sensitive instruments and gloves.

Glutaraldehyde

- Preferred over formaldehyde to sterilize surgical instruments, plastic endotracheal tubes, face masks, corrugated rubber tubes, endoscopes, respirators, thermometers, etc.
- 2% Glutaraldehyde solution is used to treat hyperhidrosis of palms and soles.

5. Oxidizing Agents

They act by releasing nascent oxygen which oxidizes the bacterial protoplasm.

Hydrogen peroxide

- Colourless liquid.

- Effervescence is seen when applied to tissues due to the presence of enzyme catalase, which degrades hydrogen peroxide.
- Used for cleaning wounds and abscess cavities, removal of slough and ear wax.
- Can also be used to disinfect contact lenses, plastic implants and surgical prostheses.

Potassium permanganate

- Dark purple crystals, which are water soluble.
- Condy's lotion is 1:4000–1:10,000 solution of potassium permanganate. It is used for gargling.
- 5% Potassium permanganate solution is used as a styptic.
- 1% Potassium permanganate solution is used for fungal infections – athlete's foot.
- Used for stomach wash in alkaloid poisoning.
- Can also be used for purification of well water.
- Concentrated solution can cause burns and blisters on topical application.

6. Halogens

They are oxidizing agents.

Chlorine: It is used for disinfection of water. Some of its preparations are:

Chloramines: They act by releasing chlorine. They can be used as mouthwash and for dressing of wounds.

Chlorinated lime (bleaching powder)

- 1) Acts by releasing chlorine.
- 2) Used to disinfect drinking water and toilets.
- 3) Disadvantage is that it is highly unstable and loses its activity on storage.

Sodium hypochlorite

- Used as a root canal disinfectant.
- It is cheap but it needs to be freshly prepared and has corrosive effect on metals.

Iodine

- It has the property of oxidizing the protoplasm of microbes.
- Hypersensitivity reactions can occur with iodine.
- Its preparations are
 - 1) Tincture iodine (2% iodine in alcohol)
 - a) Used as an antiseptic on skin for wounds and prior to surgery
 - b) It stains the skin
 - 2) Mandl's paint
 - a) It contains iodine in potassium iodide and glycerine.
 - b) Used topically in tonsillitis and pharyngitis.
 - 3) Lugol's iodine
 - a) Contains 5% iodine in 10% solution of potassium iodide.
 - b) Used in thyrotoxicosis.

Iodophores

- 1) Act by releasing iodine, e.g. povidone iodine.
- 2) Nonirritant.
- 3) Used in burns, boils, prior to surgery, etc.

7. Acids

Antiseptic activity is mainly due to their antibacterial activity.

Boric acid and sodium borate (Borax)

- Fungistatic and bacteriostatic.
- It is a component of prickly heat powder.

- Systemic absorption can cause abdominal pain, diarrhoea, vomiting and kidney damage.

Benzoic acid

- Antibacterial and antifungal.
- Whitfield's ointment (6% benzoic acid + 3% salicylic acid) is used for ring-worm infections.

8. Metallic Salts**Zinc sulphate**

- It has antiseptic and astringent properties.
- It decreases sweating, hence used as a component in deodorants.
- Zinc salts are one of the components in calamine lotion which is used in urticaria and eczema as an antipruritic agent.

Silver nitrate

- It is an astringent and antiseptic.
- It can be used as an antiseptic on oral ulcers.

9. Dyes

They are used topically as antiseptic. They stain the skin on application.

- Gentian violet and brilliant green are used in gingivitis, oral thrush, bed sores, chronic ulcers, burns, etc.

10. Surface Active Agents (Surfactants)

They act by lowering the surface tension of solutions. There are two types of surfactants:

Anionic surfactants: They are common soaps. Soaps contain fatty acids with alkali (sodium or potassium hydroxide).

Cationic surfactants: They are benzalkonium chloride, cetrimide and cetylpyridinium chloride.

- Most commonly used antiseptics.
- Benzalkonium chloride is used as an antiseptic on skin prior to surgery and to store sterilized instruments.
- Savlon (cetrimide + chlorhexidine) is used to disinfect thermometers.

11. Gases

Ethylene oxide and β -propiolactone gases are used for sterilization.

Ethylene oxide

- Acts by alkylating proteins and nucleic acids.
- Highly inflammable and explosive.
- Used for sterilization of heart–lung machines, plastic equipment, sutures, dental equipment and cardiac catheters.
- Not used for fumigation as it is explosive.

Vitamins

They are organic substances that are required in small quantities to meet the metabolic demands of the body. Most of them are supplied through the diet. They are converted in the body to coenzymes, which participate in metabolic reactions. Usually, a well-balanced diet provides required amount of vitamins to the body. Vitamins A, D, E and K are fat-soluble vitamins (Table 12.4). Water-soluble vitamins include vitamin B complex and vitamin C (Table 12.5).

Table 12.4 ■ Fat-soluble vitamins

Vitamin	Sources	Daily requirement (adult)	Functions	Deficiency (signs and symptoms)	Uses
Vitamin A (retinol)	Leafy vegetables (spinach, cabbage, etc.), carrot, pumpkin, mango, orange, papaya, fish liver oils, liver, egg, butter, cheese, milk, etc.	4000 IU	- Necessary for synthesis of retinal pigments which are required for dark adaptation (vision in dim light) - Maintains the integrity of epithelial cells - Stimulates cell-mediated immunity and supports skeletal growth	- Night blindness - Dryness of conjunctiva and cornea (keratomalacia and xerophthalmia – dry eye) - Dryness of skin (phrynoderma) with papular eruptions	- Prophylaxis: 4000 IU/day p.o. - Treatment: 50,000–100,000 IU/day p.o. for 3 days
Vitamin D	Fish liver oil, dairy products; synthesized in the skin on exposure to sunlight	100–200 IU	Increases plasma calcium and phosphate by acting on GIT, kidney and bone	Rickets in children and osteomalacia in adults	- Prophylaxis: 400 IU/day - Treatment: 4000 IU/day
Vitamin E (α-tocopherol)	Wheat germ oil, nuts, cereals, green leaves	5–15 mg	As an antioxidant	Affects fertility; degenerative changes in skeletal muscle, CNS and myocardium	- Muscle cramps - Fibrocystic breast disease
Vitamin K	Spinach, cabbage, cauliflower, tomato, butter, meat, milk, liver	70–140 mcg	Helps in the synthesis of clotting factors II, VII, IX and X	Increased tendency to bleed	- Prevention and treatment of bleeding associated with vitamin K deficiency - Routinely given to neonates - Warfarin toxicity

