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FOR MEDICAL GRADUATES

THIRD EDITION

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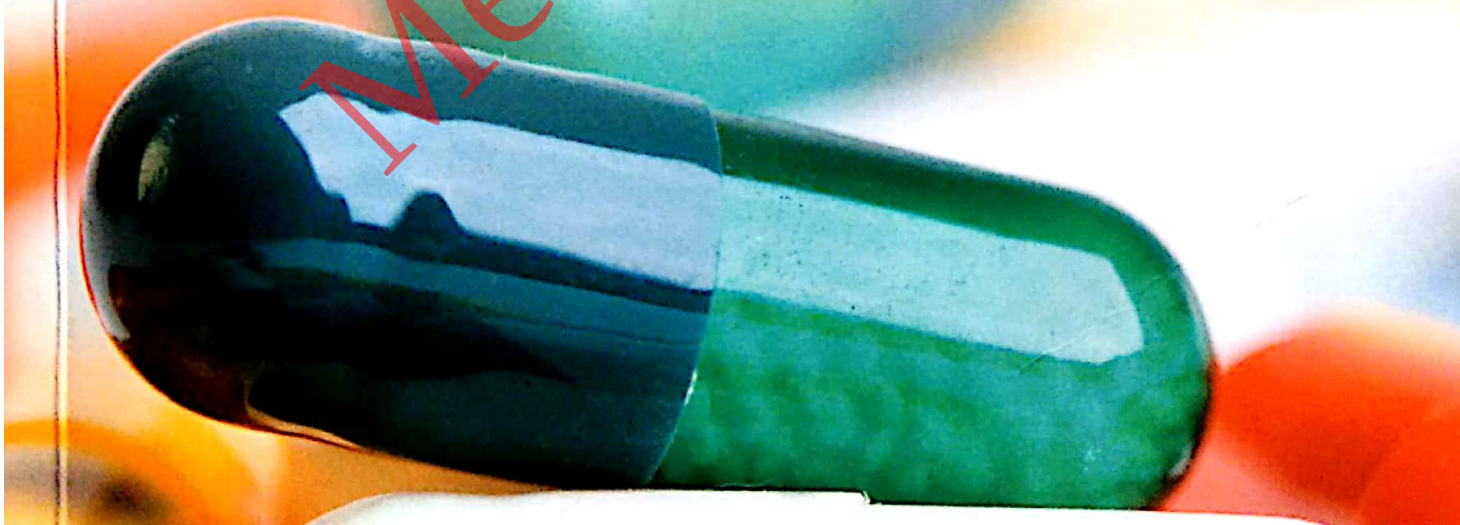

Tara V Shanbhag
Smita Shenoy

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PHARMACOLOGY

for Medical Graduates

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PHARMACOLOGY
for Medical Graduates

Third Edition

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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 Third Edition

Pharmacology is one of the fast-growing branches of medical science and requires addition of latest information from time to time. Now in its third edition this book is aptly named *Pharmacology for Medical Graduates* and includes significant expansion and revision of the second edition. The style and presentation form has been retained – simple diagrams, self-explanatory flowcharts, tables and student-friendly mnemonics. Some new topics like cognitive enhancers, CNS stimulants, drugs for the treatment of psoriasis and acne vulgaris have been included. The textual presentation in tabular format helps in quick reading and recall. Definitions and treatment schedules have been incorporated as per WHO guidelines. This extensively revised and updated edition will be useful not only for the students of medicine but also for practicing doctors as well.

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 Shemoy

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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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CHAPTER 1
General Pharmacology

INTRODUCTION (DEFINITIONS AND SOURCES OF DRUGS)

- **Pharmacology:** It is the science that deals with the effects of drugs on living systems.
- **Drug:** 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 the 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 the 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.

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- **Orphan drug:** Drugs that are used for the 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, non-prescription 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), the European Pharmacopoeia (EP) 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 drug 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, dosage, adverse effects, contraindications, precautions, warnings and guidance on selecting the right drug for a range of conditions.

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Drug Nomenclature

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

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

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 for paracetamol. It is not suitable for use in a prescription.
2. **Non-proprietary name:** It is assigned by a competent scientific body/authority, e.g. the United States Adopted Name (USAN) council. It is

commonly used as generic name. The WHO* along with the national nomenclature committees of its member countries selects the International Nonproprietary Name (INN) for a drug. It is uniform throughout the world and denotes the active pharmaceutical ingredient. Ideally, generic names should be used in prescriptions because it is economical and generally uniform all over the world than the branded counterparts, e.g. 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. 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.

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 are:

1. *Plants:*
   (a) Alkaloids, e.g. morphine, atropine, quinine, reserpine, ephedrine.
   (b) Glycosides, e.g. digoxin, digitoxin.
2. *Animals:* Insulin, heparin.
3. *Minerals:* Ferrous sulphate, magnesium sulphate.
4. *Microorganisms:* Penicillin, streptomycin, griseofulvin.
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

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:

1. Characteristics of the drug.
2. Emergency/routine use.
3. Condition of the patient (unconscious, vomiting and diarrhoea).
4. Age of the patient.
5. Associated diseases.
6. Patient's/doctor's choice (sometimes).

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

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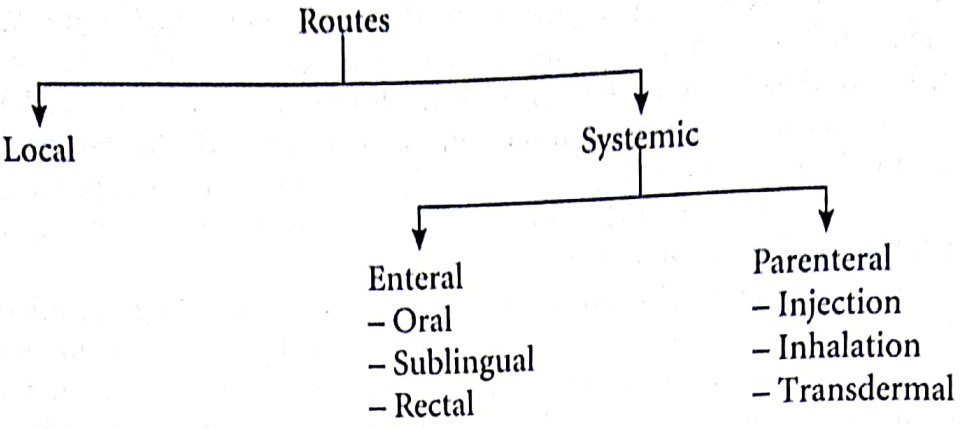

Routes of drug administration

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:** A drug is applied to the skin or mucous membrane at various sites for localised 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 and jelly, 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:*
      (i) 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 the rectum.
         - Retention enema: For example, methylprednisolone in ulcerative colitis.
      (ii) 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

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administration of some anticancer drugs, e.g. for treatment of malignancy involving limbs.

3. Administration of the drug into some 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, syrup, mixture, etc., e.g. paracetamol tablet for fever, omeprazole capsule for peptic ulcer are given orally.

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.
- Not suitable for emergency as onset of action of orally administrated drugs is slow.

Sublingual Route

The preparation is kept under the tongue. The drug is absorbed through the buccal mucous membrane and enters the systemic circulation directly, e.g. nitroglycerin for acute anginal attack and buprenorphine for myocardial infarction.

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.

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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.

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.

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Injections (Fig. 1.1)

Intradermal route: The drug is injected into the layers of the 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 tissues 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 non-irritant drugs.
- Drug absorption is slow, hence not suitable for emergency.

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.

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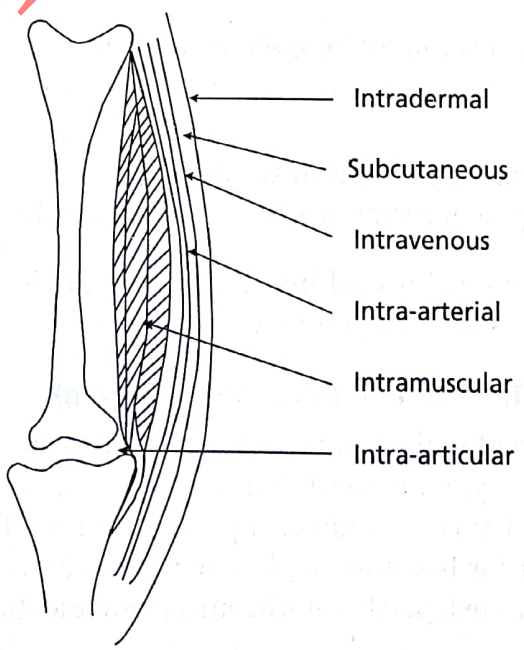

FIGURE 1.1 Injectable routes of drug administration.

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 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 patch/ointment for prophylaxis of angina, oestrogen patch for hormone replacement therapy (HRT), clonidine patch for hypertension, fentanyl patch for chronic pain, nicotine patch for tobacco de-addiction, etc.

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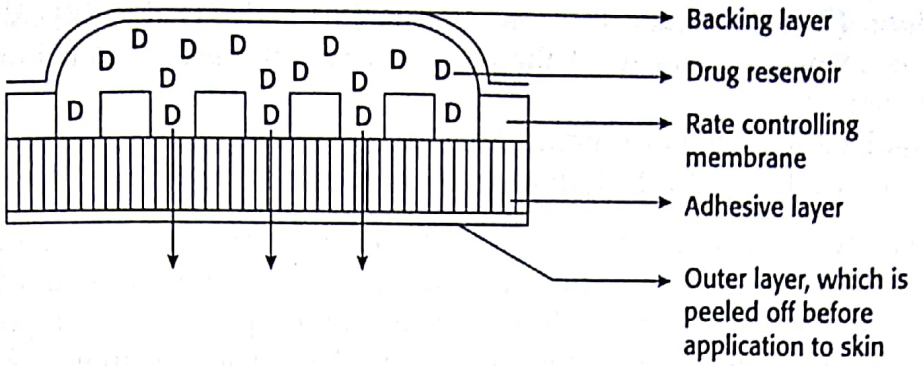

FIGURE 1.2 Transdermal drug delivery system.

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

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.
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 anti-cancer drugs using monoclonal antibodies.
5. **Drug-eluting stents:** e.g. paclitaxel releasing stents used in coronary angioplasty.
6. **Computerised, miniature pumps,** e.g. insulin.

PHARMACOKINETICS

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

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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.
2. **Filtration:** Filtration depends on the molecular size and weight of the drug. If the drug molecules are smaller than the pores, they are filtered easily through the membrane.
3. **Specialized transport:**
   (a) *Active transport*: The 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.
   (b) *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.

Drug absorption

The 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 the water-soluble and ionised 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.

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(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.

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, ionise 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 of the 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 the 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 gastrointestinal (GI) mucosal oedema that reduces absorption of drugs.

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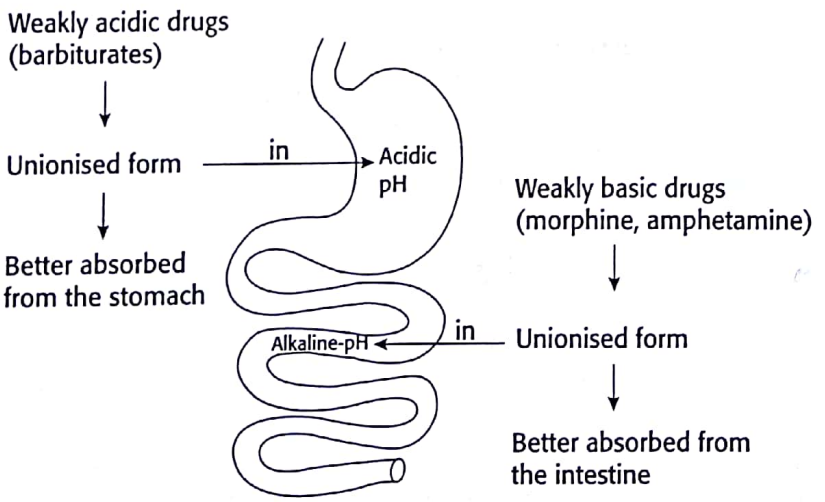

FIGURE 1.3 Effect of pH and ionisation on drug absorption.

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 (physicochemical properties of the drug, route of drug administration, pH and ionization, food, presence of other drugs, area of absorbing surface, gastrointestinal 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. 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 (Fig. 1.4). 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:

   (i) Drugs which undergo extensive first-pass metabolism are administered parenterally, e.g. lignocaine is administered intravenously in ventricular arrhythmias.

   (ii) Dose of a drug required for oral administration is more than that given by other systemic routes, e.g. nitroglycerin.

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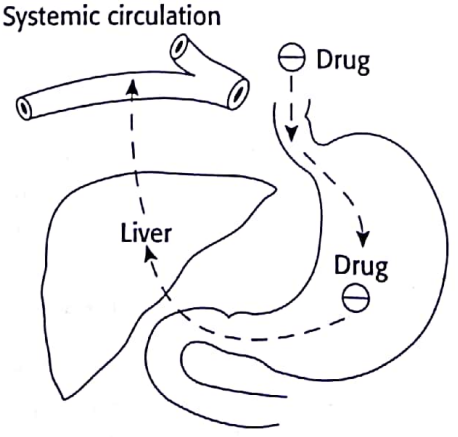
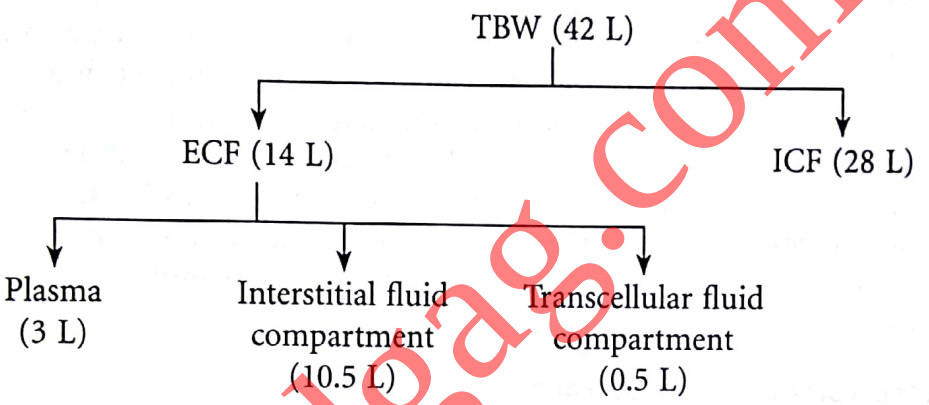


FIGURE 1.4 First-pass metabolism.

2. **Hepatic diseases:** They result in a decrease in drug metabolism, thus increasing the bioavailability of drugs that undergo first-pass metabolism, e.g. propranolol and lignocaine.
3. **Enterohepatic cycling:** It increases the bioavailability of drugs, e.g. morphine and doxycycline.

Drug Distribution

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:



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

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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.

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

- 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, 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 overdosage.

- 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 uremia, 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

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) and into the 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 the 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 unionised form of drugs can pass through BBB and reach the brain, e.g. barbiturates, diazepam, volatile anaesthetics, amphetamine, etc. Lipid-insoluble and ionised 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

Certain drugs administered to the pregnant woman can cross placenta and affect the fetus/newborn, e.g. anaesthetics, morphine, corticosteroids, etc. Quaternary ammonium compounds, e.g. d-tubocurarine (d-TC) and substances with high molecular weight like insulin cannot cross the placental barrier.

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Plasma Protein Binding

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

Clinical importance of plasma protein binding

1. Drug —Absorption→ Enters circulation
   ↓
   Binds to plasma protein (Acidic drugs to albumin, basic drugs to α_1 acid glycoprotein)
   ↓
   Free form (Pharmacologically **active**) ⇌ **Bound form** (Pharmacologically **inactive**, acts as a 'temporary store' of the drug)
2. Plasma protein binding favours drug **absorption**.
3. Drugs that are highly bound to plasma proteins have a low volume of **distribution**.
4. Plasma protein binding delays the **metabolism** of drugs.
5. Bound form is not available for filtration at the glomeruli, hence **excretion** of highly plasma protein bound drugs is delayed.
6. 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 one week.
7. In case of poisoning, highly plasma protein bound drugs are difficult to be removed by haemodialysis.
8. In disease states like anaemia, renal failure, chronic liver diseases, etc. plasma albumin levels are low. So, there will be an increase in the free form of the drug, which can lead to drug toxicity.
9. 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.

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Biotransformation (Drug Metabolism)

Chemical alteration of the drug in a living organism is called biotransformation. The metabolism of a drug usually converts lipid-soluble and unionised compounds into water-soluble and ionised compounds. They are not reabsorbed in the renal tubules and are excreted. If the parent drug is highly polar (ionised), then it may not get metabolised 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 ⟶ Hydroxyphenobarbitone
   Phenytoin ⟶ *p*-Hydroxyphenytoin
2. *Active drug to active metabolite*
   Codeine ⟶ Morphine
   Diazepam ⟶ Oxazepam
3. *Inactive drug (prodrug) to active metabolite*
   Levodopa ⟶ Dopamine
   Prednisone ⟶ 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 the blood–brain barrier (BBB). So it is given in the form of a prodrug, levodopa. Levodopa crosses the BBB and is then converted into dopamine.

$$\text{Levodopa} \xrightarrow[\text{BBB}]{} \text{Levodopa} \xrightarrow{\text{Dopa decarboxylase}} \text{Dopamine}$$

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 the 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:**

$$\text{Methenamine} \xrightarrow{\text{acidic pH of urine}} \text{Formaldehyde (acts as urinary antiseptic)}$$

Pathways of Drug Metabolism. Drug metabolic reactions are grouped into two phases. They are Phase I or non-synthetic 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
- There are several cytochrome P450 isoenzymes
- They are numbered as 1,2,3,4... (to denote families) and each as A,B,C,D (sub-families)
- More than 50% of drugs undergo biotransformation reactions by CYP3A4/5

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Table 1.1	Phase I reactions	
Oxidation	Addition of oxygen/ removal of hydrogen	Phenytoin, phenobarbitone, pentobarbitone, 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

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

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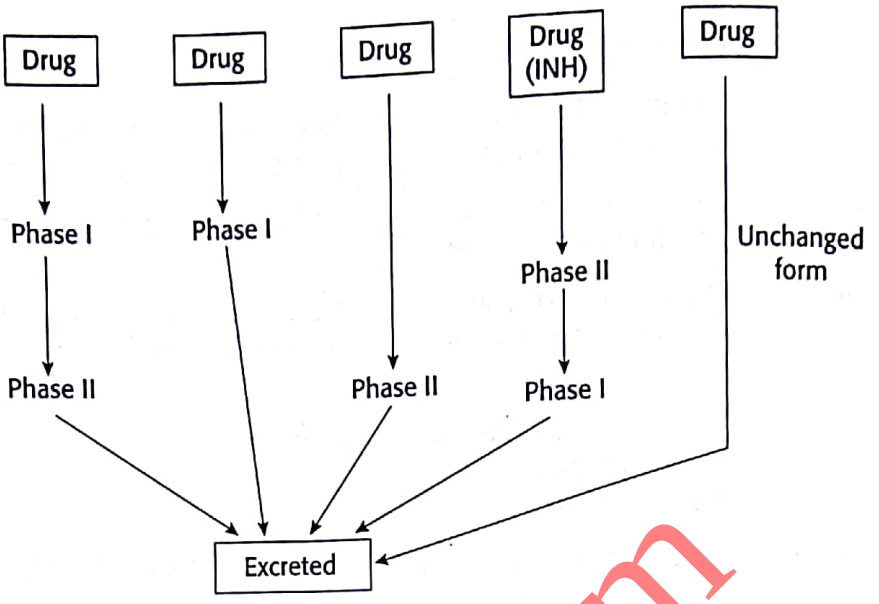

FIGURE 1.5 Phases of biotransformation.

Drug-Metabolizing Enzymes

They are broadly divided into two groups—microsomal and non-microsomal 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

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Table 1.3 Microsomal and non-microsomal enzymes

Microsomal enzymes	Non-microsomal 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	Oxidation, reduction (few), hydrolysis. All conjugations except glucuronide conjugation
Inducible	Not inducible – may show genetic polymorphism

microsomal enzymes. Neonates conjugate chloramphenicol more slowly, hence develop toxicity—gray 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, e.g.:
   (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 apnoea due to paralysis of respiratory muscles, which is dangerous. This is known as succinylcholine apnoea.
   (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 D_3.

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5. Enzyme inducers 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.

Drug Excretion

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
   (a) *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.
   (b) *Passive tubular reabsorption:* The main factor affecting passive reabsorption is the pH of renal tubular fluid and the degree of ionisation. Strongly acidic and strongly basic drugs remain in ionised form at any pH of urine, hence are excreted in urine.
      (i) Weakly acidic drugs (e.g. salicylates, barbiturates) in acidic urine remain mainly in 'unionised' form, so they are reabsorbed into the circulation. If the pH of urine is made alkaline by sodium bicarbonate, the weakly acidic drugs get 'ionised' and are excreted easily.
      (ii) Similarly, weakly basic drugs (e.g. morphine, amphetamine, etc.) in alkaline urine remain in 'unionised' form, hence are reabsorbed.

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If the pH of urine is made acidic by vitamin C (ascorbic acid), these weakly basic drugs get 'ionised' and are excreted easily.

(c) *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 tubules. 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 that are not completely absorbed from the GI tract are excreted in faeces, e.g. purgatives like senna, cascara, etc.
4. **Bile:** Some drugs are excreted via bile but after reaching the intestine they are reabsorbed → liver → bile and the cycle is repeated—such recycling is called enterohepatic circulation and it increases the bioavailability as well as the duration of action of the drug, e.g. morphine and doxycycline.
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 non-invasive monitoring of lithium therapy.
7. **Milk:** Drugs taken by lactating women may appear in milk. It has acidic pH, hence basic drugs like tetracycline, chloramphenicol, morphine, diazepam, etc. remain in ionised form and are excreted through milk; they may affect the suckling infant.

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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. 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 a drug 'A' with a plasma $t^{1}/_{2}$ of 1 hour, following first-order kinetics of elimination and having an initial plasma concentration of 100 mcg/mL.

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

   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. The rate of elimination is *independent* of plasma drug concentration, e.g. ethanol is eliminated from the body at the rate of about 10 mL/h. The $t^{1}/_{2}$ of the drug following zero-order kinetics is never constant.

   For example, assume a drug 'B' with an initial plasma concentration of 200 mcg/mL and eliminated at the rate of 10 mcg/h. Its elimination will be as follows:

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

Drugs like phenytoin and aspirin

↓

At low doses, follow *first-order* kinetics

↓ As the plasma concentration increases

Elimination processes get saturated

↓

Kinetics changes over to *zero order* (saturation kinetics)

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.

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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. 1.6(b)]. It is attained after approximately 4–5 half-lives.

Factors Influencing Drug Dosage

Many factors have to be considered when a drug is given to a patient. The time taken to act depends mainly on the route of drug administration. For rapid effect, the drug is usually given intravenously. In general, the time taken to reach a steady state is approximately four to five half-lives of the drug during repeated administration at a constant rate.

1. **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 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.
2. **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.

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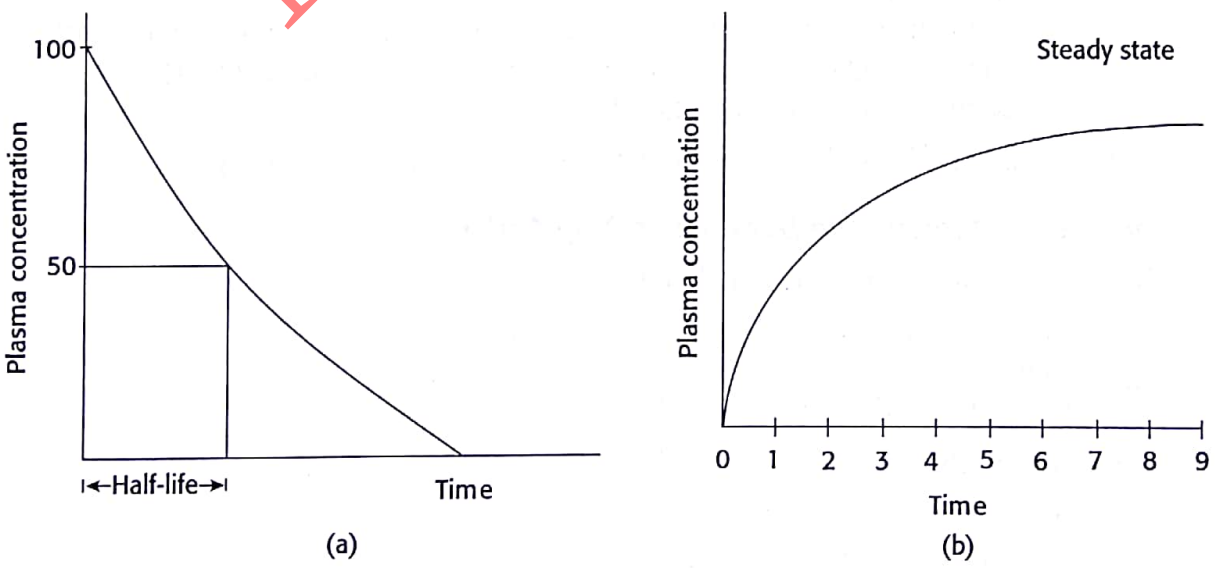

FIGURE 1.6 (a) Plasma half-life of a drug after single intravenous injection. (b) Steady state: Achieved after approximately four to five half-lives during repeated administration at a constant rate.

Therapeutic Drug Monitoring

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 anticoagulants.
2. Drugs, producing tolerance, e.g. opioids.
3. Drugs whose effect persists longer than the drug itself, e.g. omeprazole.

Fixed Dose Combination (FDC; Fixed Dose Ratio Combination)

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 for tuberculosis.
- Ferrous sulphate + folic acid for anaemia of pregnancy.
- Sulphamethoxazole + trimethoprim in cotrimoxazole (antimicrobial agent).
- Amoxicillin + clavulanic acid in Augmentin (antimicrobial agent).
- Oestrogen + progesterone as oral contraceptive.

Advantages and disadvantages of FDC are explained in Table 1.4 p. 25.

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.

Various methods to prolong the duration of drug action are:

(a) **By retarding drug absorption:**

1. **For orally administered drugs:**
   - *By using sustained release preparations:* These preparations consist of drug particles, which have different coatings that dissolve at different

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Table 1.4 Advantages and disadvantages of FDC

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

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.

2. **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. 8)

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(b) **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.

(c) **By inhibiting drug metabolism:** For example, allopurinol + 6-mercaptopurine (6-MP). 6-MP is matabolized by xanthine oxidase. Allopurinol → xanthine oxidase inhibitor → inhibits metabolism of 6-MP → prolongs action of 6-MP.

(d) **By delaying renal excretion of the drug**, e.g. penicillin/cephalosporins with probenecid.

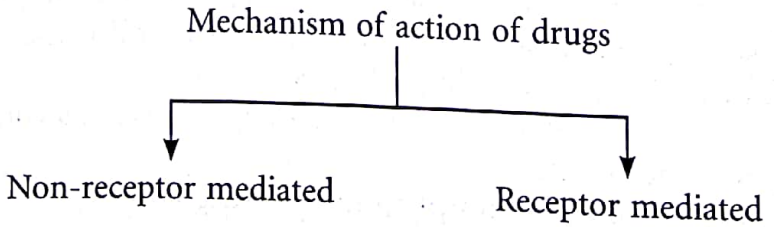
PHARMACODYNAMICS

Pharmacodynamics (*Gr. Pharmacon:* 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 Drug Action

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 sprains, joint pain and myalgia. They exert their action by:
   - Reflexly increasing local circulation in deeper structures.
   - Blocking impulse conduction in the spinal cord.
4. **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 myxedema, etc.
5. **Cytotoxic:** Drugs are selectively toxic for the infecting organism/cancer cells, e.g. antibiotics/anticancer drugs.

Mechanism of Drug Action



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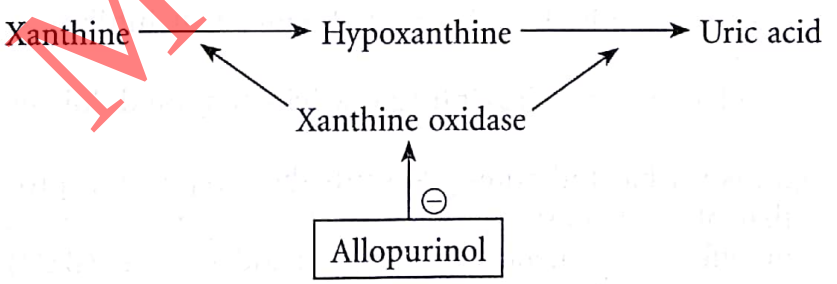
Non-Receptor-Mediated Mechanism of Action of Drugs

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:**
   (a) Antacids are weak bases – they neutralise gastric acid – useful in peptic ulcer.
   (b) 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.
   (a) *Drug action via enzyme inhibition:*
      (i) Angiotensin-converting enzyme (ACE) inhibitors, such as captopril, enalapril, etc. act by inhibiting ACE. They are used in the treatment of hypertension, CHF, etc.
      (ii) Xanthine and hypoxanthine are oxidised to uric acid by the enzyme xanthine oxidase, which is inhibited by allopurinol. Allopurinol is used in the treatment of chronic gout to reduce the synthesis of uric acid.



4. **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.
5. **Through antibody production:** Vaccines produce their effect by stimulating the formation of antibodies, e.g. vaccine against tuberculosis (BCG), oral polio vaccine, etc.
6. **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.

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7. **Others:** Anticancer drugs like cyclophosphamide produce their effect by binding to nucleic acids; drugs like colchicine bind to tubulin and prevent migration of neutrophils (hence useful in acute gout).

Receptor-Mediated Mechanism

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.

$$\text{Drug (D)} + \text{Receptor (R)} \rightleftharpoons \text{Drug-receptor complex} \longrightarrow \text{Response}$$

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 the 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 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 produce antianxiety and anticonvulsant effects by interacting with benzodiazepine (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-carbolines).