Table 12.5 ■ Water-soluble vitamins

Vitamin	Sources	Daily requirement (adult)	Functions	Deficiency (signs and symptoms)	Uses
Vitamin B₁ (thiamine)	Wheat, cereals, pulses, nuts, meat, milk, fish, egg, vegetables and fruits	1–2 mg	• Acts as a coenzyme for carbohydrate metabolism • Essential for transmission of nerve impulses	• Dry Beriberi (affects nervous system – peripheral neuritis, tingling, numbness, muscular weakness and atrophy) • Wet Beriberi (affects the heart – tachycardia, palpitation, dyspnoea and cardiac failure)	• Required for patients on regular haemodialysis • Patients with severe vomiting • Chronic alcoholics
Vitamin B₂ (riboflavin)	Liver, meat, egg, milk, cereals and pulses	2–3 mg	Acts as a coenzyme in oxidation–reduction reactions	Glossitis, cheilosis, stomatitis and seborrhoeic dermatitis	Prophylaxis and treatment of vitamin B ₂ deficiency
Vitamin B₃ (niacin)	Liver, meat, fish, egg, ground-nuts	15–20 mg	Necessary for carbohydrate and protein metabolism	Diarrhoea, dermatitis and dementia (3D) – pellagra	• Prophylaxis and treatment of pellagra • As a hypolipidaemic agent
Vitamin B₆ (pyridoxine)	Bean, milk, liver, fish, egg, cereals, vegetables	2 mg	Involved in carbohydrate, fat and protein metabolism	Peripheral neuritis, anaemia and convulsions	• Prophylaxis and treatment of vitamin B₆ deficiency • Along with INH to prevent/treat peripheral neuropathy • Along with B₁ and B₁₂ to treat neuropathies

Continued

Table 12.5 ■ Water-soluble vitamins—cont'd

Vitamin	Sources	Daily requirement (adult)	Functions	Deficiency (signs and symptoms)	Uses
Vitamin B₁₂	Synthesized in the colon by bacteria, meat, liver, egg, fish	1 mcg	Along with folic acid, it is essential for DNA synthesis	Megaloblastic anaemia, peripheral neuritis and pernicious anaemia	• Megaloblastic anaemia due to B₁₂ deficiency • Pernicious anaemia • Hydroxocobalamin is useful in cyanide poisoning
Folic acid	Fresh green leafy vegetables, liver, fruits, milk, egg, dairy products	500–800 mcg	Its active form, tetrahydrofolate is essential for biosynthesis of amino acids, purines, pyrimidines, DNA and therefore in cell division	Megaloblastic anaemia and glossitis	• Megaloblastic anaemia • Prophylaxis in pregnancy • Methotrexate toxicity
Vitamin C (ascorbic acid)	Citrus fruits, vegetables, tomato, leafy vegetables, germinating pulses, breast milk	30–50 mg	• Formation of collagen, bone, teeth, capillaries and healing of wounds • Formation of haemoglobin and maturation of RBCs	Scurvy characterized by fatigue, swollen and bleeding gums, loose teeth, resorbed dentine, conjunctiva and subperiosteal haemorrhages, delayed wound healing, osteoporosis and anaemia	• Prophylaxis: 50–100 mg/day • Treatment of scurvy: 500–1500 mg/day • May be useful in healing of wounds • To acidify urine in alkaline drug poisoning • Promote absorption of iron from the gut

Minerals

Minerals are inorganic compounds required for normal body functions. Sodium, potassium, calcium, magnesium, phosphorous, etc. are required in large amounts, hence are *major minerals*. Iron, iodine, zinc, copper, fluorine, etc. are required in minute quantities, hence are *trace elements*.

SODIUM

It is widely distributed in the extracellular fluid (ECF; 130–145 mEq/L). The daily requirement of sodium is about 5–10 g/day. It maintains ECF volume, acid–base balance, excitability of muscle and nerve tissues. Sodium chloride (common salt) is used to improve the palatability of food. Sodium is lost from the body mainly through urine and sweat.

Excessive loss of sodium can lead to *hyponatraemia*. Severe sweating, diuretic therapy, burns, diarrhoea, etc. are some of the causes of hyponatraemia. The signs and symptoms are anorexia, muscle cramps, hypotension, tachycardia, etc. It can be treated by giving salt through food or normal saline (0.9%) intravenously. Increased sodium level in the blood is *hypernatraemia*. Common causes are congestive cardiac failure, kidney diseases, etc. The manifestations are oedema, altered mental status, rise in blood pressure, etc. It can be treated with salt-restricted diet and loop diuretics.

POTASSIUM

It is an important constituent of intracellular fluid. Normal serum potassium level is 3.5–5 mEq/L. The important sources are tender coconut water, banana, orange, nuts, etc. It is required for maintenance of muscular and neuronal activity. It also helps in regulating acid–base balance, fluid and electrolyte balance. Serum potassium less than 3 mEq/L is *hypokalaemia*. Common causes are excessive sweating, severe vomiting and diarrhoea, diabetic ketoacidosis, diuretic therapy (thiazides and loop diuretics), renal diseases, etc. The clinical features are muscular weakness, lethargy, arrhythmias, hypotension, etc. It can be corrected by oral potassium salts (oral potassium should be administered by diluting in a tumbler full of water to prevent intestinal ulceration). In severe cases, potassium can be injected slow intravenously, as it has cardiac depressant effect. Serum potassium more than 5 mEq/L is *hyperkalaemia*. Renal failure, drugs (nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, potassium-sparing diuretics, etc.), tissue damage due to trauma, burns, etc. are some of the common causes of hyperkalaemia. It can cause cardiac arrhythmias, paralysis of skeletal muscles and cardiac arrest. Drugs used to treat hyperkalaemia are 10% calcium gluconate, salbutamol/terbutaline (selective β -agonists), regular insulin with glucose (insulin facilitates the shift of potassium into cells), sodium bicarbonate and sodium polystyrene sulphonate. Severe cases can be treated by haemodialysis.

MAGNESIUM

It is mainly present in bones and teeth. The daily requirement of magnesium is 0.3–0.35 g/day. The important sources are green leafy vegetables, fish, coconut, food grain, etc. The action of magnesium depends on the route of administration as depicted in [Fig. 12.1](#).

Uses

1. As an antacid: Magnesium salts (magnesium trisilicate and magnesium hydroxide) are used commonly with aluminium salts.
2. As a purgative: Magnesium salts are used as osmotic purgative.

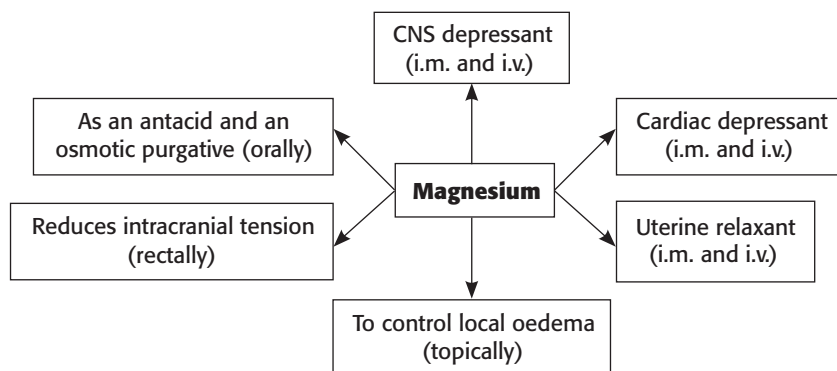


Fig. 12.1 Actions of magnesium through different routes.

3. To reduce raised intracranial tension, magnesium sulphate can be used rectally.
4. To control convulsions in eclampsia and treat cardiac arrhythmias, magnesium sulphate can be used parenterally.
5. Magnesium sulphate can be used topically to relieve local oedema.

Hypermagnesaemia is treated with 10% calcium gluconate slow intravenously. Hypomagnesaemia is treated with magnesium salts.

ZINC

It is a cofactor of many enzymes such as alkaline phosphatase, carbonic anhydrase, lactate dehydrogenase, etc. Egg, meat, liver, pulses, cereals, fruits, nuts, vegetables, etc. are important sources of zinc. Salts like zinc oxide, sulphate and carbonate have antiseptic and astringent actions. Deficiency of zinc causes delayed wound healing, alopecia, dermatitis, growth retardation, etc.

Preparations

1. **Zinc oxide:** It is used topically in eczema, haemorrhoids, skin infections, for wounds and nappy rash in children.
2. **Zinc sulphate:** It is used to facilitate healing of ulcers and conjunctivitis. It is used orally in acute diarrhoea as it helps to heal intestinal epithelium; thus decreasing the frequency and severity of diarrhoeal episodes.
3. **Zinc carbonate:** It is a major component in calamine lotion. It is available as a lotion and powder and can be used for eczema, sunburns, skin rashes, etc.

PHOSPHORUS

The important sources of phosphorus are fish, meat, egg, milk, pulses and cereals. The daily requirement of phosphorus is 0.8–1 g/day. It is required for the formation of bone and teeth along with calcium. It also helps in the maintenance of acid–base balance. *Hypophosphataemia* may occur due to dietary deficiency of phosphorus, chronic use of antacids (aluminium hydroxide and calcium carbonate), hyperparathyroidism, vitamin D deficiency, diabetic ketoacidosis, chronic alcoholism, etc. Clinical features are anorexia, muscle weakness, pain in muscle and bones. It can be treated by management of underlying disease and administration of phosphorus salts orally or intravenously depending on the severity. *Hyperphosphataemia* may occur in hyperparathyroidism, renal failure, etc.

The signs and symptoms include hypocalcaemia and bone resorption. It can be treated by administration of calcium carbonate and aluminium hydroxide. They retard the absorption of phosphorus from the gut.

IRON (SEE P. 297)

CALCIUM (SEE P. 354)

Vaccines and Antisera

PH1.54

Various immunizing agents are vaccines, immunoglobulins and antisera. Vaccines are biological substances (dead or live attenuated) used to produce specific protection against a disease. They can be live attenuated vaccines, killed vaccines, toxoid or combination vaccines. The differences between live attenuated and killed vaccines are given in [Table 12.6](#).

TOXOIDS

They are toxins which have been modified so that they are harmless but retain their antigenic property, e.g. diphtheria toxoid and tetanus toxoid.

COMBINATION VACCINES

Vaccine containing more than one antigen, e.g. diphtheria, pertussis and tetanus toxoid (DPT), measles, mumps and rubella (MMR), etc.

ACTIVE IMMUNIZATION

It can be achieved by administration of a vaccine which stimulates antibody production.

PASSIVE IMMUNIZATION

It can be achieved by administration of immunoglobulins or antisera. Immunoglobulins are antibodies and are of five classes: IgG, IgA, IgM, IgD and IgE. Antisera are serum

Table 12.6 ■ Differences between live attenuated and killed vaccines

Live attenuated vaccines	Inactivated (killed) vaccines
Consist of living organisms (bacteria, virus) whose virulence has been reduced but elicit an immune response	Consist of killed microorganisms
Produce long-lasting immunity	Produce short-lasting immunity
More efficacious	Less efficacious
Less stable at room temperature; require proper storage	More stable at room temperature
Examples: Bacterial: <i>Bacillus Calmette-Guérin</i> (BCG) Viral: Oral polio; measles, mumps and rubella (MMR)	Examples: Bacterial: <i>Haemophilus influenzae</i> (Hib) type B, typhoid, cholera, pertussis Viral: Rabies, polio (Salk), hepatitis B, hepatitis A, etc.

Table 12.7 ■ Differences between oral polio and injectable polio vaccines

Oral polio vaccine	Injectable polio vaccine
Live attenuated vaccine	Prepared from killed virus
Given orally	Given by s.c. or i.m. route
Less expensive	Expensive
Requires storage in freezer	Does not require strict storage conditions
Suitable for controlling epidemics	Not suitable for controlling epidemics

containing antibodies, prepared in animals, e.g. tetanus antitoxin, diphtheria antitoxin, antitetanus serum, antirabies serum, etc.

BCG (*Bacillus Calmette-Guérin*) Vaccine

It is a live attenuated vaccine. It is administered as a single dose intradermally to the upper arm either at birth or within 6 weeks of age. It may cause ulceration and lymphadenitis.

Polio Vaccine (Table 12.7)

- 1. Oral polio vaccine (Sabin): Prepared from live attenuated virus.
- 2. Injectable polio vaccine (Salk): Prepared from inactivated virus.

COMBINATION VACCINES

Diphtheria–Pertussis–Tetanus (Triple Antigen)

It is a combination vaccine. It gives protection against DPT. The vial should not be frozen. It is given intramuscularly deep on the lateral aspect of the thigh in infants. It can cause redness, swelling, pain and fever. Paracetamol is used to control fever.

Measles, Mumps and Rubella

It is a combination vaccine. It provides protection against MMR. It is administered intramuscularly. It may cause pain, swelling, redness, irritability, fever, etc.

Pentavalent vaccine

It consists of pertussis, hepatitis B and *Haemophilus influenza* type B (Hib) vaccines together with tetanus and diphtheria toxoids. It provides protection against five infections.

ANTISERA

Diphtheria Antitoxin

It neutralizes diphtheria toxin. It is administered i.m. or i.v.

Antisnake Venom Serum Polyvalent

Management of Snake Bite

- 1. Hospitalization.
- 2. **Symptomatic treatment:** The site should be cleaned. Paracetamol can be used to control pain. Patient should also be given tetanus toxoid. Immobilize the bitten limb with a sling or splint to prevent spread of venom from the bitten area.
- 3. Monitor blood pressure, heart rate, respiration and urine output.
- 4. Establish an i.v. line in case of suspected venomous snake bite. Polyvalent antisnake venom is given initially at a rate of 20 mL/kg/h in normal saline and slowed later.

Polyvalent antsnake venom to be infused at the rate of 1 mL/min (1 mL neutralizes 0.6 mg of cobra venom or Russell's viper venom). A test dose should be done before giving antivenom serum. Injection hydrocortisone 200 mg and pheniramine maleate 100 mg should be given prior to polyvalent antsnake venom to avoid allergic reactions.

5. Prophylactic antibiotic can be used to prevent infection.
6. Blood transfusion/packed cells if necessary (viper bite).
7. Intravenous neostigmine is given in case of cobra bite to reverse neuromuscular blockade.

Immune Globulin

Rabies immune globulin (human)

It is infiltrated into and around the wound. It provides passive immunity.

Tetanus immune globulin

It provides passive protection against tetanus. It is administered intramuscularly for prophylaxis against tetanus in persons with contaminated wounds who are either not immunized or immunization history is not known.

Drugs Used in Common Skin Diseases

PH1.57

Drugs used for treatment of skin diseases are administered topically or by systemic routes. Topical administration of drugs results in delivery of drug directly to desired site of action with minimal systemic side effects. High lipid solubility, inflammation, occlusive bandage and hydration increase penetration of drugs into skin. Drug penetration is slow in areas where skin is thick (palm, sole, etc.). Some of the preparations are discussed below.