Receptor Families. (Table 1.5)

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

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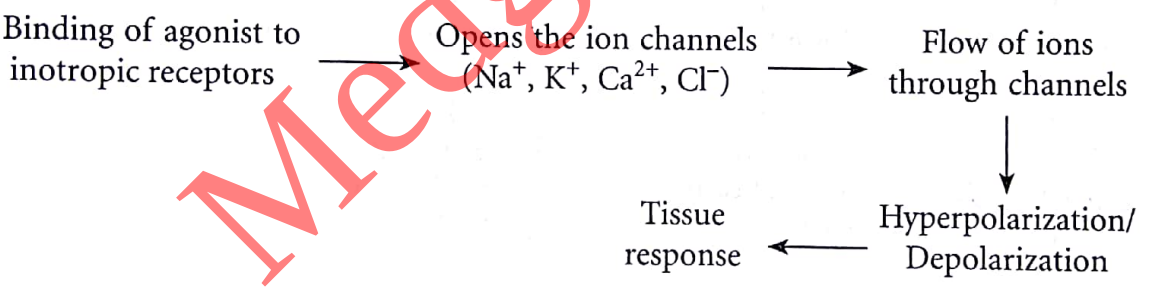
Table 1.5 Characteristics of various receptor families

	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
Coupling	Direct	G proteins (Gs, Gi, Gq, etc.)	Direct	Via DNA
Examples	Nicotinic, $GABA_A$ receptors	Muscarinic, adrenergic receptors	Insulin, growth factor, cytokine receptors	Steroid, thyroid hormone receptors
Time required for response	Milliseconds	Seconds	Minutes to hours	Hours

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



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

G-Protein Coupled Receptors (Metabo-tropic Receptors). 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.

G-Protein-Coupled Receptors: Effector Pathways and Second Messengers

G-protein-coupled receptors (GPCRs) are transmembrane receptors which control cell function via adenylyl cyclase, phospholipase C, ion channels, etc.

The agonist that binds to the receptor is the first messenger. It results in the generation or recruitment of molecules (second messengers) that initiate the signaling 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.

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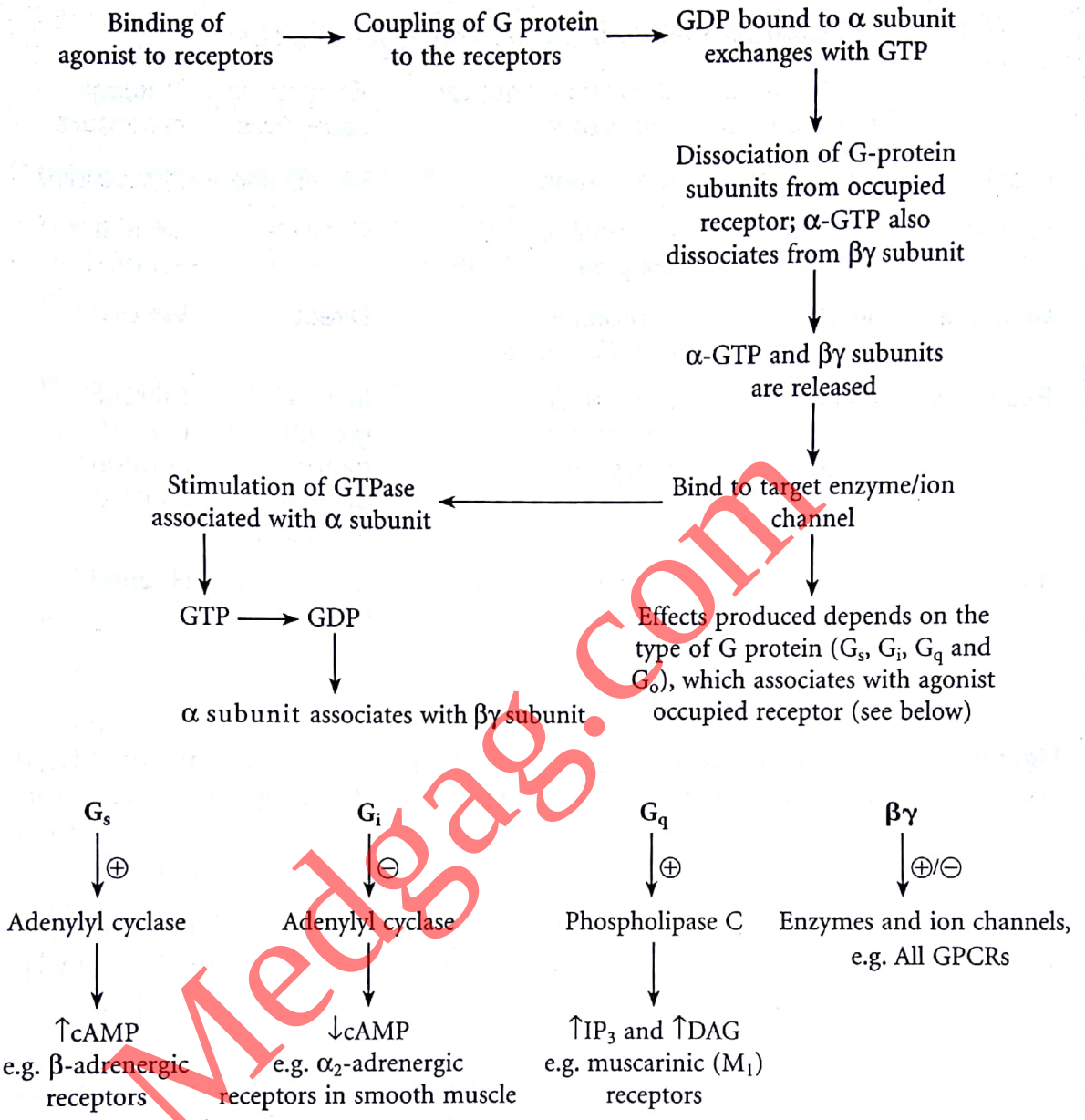

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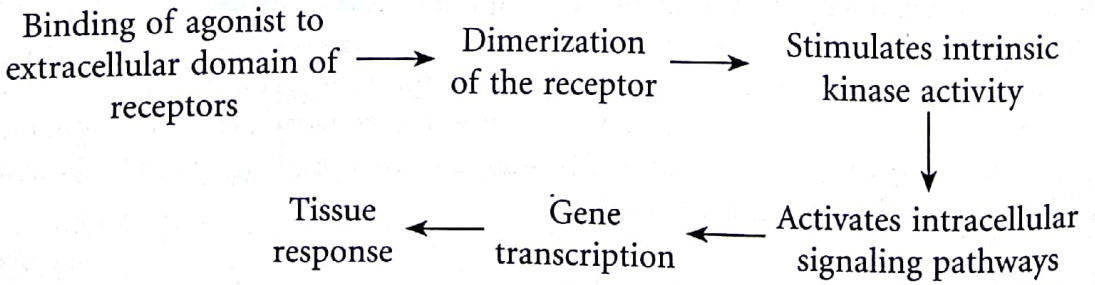
Transmembrane enzyme-linked receptors

These could be

- transmembrane enzyme-linked receptors (e.g., receptor tyrosine kinases for insulin, epidermal growth factor, etc). Intracellular part of the receptor has enzymatic activity (intrinsic enzyme activity). (Transmembrane receptors, e.g. receptors for cytokines, growth hormone, etc. have no intrinsic enzymatic activity in their intracellular part. On activation, they bind to cytosolic kinases, e.g. Janus Kinase [JAK]).



Nuclear Receptors – Regulate Gene Expression

Examples: receptors for thyroxine, vitamins A and D, sex steroids and glucocorticoids.

Regulation of Receptors

Receptors can be regulated by various mechanisms resulting in either their up-regulation or down-regulation (Table 1.6).

Dose-Response Relationship

The pharmacological effect of a drug depends on its concentration at the site of action, which in turn is determined by the 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 is sigmoid shaped [Fig. 1.7(a) and (b)].
2. **Quantal dose-response curve:** 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. 1.7(c)].

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Table 1.6 Regulation of receptors

Receptor down-regulation	Receptor up-regulation
Prolonged use of agonists ↓ ↓↓ Receptor number and sensitivity ↓ ↓↓ Drug effect For example, chronic use of salbutamol down-regulates the 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 antagonist ↓ ↑↑ Response to agonist For example, when propranolol is stopped after prolonged use, some patients experience withdrawal 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 up-regulation or supersensitivity of β-adrenoceptors to catecholamines. Therefore, propranolol should not be discontinued abruptly.

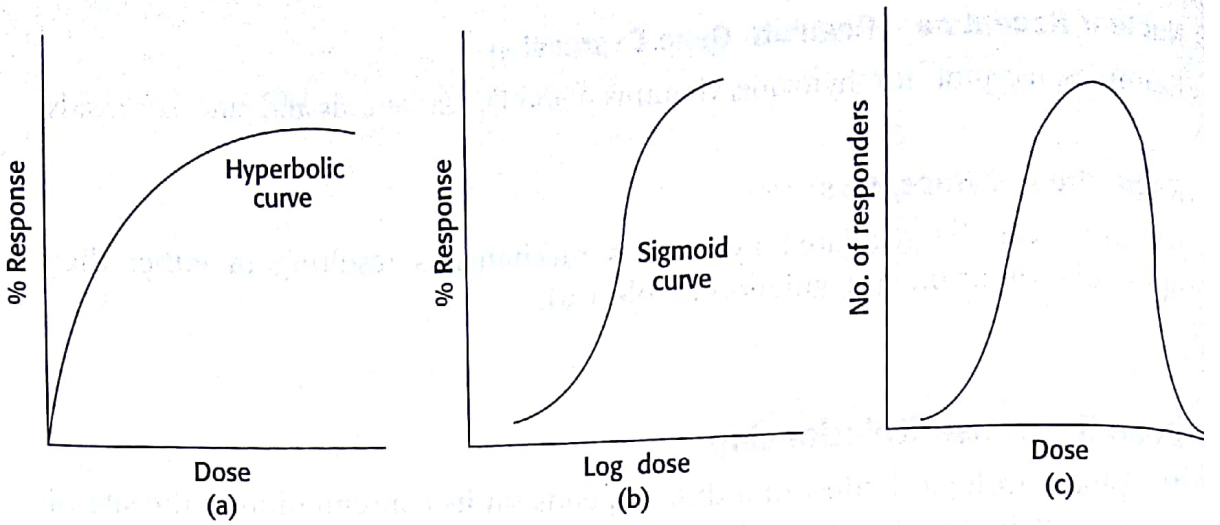

FIGURE 1.7 (a) Dose-response curve. (b) Log dose-response curve. (c) Quantal dose-response curve.

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).

(a) LD_{50}: It is the dose of a drug, which is lethal for 50% of the population.
(b) ED_{50}: 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 has a high therapeutic index; digitalis, lithium and phenytoin have narrow therapeutic index.

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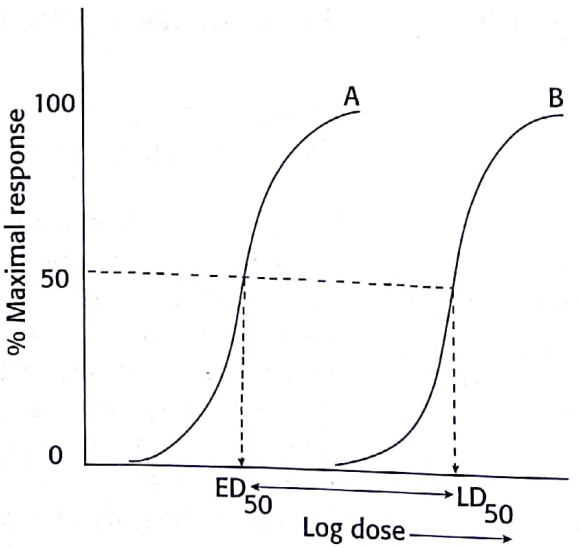

FIGURE 1.8 Dose-response curves of therapeutic effect (A) and adverse effect (B). Distance between ED_{50} and LD_{50} indicates safety margin.

Drug Potency

The amount of a drug required to produce a desired response is called the potency of the drug. The lower the dose required for a given response, the more potent is the drug, e.g. the 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. Dose-response curve (DRC) of two drugs—drug A (morphine) and drug B (pethidine)—as analgesic are compared (Fig. 1.9).

Drug Efficacy

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

Therapeutic Window

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

1. **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 the breakdown of levodopa and acetylcholine, respectively, thus enhancing their effects.

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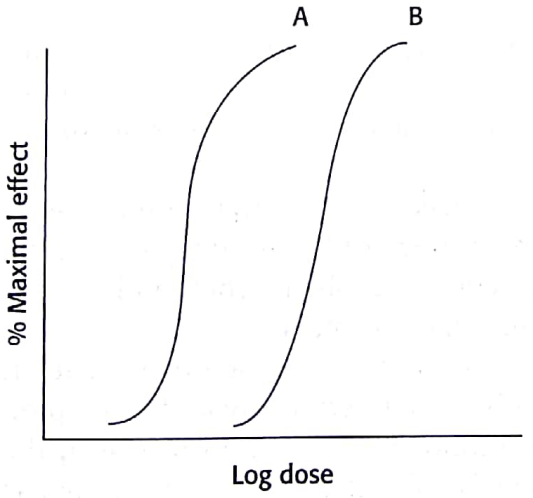

FIGURE 1.9 Relative potency of two drugs.

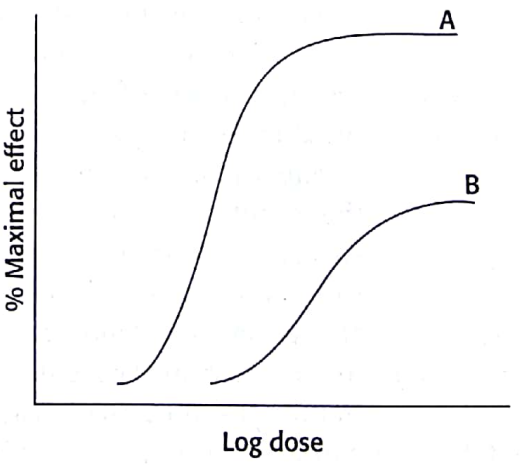

FIGURE 1.10 Relative efficacy of two drugs.

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 neutralise 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 non-competitive.
   (a) *Competitive antagonism (equilibrium type)*: In competitive antagonism, both agonist and the antagonist bind reversibly to the same site on the receptor.
   For example,

Acetylcholine	→	Muscarinic receptors	←	Atropine
Morphine	→	Opioid receptors	←	Naloxone
(Agonists)				(Antagonists)

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

   Non-equilibrium 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) *Non-competitive 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 dose-response curve (DRC) in non-competitive antagonism, e.g. diazepam and bicuculline (Fig. 1.12).

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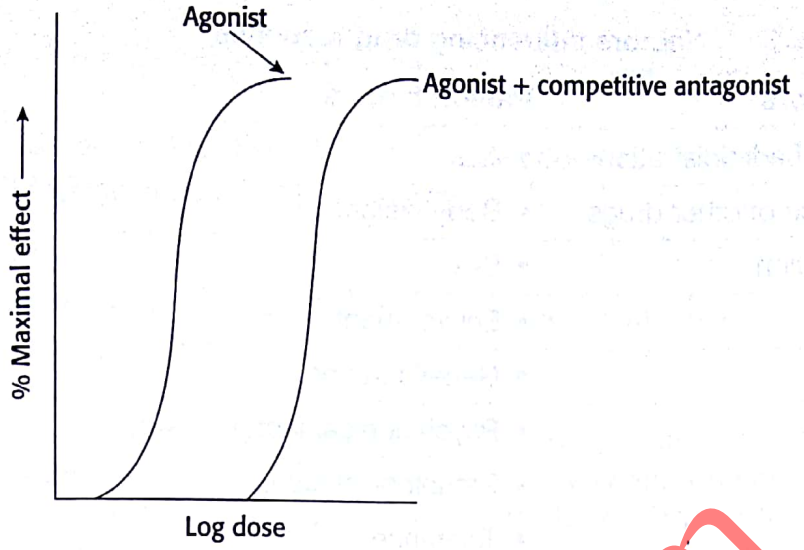

FIGURE 1.11 Competitive antagonism. (Adapted from *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12e.)

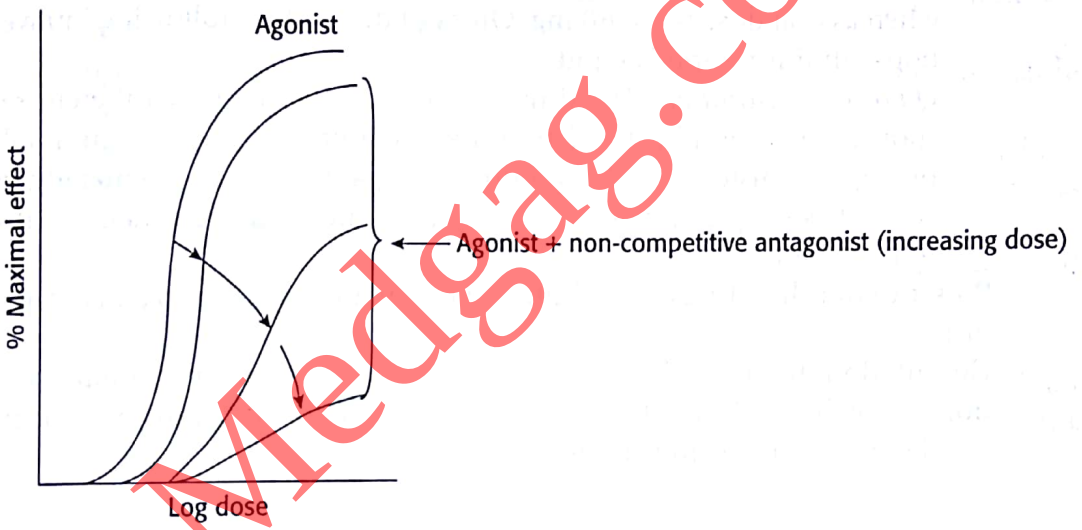

FIGURE 1.12 Non-competitive antagonism. (Adapted from *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12e.)

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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

Table 1.7 Factors influencing drug response

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

whereas oral dose is 30–60 mg. Onset of drug action following intravenous administration is rapid.

(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 the drug will result in its accumulation in the body causing toxicity, e.g. digoxin, emetine and chloroquine.

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Patient Factors

1. Age: In neonates, the metabolizing function of the liver and excretory function of the kidney is not fully developed, e.g. chloramphenicol can cause gray baby syndrome when given to neonates as the metabolizing enzymes are not fully developed. In adults, penicillin G is given six-hourly, but in infants it is given twelve-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:

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

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

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:** See p. 19 under metabolism.
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.

(a) *Uses*
   (i) Placebos are used for the relief of subjective symptoms like anxiety, headache, tremors, pain, insomnia, etc.
   (ii) Placebos are used in clinical trials in order to minimize bias.

(b) *Factors affecting placebo effect are*:
   (i) **Patient factor:** Patients with neurotic symptoms often respond to placebos.
   (ii) **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.
   (iii) **Doctor factor:** Personality of the doctor, motivation, way of instruction, doctor–patient relationship, etc. are important factors that also affect response to placebo.

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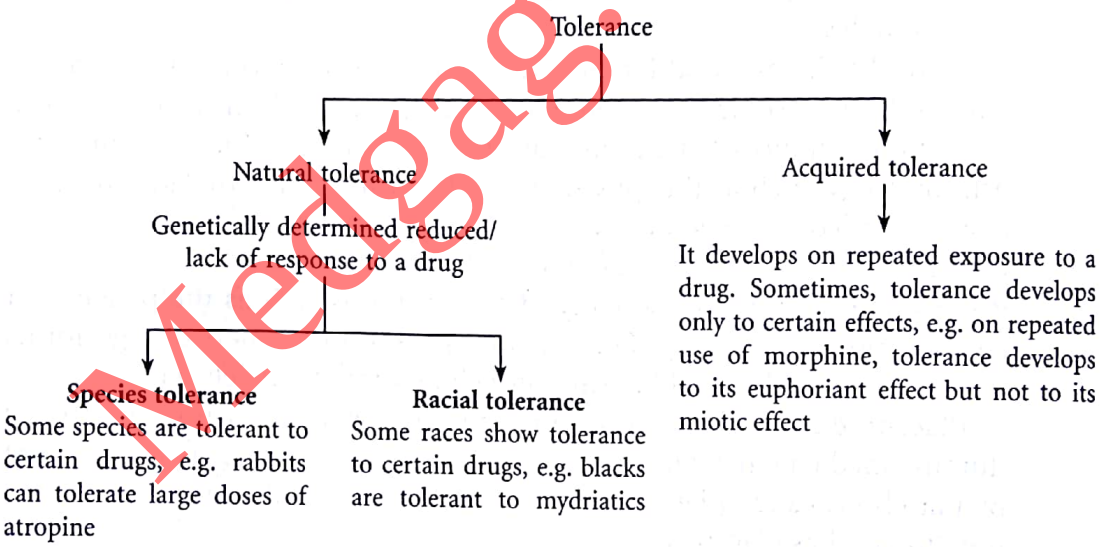
7. **Pathological states:**
   (a) *GI disorders*: Achlorhydria reduces the absorption of weakly acidic drugs in the stomach by causing their ionisation. In malabsorption syndrome, the absorption of some drugs is reduced.
   (b) *Liver disease*: In chronic liver diseases, the metabolism of drugs is greatly 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.
   (e) Patients with myxedema are more sensitive to morphine.
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.
      (i) *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 metabolising enzyme of oral contraceptives, enhances their metabolism, leading to contraceptive failure.
      (ii) *Pharmacodynamic tolerance (Functional tolerance):* The drug effect is reduced, which may be due to down-regulation 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 (down regulation).

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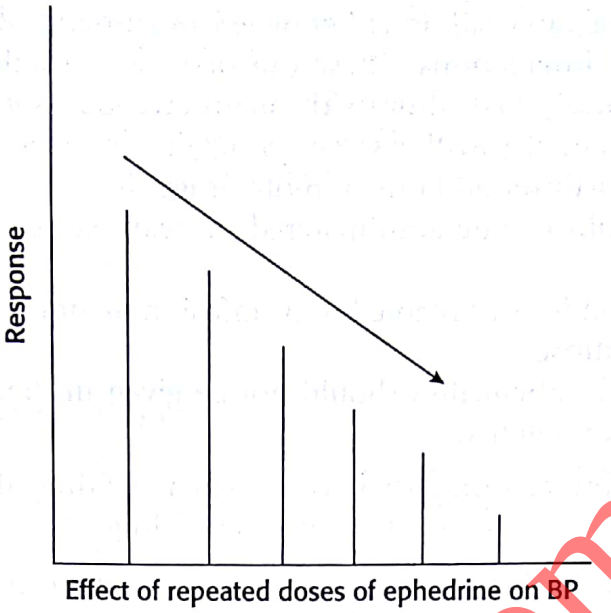

FIGURE 1.13 Tachyphylaxis. BP: Blood pressure.

(iii) *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.

(iv) *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 the 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. 44.

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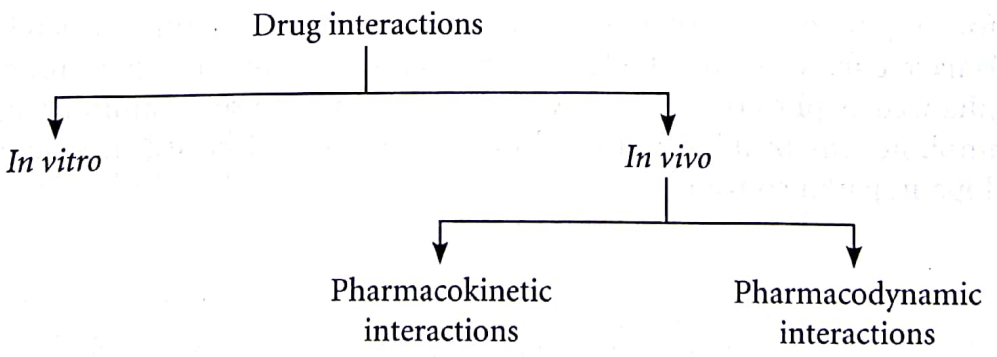
DRUG INTERACTIONS

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 aluminum, 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 gastrointestinal 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 the kidneys.
  - Salicylates interfere with the excretion of methotrexate and potentiate its toxicity.
  - Probenecid decreases renal tubular secretion of penicillins and prolongs duration of action of penicillins (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 p. 33-34). 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.

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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.

Irrationalities in Prescribing

- Unnecessary use of drugs, e.g. antibiotics for viral infections.
- Drug not prescribed as per standard treatment guidelines.
- 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.
- Emergence of drug-resistant microorganisms.
- Increase in cost of treatment.
- Financial burden to society.
- Loss of patient's faith in the doctor.

Rational Prescribing

- Define the therapeutic problem.
- Make a diagnosis.
- Define therapeutic goals to be achieved, e.g. relief of symptoms, cure, etc.
- Select the right drug - appropriate route, dose and duration of treatment. Write a complete prescription.
- Give proper instructions and information about the drug.
- Monitor therapy.

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ADVERSE DRUG EFFECTS

Adverse Effect

Adverse effect is defined as any undesirable or unwanted effect due to drug administration. The WHO suggested definition of ADR and AE are as follows:

Adverse drug reaction (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.

Adverse event: 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 ADRs

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

Adverse Drug Effects Include:

- *Side effects:* These are the unwanted pharmacological effects of a drug, which 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.
- *Drug allergy:* It is an abnormal response (local or systemic), mediated by the 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.

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Exposure to certain drugs (penicillin, aspirin, lignocaine)

↓

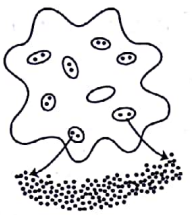
Production of IgE antibodies – fix to mast cells

↓

On re-exposure to the same drug

↓

Ag–Ab reaction occurs on the mast cell surface



Release of mediators
(Histamine, 5-HT, PGs, LTs, PAF)

↓

Hypotension, bronchospasm, angioedema, urticaria, rhinitis and anaphylactic shock

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. Intravenous fluids.

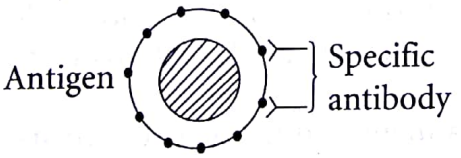
Type II hypersensitivity (cytotoxic) reactions

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

IgG- and IgM-mediated

↓

The antibody reacts with cell-bound antigens



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Activation of complement

↓

Destruction of cells

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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 antiinflammatory drugs (NSAIDs) and Stevens–Johnson syndrome with sulphonamides.

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

It is mediated by sensitized T lymphocytes. Re-exposure 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, succinylcholine apnoea, haemolytic anaemia seen with primaquine and sulphonamides.
- *Drug Dependence*
  World Health Organization (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.
  1. **Psychological dependence:** There is an intense desire to continue taking the drug as the patients feel that their well-being depends upon the drug.
  2. **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/buprenorphine substitution for morphine addiction.
  3. **Aversion therapy:** Disulfiram for alcohol addiction.
  4. **Psychotherapy**
  5. General measures: Maintain nutrition, family support and rehabilitation.

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- *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 nonsteroidal antiinflammatory drugs.
- *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)** has placed drugs in various categories (A, B, C, D, X) depending on the risk of the drug to cause birth defects. Category X drug (e.g., warfarin, methotrexate) is contraindicated for use during pregnancy as risk to fetus is proven and outweighs benefits of its use.
- *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/phototoxity) following exposure to ultraviolet radiation. Sulfonamide causes photoallergy on exposure to light, it produces dermatitis due to immune response (cell mediated). Doxycycline can cause phototoxicity – a local reaction occurs on exposure to UV light.
- *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.

Table 1.8 Teratogenic effects of some drugs

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

*Mnemonic for nephrotoxicity: VACATION.

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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 adverse drug reactions.

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 adverse drug reactions.

TREATMENT OF POISONING

Toxicology is the study of poisons—their actions, detection, prevention and treatment of poisoning. All poisoning cases require hospitalisation 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 h 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

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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, syrup ipecac, 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 gastrointestinal tract in case of poisoning due to iron, lithium, cocaine, heroin, foreign bodies, etc.

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. alkalinisation 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.

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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	Ethyl alcohol, fomepizole
Paracetamol	*N*-Acetylcysteine
Heparin	Protamine sulphate
Warfarin	Vitamin K_1 (phytonadione)
Iron compounds	Desferrioxamine

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PHARMACOECONOMICS

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

A drug should be carefully 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.

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 non-rodent). Single, graded doses are administered to small groups of animals using two routes—one that is to be used in human. 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 non-rodent) 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

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. 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. 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. It is conducted in about 50–500 patients and usually in 3–4 centres.

Phase III (Therapeutic Confirmation Trials)

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

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Phase IV (Post-Marketing Surveillance)

Once the drug is approved for marketing, post-marketing surveillance is carried out to obtain additional data about benefit and risk of use of drug in a larger number of patients following long-term use. It provides information on adverse reactions, drug interactions, new indications and evaluation of different formulations. Post-marketing 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 post-marketing data for the drug at regular intervals to the regulatory agency to continue its use.

Good Clinical Practice

Good clinical practice (GCP) 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 discussion. 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 is required to form the quorum.

Composition

1. Chairperson (from outside the institution to maintain independence of the committee).
2. One or two basic medical scientists (preferably one pharmacologist).

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3. One or two clinicians from various institutes.
4. One legal expert or retired judge.
5. One social scientist/representative of non-governmental voluntary agency.
6. One philosopher/ethicist/theologist.
7. One lay person from the community.
8. 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.

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CHAPTER 2

Drugs Acting on Autonomic Nervous System

INTRODUCTION TO AUTONOMIC PHARMACOLOGY

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 (p. 53).