1. **Astringents:** They precipitate surface proteins and form a protective coat, e.g. zinc oxide (for eczema, wounds and nappy rash), tannic acid (for bleeding gums and haemorrhoids) and alcohol (to prevent bed sores).
2. **Adsorbents and protectives:** They are insoluble, finely divided powders which can bind toxic/irritant substances, e.g. activated charcoal (to adsorb toxic substances in GIT), topical sucralfate (on ulcers and wounds), aloe vera gel (as cosmetic preparation), calamine (as an antipruritic and as a cosmetic) and dimethicone (as an antifatulent).
3. **Counterirritants:** Certain agents on topical application can cause irritation of sensory nerve endings and relieve pain in underlying tissues and joint supplied by the same nerve, e.g. methyl salicylate (for muscle and joint pain), capsaicin, turpentine oil.
4. **Demulcents:** They form a protective coating on the inflamed skin or mucous membrane and produce soothing effect, e.g. liquorice, lozenges, troche (nystatin), glycerine, etc.
5. **Emollients:** They are fatty or oily substances, which produce soothing effect on the skin. On application to the skin, they protect it from irritation, prevent drying, render it soft, e.g. liquid paraffin, olive oil, waxes, etc.
6. **Keratolytics:** They are used to soften and desquamate the superficial layers of the skin, e.g. salicylic acid, urea, propylene glycol, etc. They are used for warts and chronic dermatitis.
7. **Antipruritics:** These agents are used to relieve itching, e.g. antihistamines, glucocorticoids, calamine lotion, etc.
8. **Sunscreen:** They are preparations that prevent damage to skin by sun rays. Chemical sunscreens, e.g. octisalate, avobenzone, octinoxate, etc. absorb sun rays. Physical sunscreen, e.g. zinc oxide, titanium dioxide, etc. deflect sun rays.

- 9. **Melanizing agents:** They are used to promote pigmentation of depigmented areas of skin, e.g. vitiligo. They sensitize skin to sunlight and activate melanocytes. After drug administration (either oral or topical on the affected area), the affected area is exposed to sunlight. Examples include trioxsalen and methoxsalen. Prolonged exposure can cause blisters.
- 10. **Demelanizing agents:** They decrease pigmentation of hyperpigmented areas of the skin. They act by inhibiting melanin synthesis. Hydroquinone and monobenzone are used topically in melasma and hyperpigmented areas of skin.

Drugs Used for the Treatment of Psoriasis

PH1.57

Psoriasis is a chronic skin disorder characterized by erythematous, scaling plaques in the skin. Topical and systemic therapy is used for the treatment of psoriasis (Table 12.8).

Table 12.8 ■ Drugs used for the treatment of psoriasis

Therapy	Important points	Adverse effects
1. Topical therapy		
i. <i>Topical steroids</i> Hydrocortisone, clobetasol, triamcinolone, betamethasone	• Anti-inflammatory, immunosuppressant, antiproliferative actions • Low-potency steroids (e.g. hydrocortisone 1%) for lesions on the face • Potent steroids (betamethasone 0.05%) are used for thick plaques	Local and systemic side effects: • Cutaneous: Atrophy of the skin, telangiectasia, striae, alteration in pigmentation and delayed wound healing. • Systemic: Hypothalamic–pituitary–adrenal (HPA) axis suppression. Chronic use and high potency steroids increase the risk of HPA axis suppression.
ii. <i>Vitamin D analogues</i> Calcipotriol Calcitriol (ointment) slow response	• Decreases proliferation of keratinocytes • Combination with steroids results in better clinical response • Can be used as monotherapy or alternative/adjunct to steroids • Expensive	• Irritation • Hypercalcaemia (rare)
iii. <i>Tar</i> (solution, shampoo, lotion, cream, ointment)	• Antiproliferative effect • Use has declined	• Strong odour • Staining of skin, hair • Carcinogenic potential
iv. <i>Calcineurin inhibitor</i> Tacrolimus (ointment)	• Antiproliferative effect • Useful in facial psoriasis • Alternative to topical steroids	Risk of skin cancer

Table 12.8 ■ Drugs used for the treatment of psoriasis—cont'd

Therapy	Important points	Adverse effects
v. <i>Tazarotene</i> (prodrug) (topical retinoid: cream, gel)	• Antiproliferative effect; decreases inflammation • As adjunct in refractory cases of psoriasis	• Irritation • Teratogenic
vi. <i>Emollients</i>	• Soften skin, reduce scaling • Mild to moderate psoriasis – applied after bath	Allergic reactions
vii. <i>Salicylic acid</i>	• Keratolytic – softens scales, improves absorption of other drugs	
2. Systemic therapy		
i. <i>Acitretin</i> (oral) Systemic retinoid	• Antiproliferative effect, decreases inflammation • Used in severe cases of psoriasis	• Lipid abnormalities • Liver damage • Teratogenic potential; retained in the body for long time – women using it should avoid pregnancy for 2 years after end of treatment
ii. <i>Methotrexate</i> (oral)	• Decrease proliferation of epidermal cells • immunosuppressant • Use – severe psoriasis	Hepatic dysfunction
iii. <i>Immunosuppressants</i> Cyclosporine	• Calcineurin inhibitor • Use – severe and refractory psoriasis	Nephrotoxicity, hepatotoxicity
iv. <i>Photochemotherapy</i> <i>Psoralen ultraviolet A (PUVA)</i>	• Treatment with psoralen (P) followed by ultraviolet A (UVA) radiation. • Psoralen ultraviolet A (PUVA) interferes with DNA synthesis; • Used for extensive psoriasis.	Skin cancer and burns

Drugs for Acne Vulgaris

PH1.57

Acne vulgaris is a skin disorder commonly affecting adolescents and young adults. There is an increase in production of sebum by sebaceous glands. This favours the growth of *Propionibacterium acnes* which act on lipids present in sebum resulting in production of irritant fatty acids. These fatty acids cause inflammation. In addition, there is increased keratinization leading to blockade of follicles and formation of comedones.

Acne vulgaris can be treated with topical or systemically administered drugs.

Topical Therapy

- **Retinoids:** Topical retinoids include tretinoin, adapalene and tazarotene. They bind to nuclear receptors in keratinocytes to normalize differentiation. Retinoids decrease microcomedone formation. Topical tretinoin is not stable in the presence of benzyl peroxide. Hence, it should not be applied together with benzyl peroxide simultaneously. Adapalene can be used in combination with benzyl peroxide. The common adverse effect of topical retinoids is irritation.
- **Antimicrobials:** Clindamycin, erythromycin and nadifloxacin are useful topically – they decrease *P. acnes* population in the skin. They are used in combination with benzyl peroxide or retinoids.
- **Benzoyl peroxide:** It has comedolytic, keratolytic and oxidizing activities. It is active against *P. acnes*. Since it prevents development of resistance, it is commonly used in combination therapy of acne. Skin irritation can occur.
- **Azelaic acid:** It is active against *P. acnes* and has comedolytic property.

Systemic therapy is required in severe cases of acne vulgaris.

- **Isotretinoin** (oral) is used in severe cases of acne. It inhibits comedone formation. Adverse effects are dry skin, cheilitis, desquamation and photosensitivity. It has high teratogenic potential.
- **Antimicrobials:** Oral antimicrobials like tetracyclines, minocycline, erythromycin and clindamycin are useful in moderate to severe acne. Long-term use is not recommended to prevent development of resistance.

Drug Therapy of Scabies and Pediculosis

PH1.57

Scabies, a contagious skin infestation caused by *Sarcoptes scabiei* (itch mite), is characterized by intense itching and rash. The parasite penetrates epidermis and burrows along the skin, laying eggs in it. The lesions are mainly in the webs of the fingers, hand, wrist, forearm, legs, genitalia, trunk, etc. All the family members should be treated simultaneously.

Pediculosis is an infestation caused by lice. It can involve the head (pediculosis capitis), pubic hair (pediculosis pubis) and body (pediculosis corporis). The eggs (nits) get attached to the hair.

Agents used to kill parasites that live on the exterior (body surface) are ectoparasiticides. Drugs used in the treatment of scabies and pediculosis are mentioned in [Table 12.9](#).

Table 12.9 ■ Drugs used in the treatment of scabies and pediculosis

Drug	Formulations	Details
Permethrin	1% and 5% cream 5% lotion 5% gel 1% soap	Most efficacious and most frequently used drug for scabies and pediculosis (head and pubic lice). For scabies: 5% Permethrin is applied to the skin over the body from neck to toes followed by a bath after 10–12 hours to wash off the drug. For pediculosis: 1% Permethrin is applied to the scalp/pubis and washed off after 10 minutes. Treatment may be repeated, if necessary, after 1 week. Side effects are skin rashes, redness, itching, burning, etc.

Table 12.9 ■ Drugs used in the treatment of scabies and pediculosis—cont'd

Drug	Formulations	Details
Gamma ben- zene hexa- chloride (Lindane)	1% emulsion 1% lotion 1% cream 1% ointment 1% soap	For scabies: 1% Lindane is applied to the skin from neck to toes; a thorough scrub bath is given after 12 hours to wash off drug from the body. Application can be repeated if necessary after 7 days. For pediculosis: 1% Lindane is applied to the scalp and hair without touching the eyes. Side effects include skin rashes, headache, restlessness, convulsions and cardiac arrhythmias. Contraindicated in children, epileptics and pregnant women.
Crotamiton	10% lotion 10% cream	Used in scabies and pediculosis. It is applied to the skin over the body below the chin twice at 24 hours interval after a scrub bath. It is less efficacious, hence requires repeated administration. It can be used in children. Side effects include skin rashes, itching, dermatitis, etc.
Benzyl benzo- ate	25% emulsion 25% lotion	For scabies, 25% emulsion/lotion is applied to the skin over the body from neck to toes twice at 12 hours interval after a scrub bath; washed off 24 hours after the second application. It is a second line drug for scabies and pediculosis. Side effects are skin rashes and dermatitis.
Ivermectin	Tablet (oral) 0.2 mg/kg	Antifilarial drug used orally for scabies and pediculosis. Single dose produces almost complete cure. It is contraindicated in children, pregnant and lactating women.

Topical Drugs used for Common Diseases of Eye, Nose and Ear

PH1.58

Some of the topical drugs used for diseases of eye, nose and ear are listed in [Tables 12.10–12.12](#).

Table 12.10 ■ Some of the topical agents used for diseases of eye

Drug	Preparations	Uses
Ciprofloxacin	0.3% drops and 0.3% ointment	Bacterial conjunctivitis
Gentamicin	0.3% drops	Bacterial conjunctivitis

Continued

Table 12.10 ■ Some of the topical agents used for diseases of eye—cont'd

Drug	Preparations	Uses
Acyclovir	3% ointment	Herpes simplex keratitis
Betamethasone	0.1% drops and ointment	Allergic and inflammatory conditions of the eye
Dexamethasone	0.01% drops	Allergic and inflammatory conditions of the eye
Diclofenac	0.1% drops	Postoperative ocular inflammation
Azelastine	0.05% drops	Allergic conjunctivitis
Dorzolamide	2% drops	Glaucoma
Timolol	0.25% drops	Glaucoma
Pilocarpine	0.5% and 2% drops	Glaucoma
Tropicamide	1% drops	Uveitis, as a mydriatic for refraction testing
Atropine	1% ointment and drops	Uveitis, as a mydriatic for refraction testing

Table 12.11 ■ Some of the topical agents used for diseases of nose

Drug	Preparations	Uses
Azelastine	0.1% nasal spray	Allergic rhinitis
Beclomethasone	500 mcg/puff nasal spray	Allergic rhinitis
Oxymetazoline	0.05% nasal drops	Nasal decongestant

Table 12.12 ■ Some of the topical drugs used for diseases of ear

Drug	Preparations	Uses
Ciprofloxacin	0.2% drops	Bacterial infections
Clotrimazole	1% drops	Fungal infections
Gentamicin	0.3% drops	Bacterial infections
Betamethasone	0.1% drops	Eczema of ear, as an anti-inflammatory agent
Sodium bicarbonate	5% drops	To soften ear wax

Enzymes in Therapy

Enzymes are proteins secreted by living cells, which are capable of causing or accelerating biochemical reactions. All enzymes are proteins, hence can cause allergic reactions. Some of the important enzymes used in therapy are listed in [Table 12.13](#).

Table 12.13 ■ Enzymes used in therapy

Enzyme	Source	Availability and routes	Actions	Uses
Hyaluronidase	Mammalian testes	Topical, s.c., i.m. and intra-articular	Depolymerizes hyaluronic acid and increases permeability of tissues	To promote absorption of drugs and fluids; given s.c., i.m. or intra-articularly To aid the resorption of extravasated fluid or blood in haematoma or postoperative oedema To facilitate the diffusion of local anaesthetic in ophthalmology
Chymotrypsin	Ox pancreas	Tablet (p.o.) and topical (ointment)	Proteolytic enzyme	To reduce postoperative oedema
α -Chymotrypsin	Ox pancreas	Injection and tablet	Mucolytic and proteolytic activity	During cataract surgery to facilitate removal of the lens To reduce inflammatory oedema due to trauma, infection, surgery
Serratiopeptidase	<i>Serratia</i> species	Tablet (p.o.)	Anti-inflammatory activity	To relieve pain and inflammation due to surgery, trauma, infection and chronic conditions like osteoarthritis, rheumatoid arthritis
Urokinase	Isolated from human fetal kidney cell culture	i.v.	Fibrinolytic (dissolves clot)	Deep vein thrombosis, pulmonary embolism
Tissue plasminogen activator (t-PA)	Derived from recombinant DNA technology	i.v.	Fibrinolytic (dissolves clot)	Acute MI, deep vein thrombosis, pulmonary embolism
L-Asparaginase	<i>Escherichia coli</i>	i.v.	Catalyses the hydrolysis of asparagine to aspartic acid	Acute lymphoblastic leukaemia

Drug Treatment of Medical Emergencies

Drug treatment of medical emergencies is listed in [Table 12.14](#).