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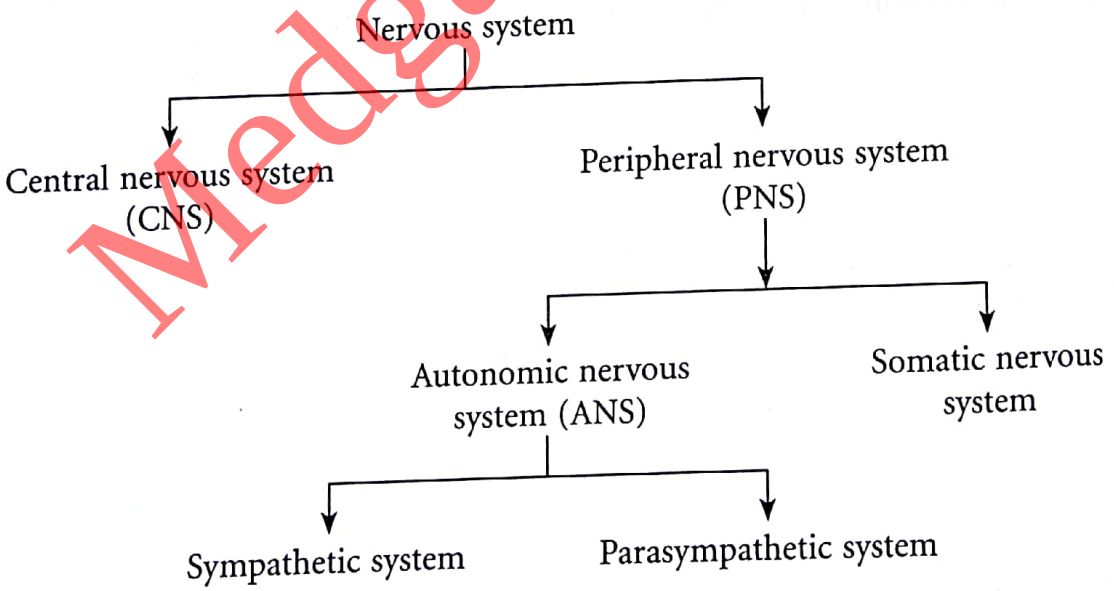
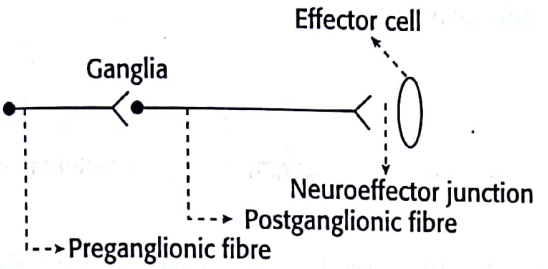
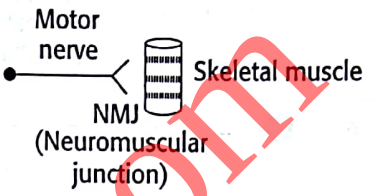


The ANS has two divisions—sympathetic and parasympathetic (Fig. 2.1, p. 53).

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 other hand, the parasympathetic preganglionic fibres are long and postganglionic fibres are short (Fig. 2.2, p. 54). Most of the visceral

Table 2.1 Differences between ANS and somatic nervous system

Autonomic nervous system	Somatic nervous system
Auto: self; *nomos:* 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 muscle
	
It innervates the heart, smooth muscles and exocrine glands	It innervates skeletal muscle
It controls visceral functions such as circulation, digestion, excretion, etc.	It controls skeletal muscle tone

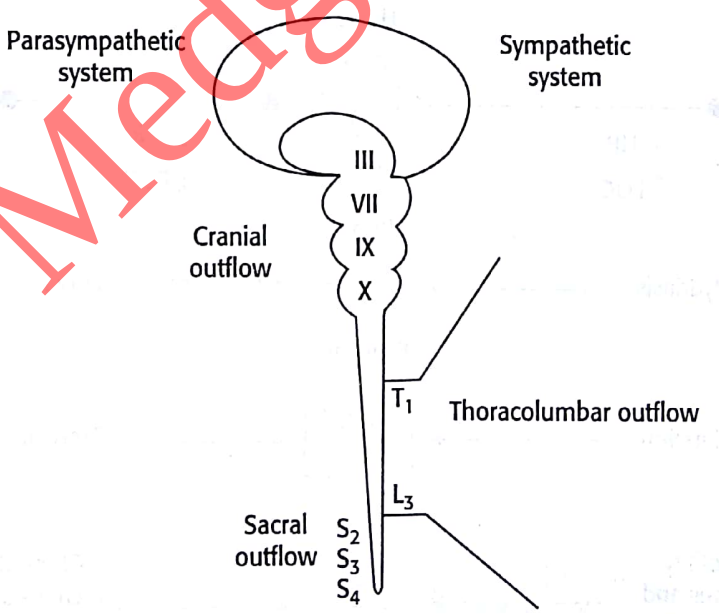


FIGURE 2.1 Divisions of ANS.

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. 2.3, p. 54).

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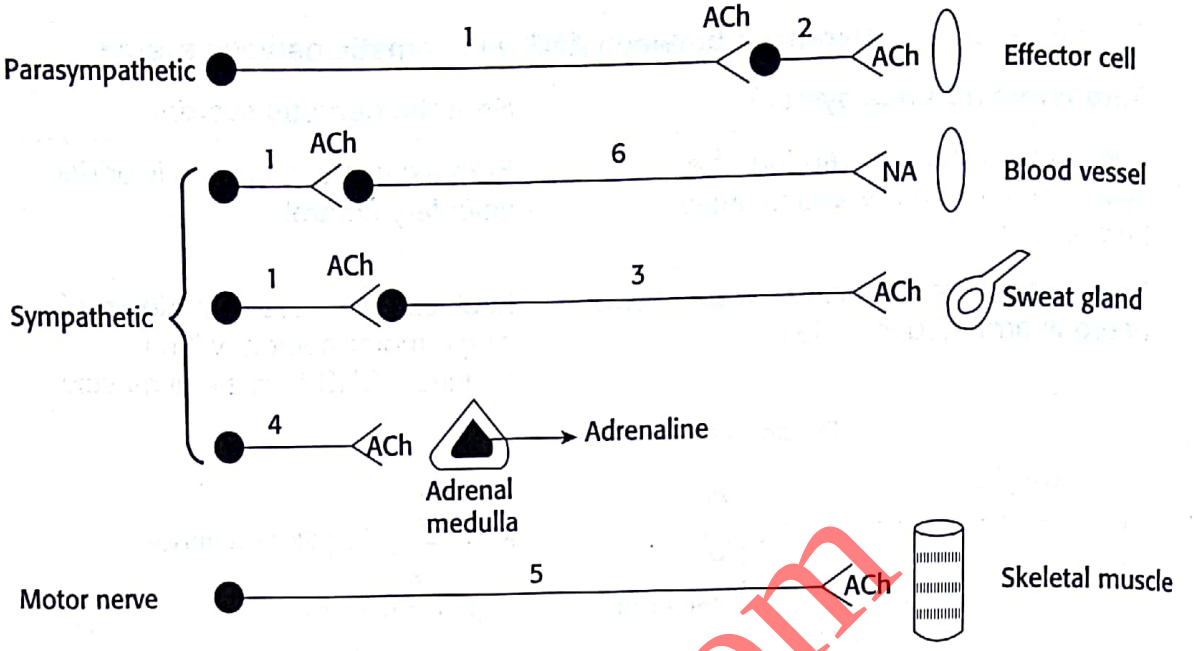

FIGURE 2.2 Sites of acetylcholine (ACh) and noradrenaline (NA) release in the PNS: 1, preganglionic fibres of both sympathetic and parasympathetic system; 2, postganglionic fibres of parasympathetic system; 3, sympathetic postganglionic fibres supplying the sweat glands; 4, nerve fibres supplying the 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.

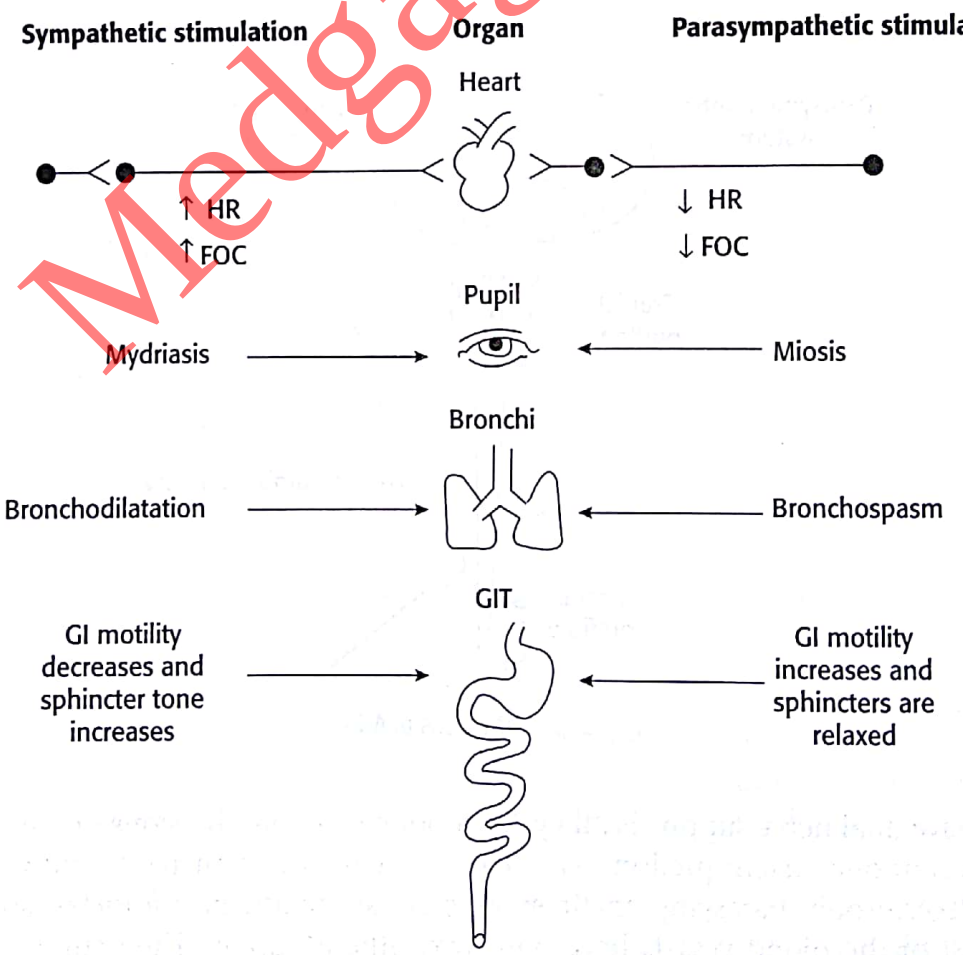

FIGURE 2.3 Effects of sympathetic and parasympathetic stimulation on various organs. HR, Heart rate; FOC, Force of contraction; and GIT, Gastrointestinal tract.

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CHOLINERGIC SYSTEM

Cholinergic Transmission

Acetylcholine (ACh) is the neurotransmitter in the cholinergic system. The sites of cholinergic transmission are shown in Fig. 2.2, p. 54. The neurons that synthesize, store and release ACh are called cholinergic neurons (Fig. 2.4).

Synthesis of Acetylcholine (Fig. 2.4)

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 the 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, the ACh is rapidly hydrolysed by acetylcholinesterase (AChE) enzyme.

Cholinesterases

Acetylcholine is rapidly hydrolysed to choline and acetic acid by enzymes cholinesterases. There are two types of cholinesterases:

1. **True cholinesterase or AChE:** It is found in cholinergic neurons, ganglia, RBCs and neuromuscular junction (NMJ). It rapidly hydrolyses ACh and methacholine.

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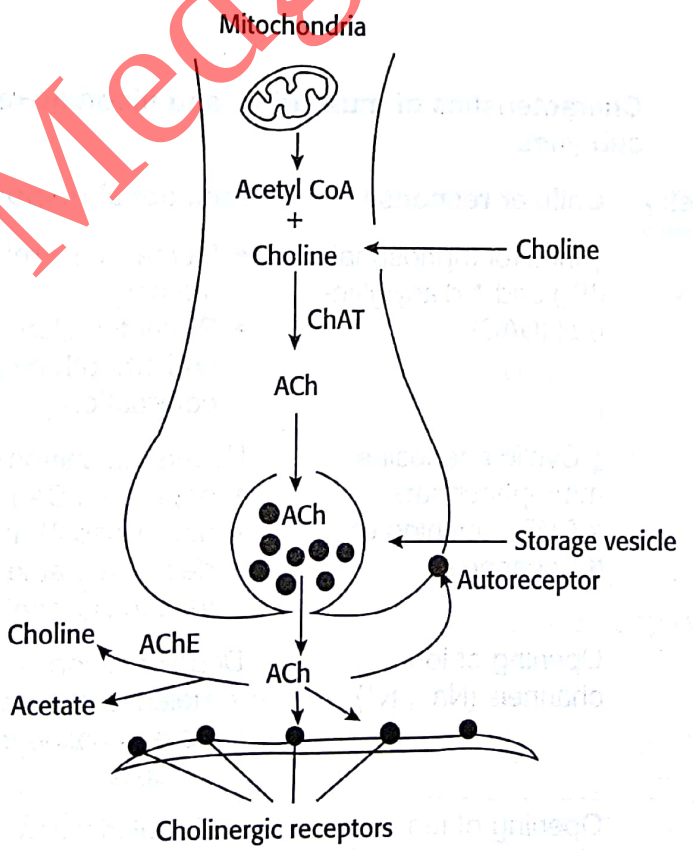

FIGURE 2.4 Synthesis, storage and fate of released ACh at the cholinergic nerve endings. ChAT, choline acetyltransferase; AChE, acetylcholinesterase.

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 the CNS. All muscarinic receptors are G-protein-coupled receptors and regulate the production of intracellular second messengers.

Muscarinic receptor subtypes with their location(s)

- **M_1**
  - Gastric glands
  - Autonomic ganglia
  - CNS
- **M_2**
  - Heart
- **M_3**
  - Smooth muscles
  - Exocrine glands
  - Endothelial cells
- **M_4 and M_5**
  - CNS

Nicotinic receptors are divided into two subtypes—N_N and N_M. Activation of these receptors directly open the ion channels and causes depolarization of the membrane. The characteristics of muscarinic and nicotinic receptors are shown in Table 2.2.

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Table 2.2 Characteristics of muscarinic and nicotinic receptor subtypes

Receptor type(s)	Cellular response	Functional 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 noradrenaline from adrenal medulla
N_M	Opening of ion channels (Na^+, K^+)	• Depolarization • Skeletal muscle contraction

Nicotinic receptor subtypes with their location(s)

N_N
- Autonomic ganglia
- Adrenal medulla

N_M
- Neuromuscular junction

CHOLINERGIC AGENTS (CHOLINOMIMETICS, PARASYMPATHOMIMETICS)

Acetylcholine 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

Cholinergic agonists

Directly acting

Choline esters
- Acetylcholine
- Bethanechol
- Carbachol

Alkaloids
- Pilocarpine
- Muscarine

Indirectly acting (anticholinesterases)

Reversible

Carbamates
- Physostigmine
- Neostigmine
- Pyridostigmine
- Edrophonium
- Rivastigmine
- Donepezil
- Galantamine
- Carbaryl } used as insecticides
- Propoxur (Baygon) } used as insecticides

Irreversible

Organophosphorus (OP) compounds
- Parathion
- Malathion
- Sarin, soman, tabun (nerve gases)
- Dyflos
- Echothiophate

Choline Esters

Choline esters include acetylcholine, carbachol and bethanechol.

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Acetylcholine

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

Muscarinic Actions

1. **Cardiovascular system**
   (a) **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. 2.5).

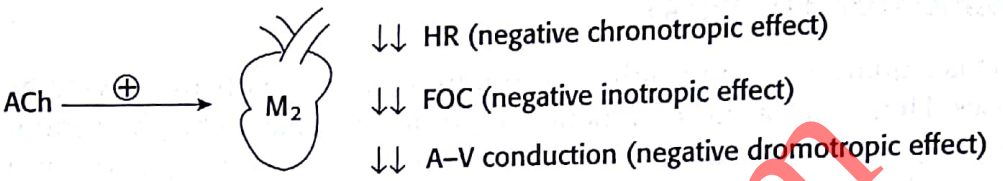

FIGURE 2.5 Effects of acetylcholine (ACh) on heart.

   (b) **Blood vessels:** Acetylcholine 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. 2.6).