Table 12.14 ■ Drug treatment of medical emergencies

Emergency condition	Drug treatment
1. Anaphylactic shock	• Inj. Adrenaline (1:1000) 0.3–0.5 mL i.m. • Inj. Hydrocortisone 200 mg i.v. • Inj. Diphenhydramine 25–50 mg i.v./i.m.
2. Hypoglycaemia	If the patient is conscious, oral glucose or fruit juice is given. If hypoglycaemia is severe (patient is unconscious), 50 mL of 50% glucose is injected intravenously
3. Adrenal crisis	• Inj. Hydrocortisone 200 mg i.v. • Intravenous normal saline with 5% glucose • Correct fluid and electrolyte imbalance
4. Acute attack of angina/ myocardial infarction (MI)	Tab. Nitroglycerin 0.5 mg sublingually. If the pain is relieved, spit out the tablet. If pain is not relieved, the tablet can be repeated after 5 minutes but not more than three tablets in 15 minutes. If pain is not relieved, it could be MI. Give tablet aspirin 325 mg orally, then refer the patient to a cardiologist.
5. Status asthmaticus (acute severe asthma)	• Humidified oxygen by mask • Salbutamol 5–10 mg + ipratropium bromide 0.5 mg continuous nebulization • Inj. Salbutamol 0.4 mg i.m. • Inj. Hydrocortisone hemisuccinate 200 mg i.v. stat and 100 mg q6h till the attack subsides • Cap. Amoxicillin 500 mg p.o. t.d.s.
6. Acute bronchial asthma	Salbutamol metered dose inhaler (MDI) 100 mcg/puff: 1–2 puffs stat and as and when required (not more than 8 puffs per day)
7. Seizures (epileptic/drug induced)	• Inj. Diazepam 5–10 mg i.v. slowly; repeat the dose, if necessary Or • Inj. Lorazepam 0.1 mg/kg i.v. slowly
8. Tetany	Inject 10–20 mL of 10% calcium gluconate i.v. slowly
9. Fainting	Aromatic ammonia vapouroles held near the nostrils
10. Hypertensive crisis	Nicardipine i.v. infusion: Start 5 mg/h, increase every 5 min by 2.5 mg/h, max 15 mg/h Or Nitroglycerine i.v. infusion: Initial 5 mcg/min; increase by 5 mcg/min every 3–5 min to a maximum of 20 mcg/min
11. Thyrotoxic crisis	• Tab. Propylthiouracil 150–300 mg p.o. q6h • Iodate sodium 0.5 g p.o. daily • Sodium iodide 1 g i.v. slowly • Inj. Propranolol 0.5–2 mg i.v. slowly q4h • Inj. Hydrocortisone 100 mg i.v. q8h

Drug Dosage Forms

PH1.3

Drugs can be administered to a patient in various forms. They are available as solid, semisolid and liquid dosage forms.

SOLID DOSAGE FORMS

Solid dosage forms of a drug are tablet, capsule, powder, suppository, troche, lozenge, etc. (Box 12.1).

Tablet

It is the commonly used solid dosage form (Fig. 12.2 a, b). A tablet may be scored and can be broken along the line, if required, e.g. paracetamol. Tablets can be uncoated or coated (covered with a thin film of another substance) to improve its taste, delay absorption, prevent its degradation in the stomach, etc. Sugar-coating of a tablet helps to improve its taste, e.g. metronidazole.

- **Enteric-coated tablet:** It is coated with a material that delays the release of medication till it reaches the intestine. Enteric coating of a drug prevents the destruction of the drug by gastric acid, e.g. enteric-coated tablet of erythromycin, or decreases the gastric irritation by the drug, e.g. enteric-coated tablet of diclofenac.
- **Sustained-release preparation:** It helps to prolong the duration of action of a drug, thereby decreasing the frequency of drug administration and improving patient compliance, e.g. sustained release tablet of diclofenac (for pain). Enteric-coated and sustained-release tablets should not be crushed.
- **Chewable tablet:** It should be chewed and swallowed. This helps to increase the effectiveness of the drug, e.g. chewable antacid tablet used for gastritis and chewable albendazole tablet for worm infestation.
- **Dispersible tablet:** It is a tablet that has to be dispersed in water before administration, e.g. dispersible tablet of aspirin.
- **Mouth dissolving tablet:** It is placed on the tongue - disintegrates rapidly within few seconds, eg. mouth dissolving tablet of ondansetron. It is easy to administer, convenient for patient and water is not required for swallowing. The tablet should be handled carefully. It is not suitable for patients with dry mouth (eg. those on anticholinergics)

Box 12.1 ■ Solid dosage forms

■ Tablet	■ Lozenge
■ Capsule	■ Suppository
■ Troche	■ Powder

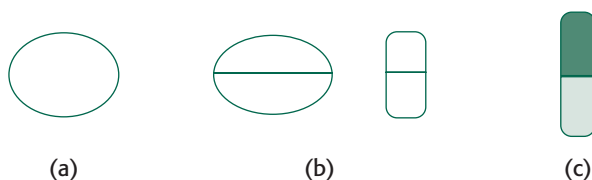


Fig. 12.2 (a) Tablet (b) Scored tablets (c) Capsule.

Capsule

It is a solid dosage form where the drug is enclosed within a soluble sheath. Capsules can be oval, cylindrical or spherical (Fig. 12.2c), e.g. amoxicillin.

Sustained-release and enteric-coated capsules are also available. Spansules and timsules are sustained-release forms. Time-release forms may have the suffix like SR (sustained release), CR (controlled release), ER (extended release), SA (sustained action), contin (continuous), retard, etc. Some capsules, eg. venlafaxine(antidepressant) extended release capsules, can be opened, contents sprinkled on soft food and swallowed (not chewed) immediately followed by a glass of water.

Troche

It is a solid dosage form to be placed in the mouth where they dissolve slowly to liberate the active ingredient, e.g. clotrimazole troche for oral candidiasis (oral thrush).

Lozenge

It is a solid dosage form placed in the mouth and sucked; it dissolves slowly to liberate the active ingredient. It soothes the irritated mucosa of the throat. Some of the lozenges have systemic effect, e.g. nicotine lozenges to reduce withdrawal symptoms and craving associated with cessation of smoking; dyclonine (local anaesthetic) lozenge for sore throat.

Suppository

It is a solid dosage form, either cylindrical or cone shaped, that is inserted into the rectum, urethra or vagina. It is solid at room temperature, but readily melts at body temperature. A suppository is to be stored in a refrigerator (not to be freezed), e.g. bisacodyl suppository for constipation.

Pessary: It is a vaginal suppository, e.g. nystatin pessary for vaginal candidiasis.

Powder

It is the finely divided form of a drug for internal or external use, e.g. oral rehydration salt (ORS) powder for dehydration; a combination of neomycin polymyxin B and bacitracin (neosporin) in powder form for external application to skin as antiseptic (anti-bacterial agent); antifungal agents for athletes foot.

LIQUID DOSAGE FORMS

Different types of liquid dosage forms are discussed below (Box 12.2).

Box 12.2 ■ Liquid dosage forms	
■ Mixture	■ Mouth rinse
■ Emulsion	■ Liniment
■ Suspension	■ Lotion
■ Syrup	■ Tincture
■ Elixir	■ Irrigation solution
■ Linctus	■ Drops
■ Gargle	■ Spray

Mixture

It is a liquid containing two or more ingredients for oral use, e.g. gripe water mixture used in infants to reduce griping and carminative mixture to expel gas from stomach and intestine.

Emulsion

It is a mixture of two immiscible liquids made miscible by using an emulsifying agent, e.g. cod liver oil emulsion for vitamin D deficiency.

Suspension

It contains one or more insoluble ingredients suspended in a liquid, e.g. antacid suspension. It should be shaken well before use.

Syrup

It is a concentrated solution of sugar containing the drug to mask the bitter taste of drug, e.g. cough syrup.

Elixir

It is a clear, flavoured liquid dosage form that contains a drug dissolved in water and alcohol, e.g. promethazine elixir for suppressing dry cough.

Linctus

It is a viscous liquid preparation. It is usually used for relief of cough, e.g. linctus codeine.

Liniment

It is a liquid preparation containing alcohol, oil or soap as vehicle meant for application to the skin with friction for sprain, joint pain, myalgia, etc., e.g. turpentine liniment. Liniment should not be applied to bruised skin or wounds.

Lotion

It is a liquid preparation meant for application to skin without friction, e.g. calamine lotion for eczema, sunburn, etc.

Tincture

It is an alcoholic preparation of a drug, e.g. tincture iodine used as an antiseptic.

Drops

They are liquid preparations meant for oral (vitamin drops, paracetamol drops) or local (eye, ear and nose) administration.

Spray

It discharges the drug in droplet form for topical application—nose (nasal decongestants), skin (diclofenac), etc., or for systemic effect (e.g. nitroglycerin lingual spray).

SEMISOLID DOSAGE FORMS

Different types of semisolid dosage forms are discussed below ([Box 12.3](#)).

Box 12.3 ■ Semisolid dosage forms

■ Ointment

■ Cream

■ Paste

■ Gel

Ointment

It is a semisolid preparation having a greasy base for application to the skin or mucosa, e.g. neomycin ointment for skin and eye infections. It can also be used for systemic effect, e.g. nitroglycerin ointment for angina pectoris.

Cream

It is a semisolid emulsion for local application, e.g. ketoconazole cream for fungal infections; glucocorticoid (betamethasone) intraoral cream for severe aphthous stomatitis, etc.

Paste

It is a semisolid preparation with a less greasy base generally meant for topical use, e.g. triamcinolone acetonide paste for oral inflammatory lesions. Pastes are stiffer and easily washable than ointments.

Gel

It is a jelly-like substance formed by aqueous suspension of insoluble drugs, e.g. diclofenac gel for pain, lignocaine gel as a local anaesthetic, povidone iodine gel for sore throat, glucocorticoid (betamethasone) gel for severe aphthous stomatitis, etc.

INJECTABLE DOSAGE FORMS

The drugs to be administered as injections are available as powder (e.g. benzyl penicillin G), suspension (e.g. procaine penicillin G) and solution (e.g. adrenaline). Those available as powder have to be mixed with diluent (reconstituted) before administration to the patient. All instructions should be read carefully before injecting a drug.

Calculation of Dosage of Drugs

PH1.12

WEIGHTS AND MEASURES

Metric System

It is a commonly used system of measurement today. In this system, the primary unit of length is metre, of weight is gram and of volume is litre (Table 12.15).

Table 12.15 ■ Metric system of measurement

Weight		Volume		Length	
Unit	Abbreviation	Unit	Abbreviation	Unit	Abbreviation
nanogram	ng	microlitre	μL	millimetre	mm
microgram	mcg	millilitre	mL	centimetre	cm
milligram	mg	decilitre	dL	metre	m
gram	g	litre	L		
kilogram	kg				

Household System

This system of measurement is not very accurate. It involves the use of cups, spoons, glasses, etc.

Volume	Length
Drops (gtt.)	Inch (in)
Teaspoon (tsp)	
Tablespoon (tbsp)	

Conversion from One System to Another

Weight	Volume
1 kilogram (kg) = 1000 grams (g)	1 litre = 1000 millilitre (mL)
1 gram (g) = 1000 milligrams (mg)	1 decilitre (dL) = 100 millilitre (mL)
1 milligram (mg) = 1000 micrograms (mcg)	1 millilitre (mL) = 1000 microlitre (μL)
1 microgram (mcg) = 1000 nanograms (ng)	1 ounce (oz) = 30 millilitre (mL)
1 kilogram (kg) = 2.2 pounds (lb)	1 mL = 16 drops
1 grain (gr) = 60 milligrams (mg)	1 pint = 480 mL (16 oz)
	1 teaspoonful = 5 mL
	1 tablespoonful = 15 mL
	1 teacupful = 150 mL
	1 tumblerful = 250 mL

CALCULATION OF DRUG DOSAGE

The following formulae are useful in calculating the drug dosage:

1. For children:

■ Young's formula

$$\text{Child dose} = \frac{\text{Age (years)}}{\text{Age} + 12} \times \text{Adult dose}$$

■ Clark's formula

$$\text{Child dose} = \frac{\text{Weight (pounds)}}{150} \times \text{Adult dose}$$

2. Based on body weight, drug dose for lean or obese individuals and children is calculated by the following formula:

$$\text{Individual dose} = \frac{\text{Body weight (kg)}}{70} \times \text{Average adult dose}$$

3. Based on body surface area (BSA):

$$\text{Individual dose} = \frac{\text{Body surface area (m}^2\text{)}}{1.7} \times \text{Average adult dose}$$

BSA can be calculated by the following formula:

$$\text{Body surface area (BSA)} = \text{Body weight (kg)}^{0.426} \times \text{Height (cm)}^{0.725} \times 0.007184$$

BSA can also be obtained from a nomogram. Calculation of drug dosage by using BSA is cumbersome. It is mainly used to calculate the dose of anticancer drugs.

4. Based on kidney function: In patients with renal failure, dosage of certain drugs have to be calculated based upon creatinine clearance. For example, dose of aminoglycosides, amphotericin B, etc. should be modified in patients with impaired renal function.

CALCULATION OF DOSAGE OF ORALLY ADMINISTERED DRUGS

Solid Dosage Form

Problem 1: The doctor has prescribed 500 mg of amoxicillin. The amoxicillin strip reads 250 mg per capsule. How many capsules will you give?

$$\text{Number of capsules} = \frac{\text{Required dose}}{\text{Available strength of the tablet}} = \frac{500 \text{ mg}}{250 \text{ mg}} = 2$$

You will give two capsules (each 250 mg) to the patient to get the required 500 mg as prescribed.

Problem 2: The doctor has prescribed 250 mg of paracetamol to a child. The tablet is available as 500 mg. How will you administer the required dose?

$$\text{Number of tablets} = \frac{\text{Required dose}}{\text{Available strength of the tablet}} = \frac{250 \text{ mg}}{500 \text{ mg}} = 1/2$$

Half a tablet is to be administered (Fig. 12.3).

Note: Only scored tablets can be broken into 1/2 or 1/4. Capsules and coated tablets should not be divided.

Problem 3: The doctor has prescribed drug A in a dose of 0.250 mg. The tablet is available as 62.5 mcg. How many tablets should be administered to the patient?

Convert drug dosage to same units. That is, convert 0.250 mg to mcg (1 mg = 1000 mcg).

Therefore, 0.250 mg = $0.250 \times 1000 \text{ mcg} = 250 \text{ mcg}$

$$\text{Number of tablets} = \frac{\text{Required dose}}{\text{Available strength of the tablet}} = \frac{250 \text{ mcg}}{62.5 \text{ mcg}} = 4$$

Note: Unit of required dose and available dose must be the same.