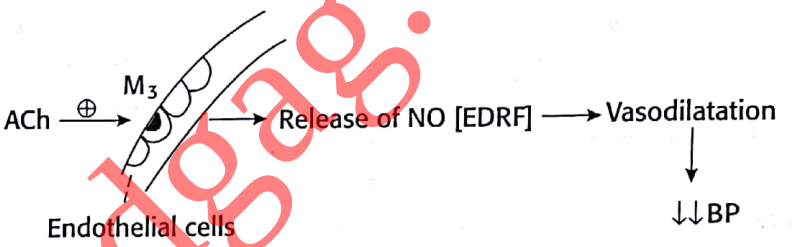

FIGURE 2.6 The effect of acetylcholine (ACh) on blood vessels.

2. **Smooth muscles**
   (a) **Gastrointestinal tract** (Fig. 2.7)

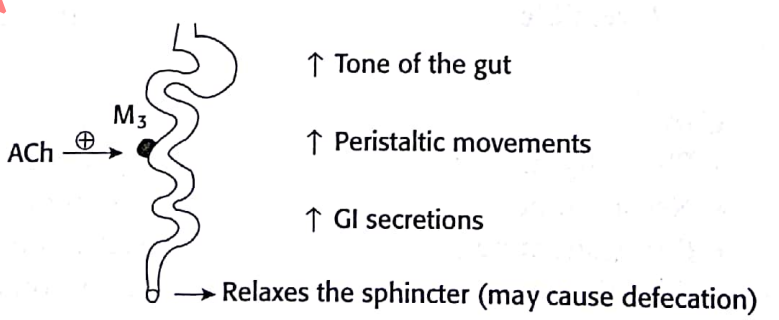

FIGURE 2.7 Effects of acetylcholine (ACh) on gastrointestinal (GI) tract.

   (b) **Urinary bladder** (Fig. 2.8)

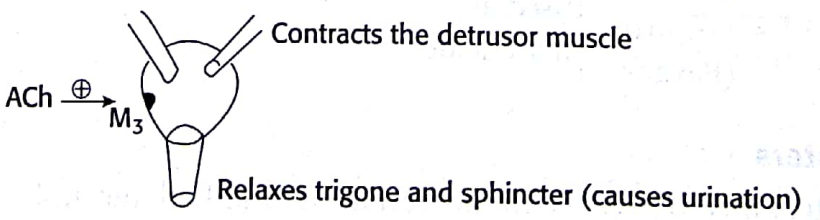

FIGURE 2.8 Effects of acetylcholine (ACh) on urinary bladder.

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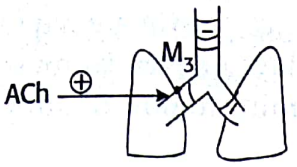
(c) **Bronchi** (Fig. 2.9)



Contracts the bronchial smooth muscle (bronchospasm)
Increases tracheobronchial secretion – therefore, cholinergic drugs are contraindicated in asthmatics

FIGURE 2.9 The effect of acetylcholine (ACh) on bronchi.

3. **Exocrine glands:** Increase in salivary, lacrimal, sweat, bronchial, gastric and other gastrointestinal (GI) secretions.
4. **Eye** (Fig. 2.10): ACh does not produce any effect on topical administration because of its poor penetration through tissues.

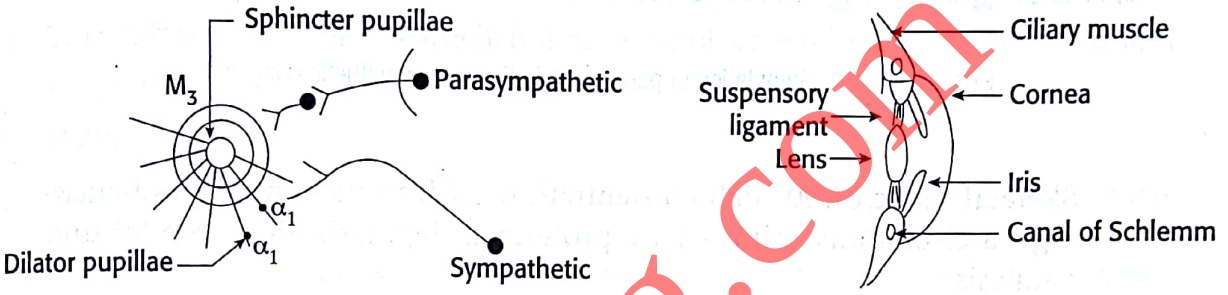


FIGURE 2.10 Autonomic innervation of the eye.

Action of ACh on eye can be depicted as follows:

Acetylcholine (i.v.), pilocarpine, physostigmine
⊕
↓
M_3 receptors
↓
Contract sphincter pupillae (miosis) + Contract ciliary muscle → Spasm of accommodation
↓
Open the trabecular meshwork around the canal of Schlemm
↓
Facilitate drainage of aqueous humour and reduce intraocular pressure (IOP) in glaucoma

Ciliary muscle contraction → relaxation of suspensory ligaments of lens
↓
Bulging of lens
↓
Vision fixed for near distance

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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 as well as parasympathetic ganglia (Fig. 2.11) causing tachycardia and rise in BP.

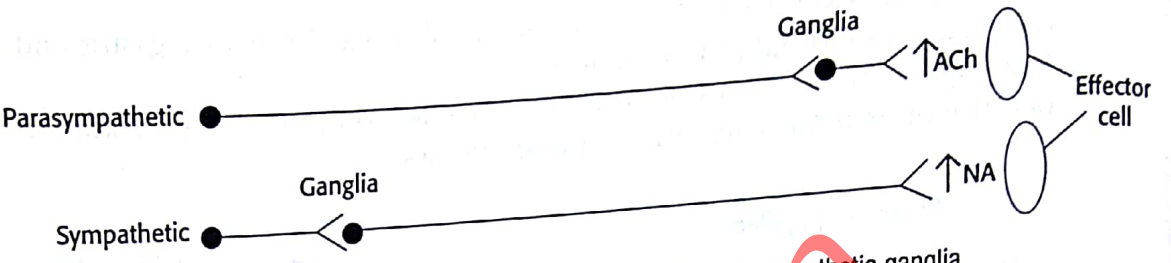

FIGURE 2.11 Stimulation of parasympathetic and sympathetic ganglia.

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

- it has a wide margin of safety.
- it has no nicotinic actions.
- its muscarinic side effects are completely antagonized by atropine.
- in urinary retention, it causes voiding of urine by contracting the detrusor muscle and relaxing the trigone sphincter.
- in paralytic ileus, it stimulates peristaltic movement and increases the tone by interacting with M_3 receptors of the gut.

Table 2.3 Pharmacological properties and uses of choline esters

	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

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Table 2.3 Pharmacological properties and uses of choline esters—cont'd

	Choline esters		
	Acetylcholine	**Carbachol**	**Bethanechol**
Uses	Not useful in therapy because of very short duration of action	Glaucoma	Postoperative-urinary retention and paralytic ileus

+, present; –, absent.

Cholinomimetic Alkaloids

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

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 and acute congestive glaucomas**. It increases the tone of the ciliary muscle and causes miosis by contracting sphincter pupillae, opens the trabecular meshwork around the Schlemm's canal, facilitates drainage of aqueous humour and reduces IOP. It acts rapidly but has short duration of action. Pilocarpine ocusert that releases the drug slowly over 7 days is available (see p. 9).
2. It is used alternatively with mydriatics to **break adhesions between the iris and the 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 below:

Mushroom poisoning

Rapid onset type
Caused by *Inocybe* species. It is characterized by excessive muscarinic effects, vomiting, diarrhoea, bradycardia, salivation, sweating, bronchospasm, hypotension, etc. (due to toxin muscarine). It responds

Hallucinogen type
Caused by *Amanita muscaria* and Psilocybe species. Toxin is muscimol. It produces mainly central effects. There is no specific antidote; atropine is contraindicated. Supportive care should be given.

Delayed onset type
Caused by *Amanita phalloides*. Toxin is amatoxin. It results in delayed gastroenteritis, hepatic and renal damage. It does not respond to atropine and is treated with thioctic acid. Supportive care is required.

Treatment of mushroom poisoning is mainly supportive.

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Arecoline

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

Anticholinesterases (Fig. 2.12)

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

Reversible Anticholinesterases

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

ACh binds to anionic and esteratic sites of cholinesterase → acetylated enzyme → rapid hydrolysis → acetate and free enzyme

- Carbamates (except edrophonium) bind to both the sites (i.e. anionic and esteratic) of cholinesterase → carbamoylated enzyme → slow hydrolysis
- Edrophonium binds only to anionic site of ChE, has an inhibition duration of 8–10 min. It diffuses away from the enzyme.
- 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.

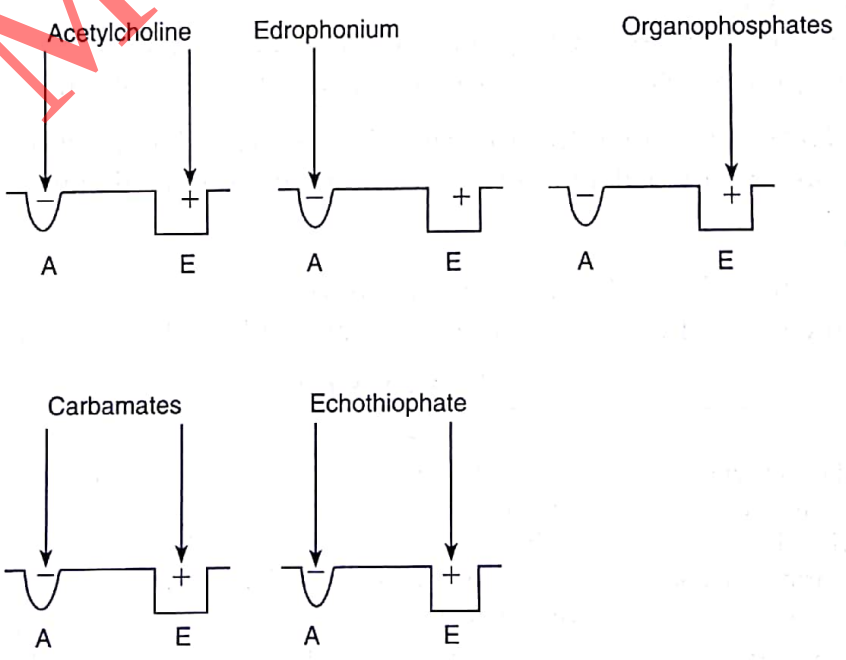

FIGURE 2.12 Inactivation of acetylcholine and mechanism of action of anticholinesterases. A, Anionic site; E, Esteratic site.

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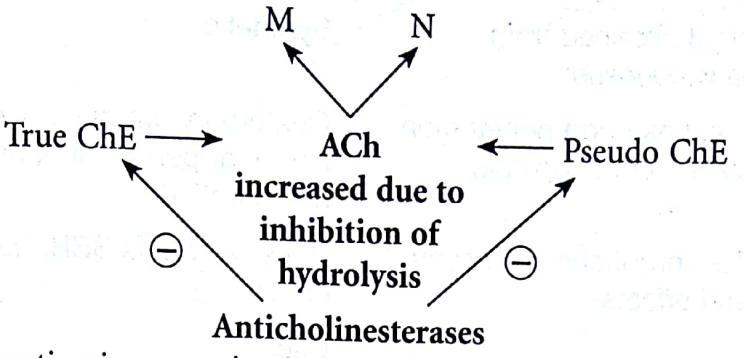
- Reversible anticholinesterases inhibit both true and pseudocholinesterases reversibly.



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.

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)

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 over 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 over neostigmine in myasthenia gravis. Even though pyridostigmine is less potent than neostigmine, it is better tolerated by myasthenic patients.

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Table 2.4 Comparative features of physostigmine and neostigmine

Physostigmine	Neostigmine
Natural alkaloid obtained from *Physostigma venenosum*	Synthetic
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

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 non-depolarising 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. 2.13).

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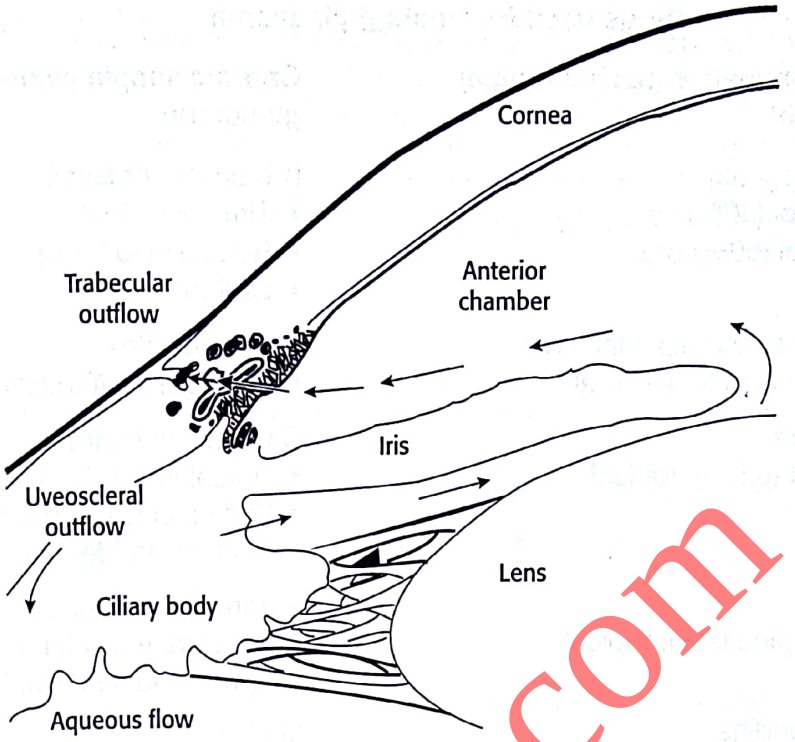

FIGURE 2.13 Aqueous humour secretion and its pathway.

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Glaucoma is a progressive optic neuropathy, which leads to damage of optic nerve with loss of visual function that is frequently associated with raised IOP. Normal IOP varies between 10–20 mmHg. 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. 2.13).

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

1. **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.
2. **Carbonic anhydrase inhibitors:** Acetazolamide (oral, i.v.), dorzolamide (topical) and brinzolamide (topical) are carbonic anhydrase inhibitors. They inhibit carbonic anhydrase enzyme and lower IOP by decreasing the formation of aqueous humour. Topical carbonic anhydrase inhibitors, which have a much lower risk of systemic side effects, are preferred over systemic carbonic anhydrase inhibitors in chronic simple glaucoma. In acute congestive glaucoma, acetazolamide is administered i.v. and orally.

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 inhibitors • 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 • Dipivefrine (0.1%), topical • Apraclonidine (1%), topical
Prostaglandins • Latanoprost (0.005%), topical	Miotics • Pilocarpine (0.5%), topical

3. **β-Adrenergic blockers:** Topical nonselective β-blockers are timolol, betaxolol, levobunolol, carteolol and metipranolol. 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. (vi) 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 in bronchial asthma and heart failure.
4. **Prostaglandins (PGs):** Topical PGs such as latanoprost, travoprost and bimatoprost ($PGF_{2\alpha}$ analogues) are the preferred agents for initial therapy in open-angle glaucoma because of their longer duration of action, high efficacy and low incidence of systemic toxicity. They are also useful in acute congestive glaucoma. They reduce IOP probably by facilitating uveoscleral outflow. 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.

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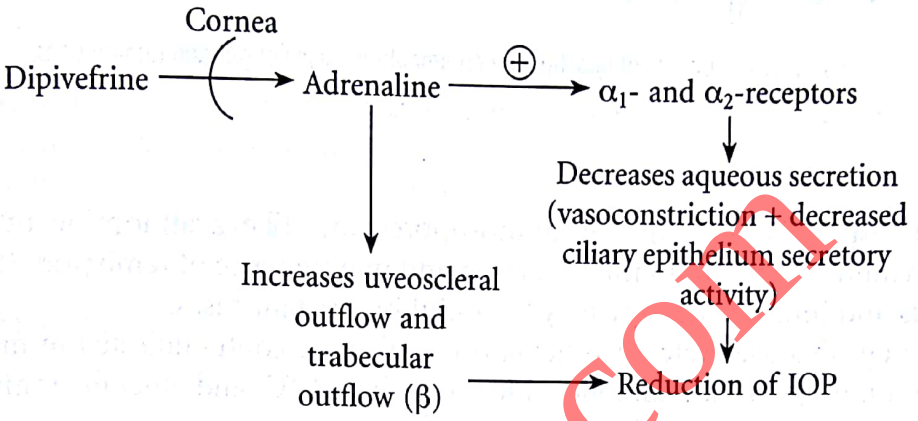
- Apraclonidine
- Brimonidine

$\Longrightarrow$ α_2-Agonists $\Longrightarrow$ Reduce formation of aqueous humour $\Longrightarrow$ Decrease IOP

(b) Dipivefrine is a prodrug of adrenaline. It penetrates the cornea and with the help of esterases, it 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 i.v. shows dramatic improvement of symptoms in patients with myasthenia gravis but not in other muscular dystrophies.
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 Nm 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 → myaesthenic 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.

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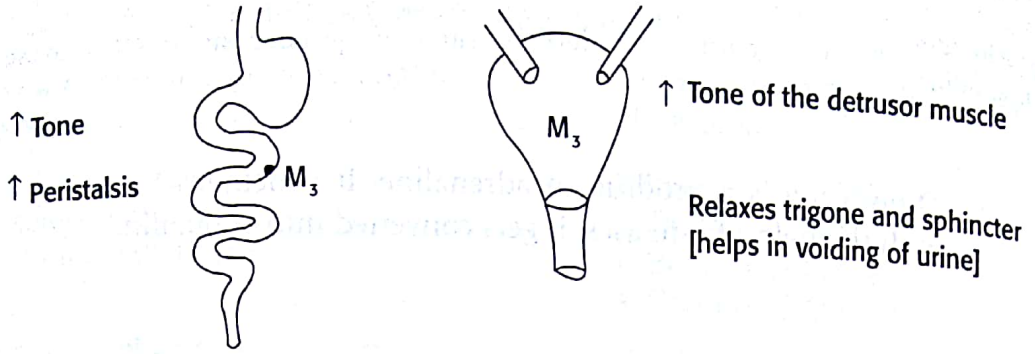

FIGURE 2.14 Effects of neostigmine on smooth muscles of gut and urinary tract.

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. 2.14)**.** Neostigmine is used because it increases the tone of the smooth muscle and relaxes the sphincters.

4. Curare Poisoning and Reversal of Non-Depolarizing Neuromuscular Blockade (see p. 83). 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. 75). 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

Organophosphorus Insecticides

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

Organophosphorus poisoning is one of the most common poisoning all over the world. Common organophosphorus 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 tracheobronchial secretions, bronchospasm, vomiting, abdominal cramps, miosis, bradycardia, hypotension, involuntary urination and defecation.

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

Diagnosis. Organophosphorus poisoning can be diagnosed by:

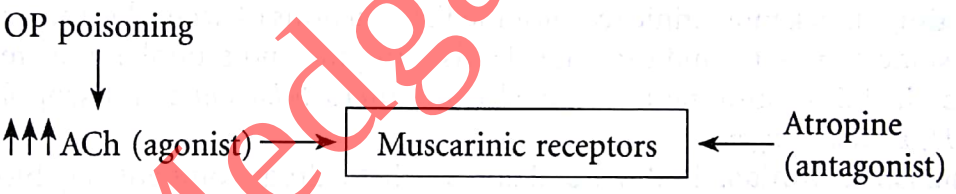
- History of exposure.
- Characteristic signs and symptoms.
- Estimating the cholinesterase activity in blood, which is decreased.

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.

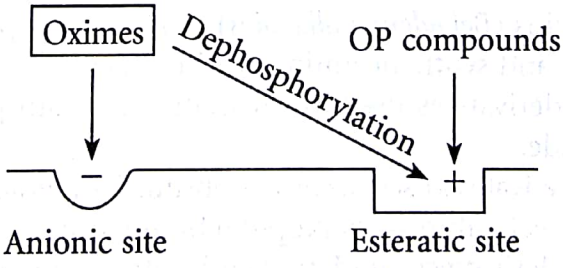
Specific Measures

1. **Atropine:** Atropine is the first drug to be given in organophosphorus 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, non-reactive 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, obidoxime, etc. Pralidoxime is administered i.v. 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, 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.

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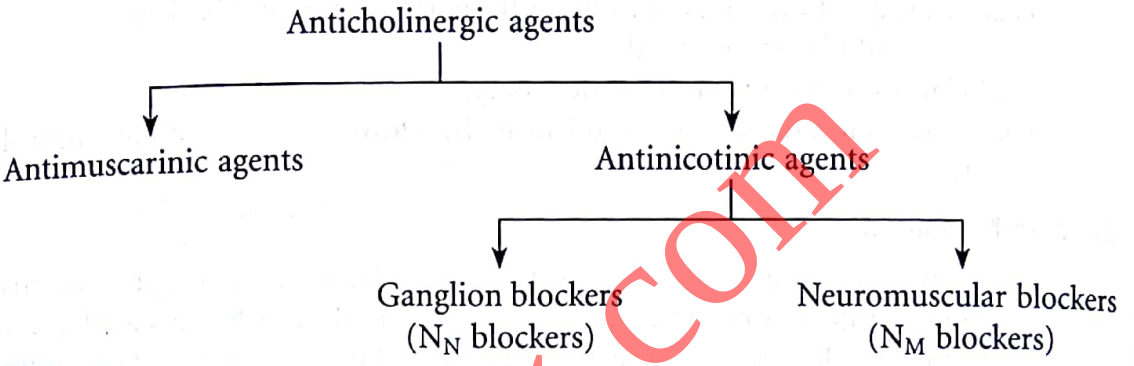
Oximes are not effective in carbamate poisoning; they also have mild anti-ChE activity

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

ANTICHOLINERGIC AGENTS (CHOLINERGIC RECEPTOR BLOCKERS)

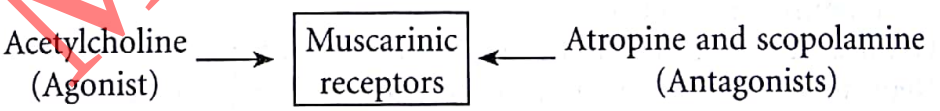
Anticholinergic agents block the actions of cholinergic drugs: Various anticholinergic agents are shown below:



ANTIMUSCARINIC AGENTS (ANTICHOLINERGIC AGENTS)

These drugs block muscarinic receptor mediated actions of acetylcholine 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 and synthetic antimuscarinic agents:
   (a) Atropine derivatives used as mydriatic—homatropine, cyclopentolate, tropicamide.
   (b) Atropine derivatives used in chronic obstructive pulmonary disease (COPD) and bronchial asthma—ipratropium bromide, tiotropium bromide.
   (c) Atropine derivatives used in peptic ulcer—pirenzepine, telenzepine, clidinium, propantheline.
   (d) Atropine derivatives used as antispasmodic—dicyclomine, valethamate, flavoxate, oxybutynin, tolterodine, darifenacin.
   (e) Atropine derivative used as preanaesthetic agent—glycopyrrolate.
   (f) Atropine derivatives used in parkinsonism—benzhexol (trihexyphenidyl), benztropine, biperiden, procyclidine.

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Atropine

Atropine is the prototype drug and the chief alkaloid of belladonna. It is a tertiary amine.

Pharmacological Actions of Atropine (Fig. 2.15)

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.

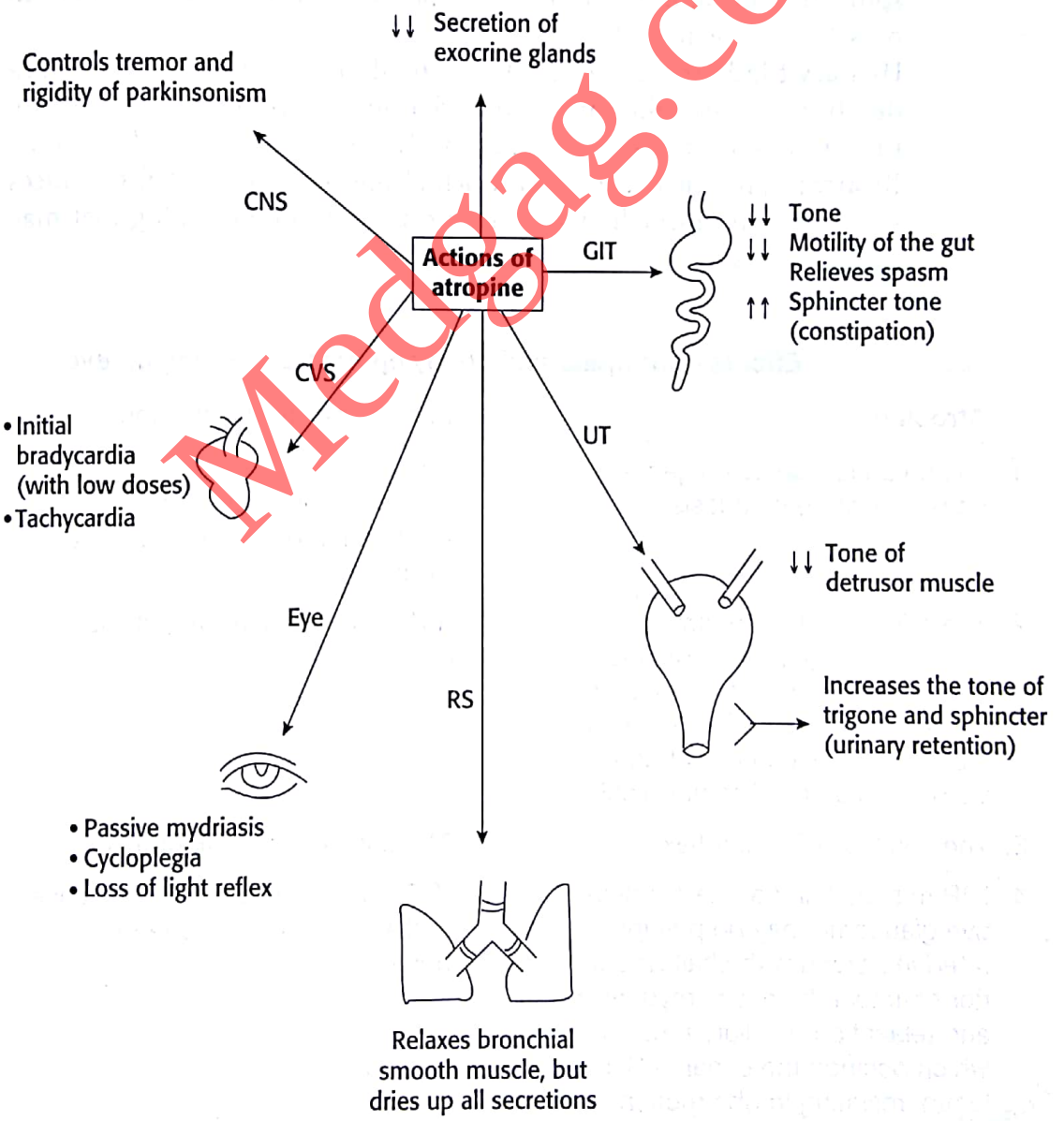

FIGURE 2.15 Actions of atropine. UT, Urinary tract; RS, Respiratory system.

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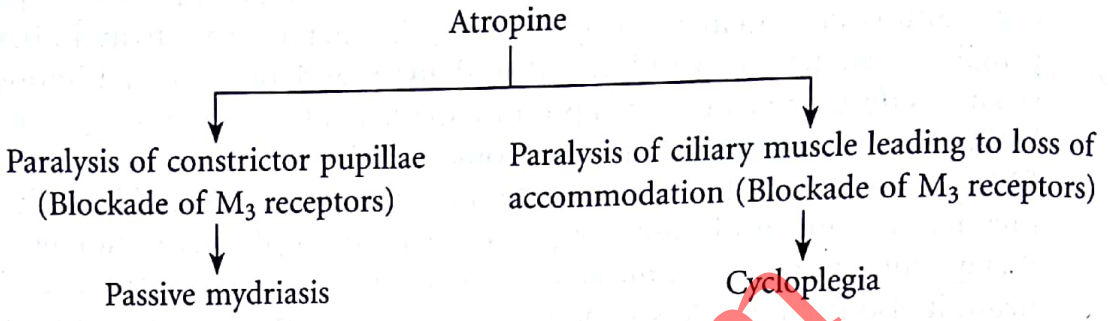
3. **Glands:** All secretions under cholinergic influence are reduced due to blockade of M_3 receptors, i.e. sweat, salivary, nasal, throat, bronchial, gastric, lacrimal, etc. Milk and bile secretions are not affected. The skin and mucous membranes become dry.
4. **Eye:** Effects of atropine on eye are depicted below (also see Table 2.6):



5. **Smooth muscles:**
   (a) **GIT:** Atropine decreases tone and motility of the gut, but increases sphincter tone and may cause constipation. It also relaxes the smooth muscle of the gall bladder.
   (b) **Urinary bladder:** Atropine relaxes the detrusor muscle of the bladder, but increases the tone of the 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.

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.

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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: These drugs are used for a selective or relatively selective action on a particular organ and to avoid undesirable effects.

1. **For eye (as mydriatic)**
   (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 vesicoselective 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*
   - Has selective action on urinary bladder (M_3) – useful for relief of spasm after urologic surgeries.
   - Is longer acting than oxybutynin.

   (g) *Drotaverine*
   - Not an anticholinergic agent.
   - Inhibits phosphodiesterase enzyme.
   - Used as antispasmodic for relief of uterine spasm, intestinal and renal colic.

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3. **Ipratropium bromide and tiotropium bromide**
   - Synthetic atropine derivatives 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 h) is longer acting than ipratropium (6 h).
   - 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 ammonium 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

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. **COPD and bronchial asthma:** Ipratropium bromide and tiotropium bromide are used in COPD and bronchial asthma. They are administered

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by metered dose inhaler or nebulizer. They produce bronchodilatation without affecting mucociliary clearance; hence are preferred over atropine.

5. **Anticholinergics** are useful as **antispasmodic** in dysmenorrhoea, intestinal and renal 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 organophosphorus poisoning, atropine is the life-saving drug (see p. 69).
   - In some types of mushroom poisoning (*Inocybe* species) atropine is the drug of choice (see p. 61).
   - 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), benztropine, 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 in case of ingested poisoning.
   3. Tepid sponging to control hyperpyrexia.
   4. Diazepam to control convulsions.

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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 as well as central effects of atropine poisoning. Hence, physostigmine is preferred over 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. 2.16). 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.