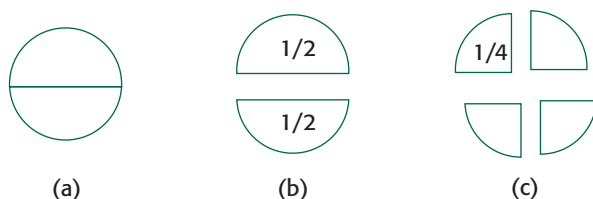


Fig. 12.3 (a) Scored tablet (b) 1/2 Tablets (c) 1/4 Tablets.

Liquid Dosage Forms

Problem 1: Doctor has prescribed 75 mg of paracetamol syrup for a child. It is available as 125 mg/5 mL syrup. How much of the syrup is to be administered to the child?

125 mg is contained in 5 mL. Therefore, 75 mg is contained in

$$\frac{5}{125} \times 75 = 3$$

So, 3 mL of the syrup is to be administered to the child.

Liquid dosage forms can be administered orally with a measuring cup, dropper, teaspoon or tablespoon. Measuring cups are calibrated in millilitre or ounce. Droppers are calibrated in millilitre. The dose of the liquids should always be measured at the lowest point of the meniscus.

CALCULATION OF DOSAGE OF PARENTERALLY ADMINISTERED FLUIDS

Strength of Solution

Concentration of solutions can be expressed as *percent* or *ratios*. The percentage concentration of solutions can be expressed as given below:

1. Percent weight in volume (w/v), i.e. 'w' g (weight) of solute in 'v' mL (volume) of solution, e.g. 1% w/v solution contains 1 g of solute in 100 mL of solution.
2. Percent weight in weight (w/w) solution, i.e. 'w' g (weight) of solute in 'w' g (weight) of solution, e.g. 1% w/w solution is 1 g of solute in 100 g of solution.
3. Percent volume in volume (v/v) solution, i.e. 'v' mL (volume) of solute in 'v' mL of solution, e.g. 1% v/v solution is 1 mL of solute in 100 mL of solution.

Commonly, solutions are expressed as w/v percent, for example,

1. 0.9% normal saline (0.9% w/v solution of sodium chloride in water)—0.9 g of sodium chloride in 100 mL of solution.
2. 5% dextrose (5% w/v solution)—5 g of dextrose in 100 mL of solution.
3. 50% dextrose (50% w/v solution)—50 g of dextrose in 100 mL of solution.
4. 20% mannitol (20% w/v solution)—20 g of mannitol in 100 mL of solution.

Solution can be expressed as v/v percent, e.g. 70% alcohol (70% v/v solution of alcohol)—70 mL of absolute alcohol in 100 mL of its aqueous solution.

Ratio solutions: w/v solutions can also be expressed in *ratios*, for example,

1. 1:100 is 1 g of solute in 100 mL of solution.
2. 1:1000 is 1 g of solute in 1000 mL of solution, e.g. adrenaline 1:1000 solution means 1 g of adrenaline is present in 1000 mL of its solution.

Intravenous fluids (i.v. fluids): The commonly used i.v. solutions are mentioned below:

Intravenous fluid	Abbreviation
Normal saline	NS
Half-strength saline	0.45%
5% Dextrose	5% D
10% Dextrose	10% D
50% Dextrose	50% D
Dextrose normal saline	DNS
Ringer lactate	RL

Intravenous fluid rate should be calculated as drops/min or mL/h. **Drop factor** is the number of drops required to deliver 1 mL (gtt./mL) and is used in calculating the number of drops per minute. The drop factor is mentioned on the infusion set. A macrodrip set usually delivers 10, 15, 16 or 20 drops/mL. A microdrip set delivers 60 drops/mL.

Drip rate of a solution is the number of drops per minute (drops/min, gtt/min). **Flow rate** of a solution is the number of millilitre per minute or per hour. In microdrip set, the drip rate is the same as flow rate (e.g. if flow rate is 150 mL/h, then drip rate is 150 drops/min).

$$\text{Drip rate, i.e. drops/min (gtt/min)} = \frac{\text{Total volume (mL)} \times \text{Drop factor (gtt/mL)}}{\text{Time (min)}}$$

CALCULATION OF DOSAGE OF PARENTERALLY ADMINISTERED DRUGS

Problem 1: Infuse 1000 mL dextrose normal saline over 5 h. Calculate the flow rate and drip rate. The drop factor for the infusion set is 15 gtt/mL.

$$\text{Flow rate} = \frac{\text{Total volume (mL)}}{\text{Total number of hours}} = \frac{1000 \text{ mL}}{5 \text{ h}} = 200 \text{ mL/h}$$

To express as mL/min, convert 1 h to 60 min.

Therefore, 200 mL can be given in 60 min.

That is, in 60 min the amount of fluid to be infused is 200 mL.

So, in 1 min the amount of fluid to be infused is $200/60 \text{ mL} = 3.33 \text{ mL}$.

Therefore, the flow rate is 200 mL/h or 3.33 mL/min.

$$\text{Drip rate} = \frac{\text{Total volume (mL)} \times \text{drop factor (gtt/min)}}{\text{Time (min)}} = \frac{200 \times 15}{60 \times 5} = 10 \text{ gtt/min}$$

The drip rate is 10 gtt/min.

Problem 2: A doctor has prescribed 50 mg of drug X to be administered. The ampoule contains 100 mg/2 mL. What amount of the drug will you administer?

$$\frac{\text{Required dose}}{\text{Available dose}} \times \text{Volume} = \frac{50 \text{ mg}}{100 \text{ mg}} \times 2 \text{ mL} = 1 \text{ mL}$$

One millilitre of the drug X is to be administered to the patient to get the required dose of 50 mg as prescribed by the doctor.

Problem 3: A patient has been prescribed 10,000 units of heparin subcutaneously. The vial contains 5000 units/mL of heparin. What volume of heparin should the patient receive?

$$\frac{\text{Required dose}}{\text{Available strength}} \times \text{Volume} = \frac{10,000 \text{ mg}}{5000 \text{ mg}} \times 1 \text{ mL} = 2 \text{ mL}$$

Therefore, 2 mL of heparin is to be injected to the patient.

Problem 4: A doctor has prescribed injection ampicillin 125 mg intramuscularly. It is available as 500 mg in powder form in a multiple dose vial. The direction on the label for reconstitution of the powdered drug is to add 1.8 mL of sterile diluent to obtain 250 mg/mL of ampicillin.

Add 1.8 mL of sterile diluent to the powder in the multiple dose vial. Shake the vial to dissolve the drug. The resulting solution contains 250 mg/mL of ampicillin.

There is 250 mg of ampicillin in 1 mL of solution.

$$\begin{aligned}\text{Therefore, 125 mg of ampicillin is present in } & 1/250 \times 125 \text{ mL of solution} \\ & = 0.5 \text{ mL of solution}\end{aligned}$$

Therefore, 0.5 mL of the reconstituted drug is drawn into a syringe and administered intramuscularly/intravenously.

Note: The label on the vial or the package insert will contain directions for reconstitution of the drug and for how long the reconstituted drug can be stored. For a single-dose vial, the reconstituted drug is used immediately and the vial is discarded.

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