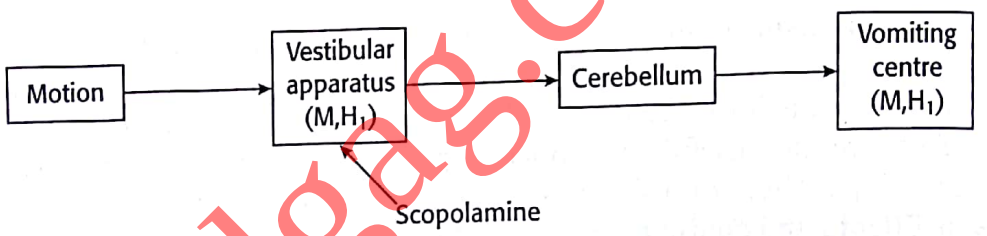

FIGURE 2.16 Sites of action of scopolamine in motion sickness. M, Muscarinic receptor; H, Histamine receptor.

Drug Interactions of Anticholinergics. H_1-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. 2.17).

The ganglion blockers have 'atropine-like' action on heart (palpitation and tachycardia), eye (mydriasis and cycloplegia), GIT (dryness of mouth and constipation), bladder (urinary retention), impotence in males and decreased sweat secretion. Blockade of sympathetic ganglia results in marked postural hypotension.

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

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. Nicotine is of no

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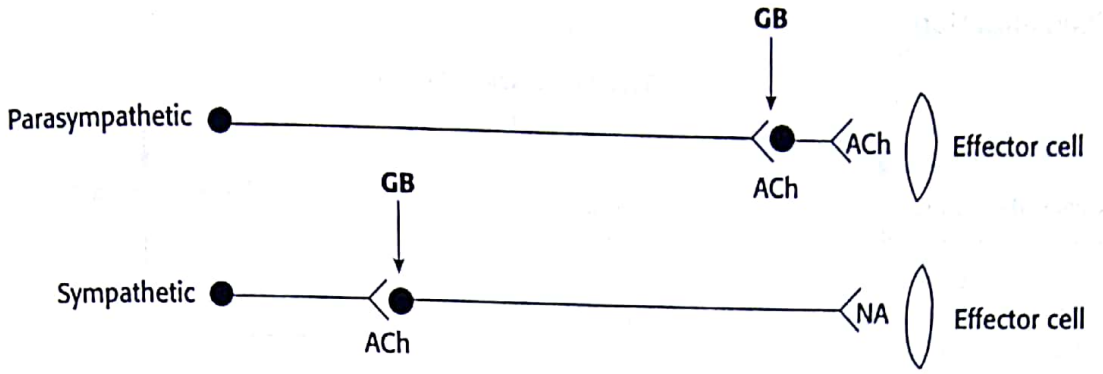

FIGURE 2.17 Site of action of ganglion blocker (GB).

value in clinical practice except in the form of transdermal patch and chewing gum for the treatment of tobacco addiction.

Bupropion: It inhibits NE 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.

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.

SKELETAL MUSCLE RELAXANTS

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

Physiology of Skeletal Muscle Contraction

Motor nerve impulse
↓
Release of acetylcholine
↓
Binds with N_M receptors at NMJ
↓
Depolarization and development of end-plate potential (EPP) at motor end plate (Mainly due to influx of Na^+)
↓
Muscle-action potential (MAP) – Contraction of skeletal muscle
↓
ACh is rapidly inactivated by cholinesterase leading to repolarization
↓
Muscle is ready for a fresh nerve impulse

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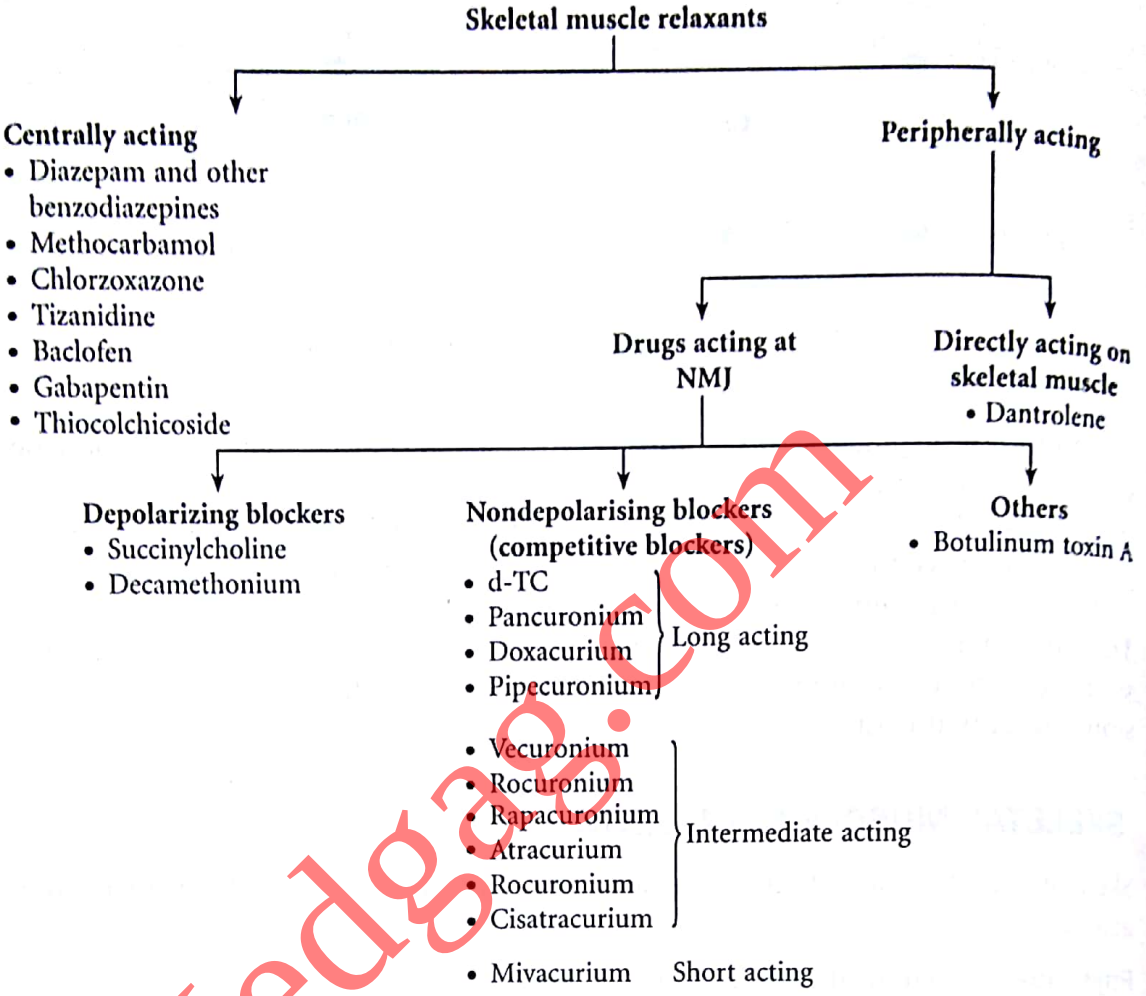
Classification



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Centrally Acting Skeletal Muscle Relaxants

Most of the centrally acting skeletal muscle relaxants are available in combination with one or other NSAIDs. All of them cause certain degree of sedation. They act by depressing polysynaptic pathways in spinal and supraspinal sites. They are used to reduce spasm associated with cerebral palsy, trauma, sprain, tetanus, multiple sclerosis, etc. (see Table 2.7, p. 79 for characteristics of these drugs).

Neuromuscular Blockers

Neuromuscular blockers include non-depolarizing (competitive) and depolarizing blockers.

Depolarizing Blockers: Succinylcholine (*Suxamethonium*)

Succinylcholine 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 which leads to phase II block, which resembles the non-depolarizing block and is partially reversed by anticholinesterases.

Table 2.7 Characteristics of centrally acting skeletal muscle relaxants

Drug	Route	Uses	Side effects
*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
†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
Thiocolchicoside	• Oral	• Sprain, muscle spasm due to trauma	Diarrhoea, drowsiness, rashes

*Block release of excitatory transmitter in the spinal cord → depress polysynaptic reflexes.

Succinylcholine is rapidly hydrolysed by pseudocholinesterase, hence has a very short duration of action (3–8 min). Transient apnoea is usually seen at the peak of its action. In people with liver disease or atypical pseudocholinesterase due to genetic defect, the metabolism of succinylcholine becomes slow which results in severe neuromuscular blockade leading to respiratory paralysis with prolonged apnoea. This is referred to as *'succinylcholine apnoea'*. There is no antidote available, therefore:

- Fresh frozen plasma should be infused.
- Anaesthesia should be continued until recovery from neuromuscular blockade.
- 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. Succinylcholine apnoea (prolonged apnoea).

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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 (Non-depolarizing 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-Tubocurarine (d-TC) is the most important alkaloid which has N_M blocking activity. d-TC is the prototype drug of competitive blockers.

Table 2.8 Features of non-depolarizing (competitive) blockers

Non-depolarizing blockers

1. **d-TC:** An alkaloid obtained from *Chondrodendron tomentosum*
   - Prototype competitive blocker
   - It causes flaccid paralysis
   - Causes histamine release, ganglionic blockade
   - Has longer duration of action
2. **Pancuronium**
   - Synthetic agent
   - Produces competitive blockade
   - Has longer duration of action
   - Minimal/no histamine release
   - Has vagolytic action, hence causes tachycardia
3. **Doxacurium**
   - Most potent non-depolarizing blocker
   - Minimal histamine release
   - Has long duration of action
   - Mainly excreted in urine
4. **Pipecuronium**
   - Has long duration of action
   - May cause bradycardia and hypotension
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 the placental barrier
6. **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
7. **Cisatracurium**
   - Has intermediate duration of action
   - More potent than atracurium
   - Does not cause histamine release
   - Undergoes spontaneous degradation in plasma (Hofmann degradation)
8. **Rocuronium**
   - Has intermediate duration of action
   - Minimal/no tendency to release histamine
   - Has a rapid onset of action
9. **Mivacurium**
   - Has short duration of action (15–20 min)
   - Rapidly inactivated by plasma cholinesterases
   - Does not require reversal
   - Causes histamine release
   - Duration of action is prolonged in patients with pseudocholinesterase deficiency

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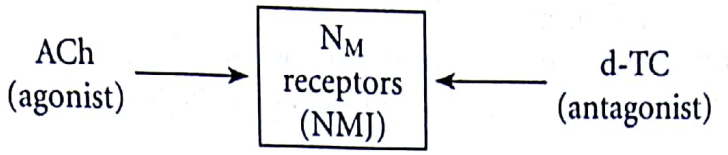
Mechanism of Action. Acetylcholine is the agonist, whereas d-TC is the antagonist at N_M receptors. Curariform drugs competitively antagonize the actions of ACh at the N_M receptors of the NMJ. Anticholinesterases (neostigmine or edrophonium) are used to reverse the effects of competitive blockers by 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 prominent with d-TC, pancuronium, atracurium and mivacurium.
- Among competitive neuromuscular blockers, rocuronium has a rapid onset of action, hence can be used for endotracheal intubation.
- Comparative features of d-TC and SCh are shown in Table 2.9.

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Table 2.9 Comparative features of d-TC and succinylcholine

d-TC	Succinylcholine
1. Natural alkaloid	1. Synthetic
2. Non-depolarizing blocker	2. Depolarizing blocker
3. Long acting (60 min)	3. Rapidly metabolized by pseudocholinesterase, hence short acting (3–8 min)
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 non-depolarizing block is partially reversed by neostigmine
7. Uses: As adjuvant to general anaesthesia (see text)	7. Succinylcholine is preferred for short procedures, e.g. diagnostic endoscopies, endotracheal intubation, orthopaedic manipulations, etc.
8. Adverse effects (see text)	8. Adverse effects (see text)

Pharmacokinetics. Neuromuscular blockers are quaternary ammonium compounds. They are highly ionized, hence poorly absorbed from GI tract. They are administered 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 non-depolarizing drugs are hypotension, respiratory paralysis, bronchospasm and aspiration of gastric contents.

Drug Interactions of Skeletal Muscle Relaxants

1. Non-depolarizing blockers × antibiotics
   Aminoglycosides inhibit the release of ACh from motor nerve and potentiate the effect of non-depolarizing blockers; hence require dose reduction in patients treated with aminoglycosides. Tetracyclines and clindamycin also potentiate the effect of non-depolarizing blockers.
2. Thiazides/loop diuretics × non-depolarizing blockers
   Hypokalaemia caused by thiazides/loop diuretics may potentiate the effect of non-depolarizing blockers.
3. Succinylcholine × thiopentone
   These drugs are chemically incompatible (in vitro; pharmaceutical interaction) hence result in precipitation when mixed in the same syringe.
4. General anaesthetics × non-depolarizing blockers
   Ether has curarimimetic effect on skeletal muscle; hence enhances the effect of non-depolarizing 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 non-depolarizing blockers by inhibiting presynaptic release of ACh.
5. **Inhalational anaesthetics:** Anaesthetics like ether, halothane, isoflurane, etc. 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. Succinylcholine is preferred for short procedures, e.g. diagnostic endoscopies, endotracheal intubation, orthopaedic manipulations, etc.
2. Succinylcholine/mivacurium is used during electroconvulsive therapy (ECT) to prevent trauma due to convulsions.
3. Tetanus and status epilepticus when not controlled by other drugs.

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4. Competitive neuromuscular blockers 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. 2.18). Mivacurium (short acting), atracurium (intermediate acting), etc. do not require reversal.

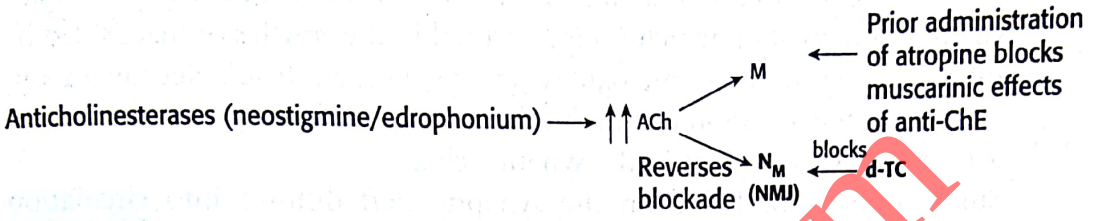

FIGURE 2.18 Reversal of neuromuscular blockade. ACh: Acetylcholine; NMJ, Neuromuscular junction; N_M: Nicotinic receptors; M: Muscarinic receptor.

Sugamadex

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 inhibits proteins necessary for the release of ACh into synaptic cleft. It is injected locally into the spastic muscles.

ADRENERGIC AGONISTS (SYMPATHOMIMETIC AGENTS)

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 DOPA by tyrosine hydroxylase and DOPA to dopamine (DA) by dopa decarboxylase. DA enters the storage vesicles of the nerve terminal

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by active transport, where it is converted to NA by the enzyme dopamine β-hydroxylase (this enzyme is present only in the storage vesicles); the 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. 2.19).

Three processes are involved in the 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 the adrenergic nerve terminals (neuronal reuptake), which is either stored in the vesicles or inactivated by mitochondrial monoamine oxidase (MAO) in the cytosol. Neuronal reuptake is the most important mechanism through which the 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 the liver by catechol-*O*-methyltransferase (COMT) and MAO.
3. Small quantity of NA is transported into other tissues (extraneuronal uptake).

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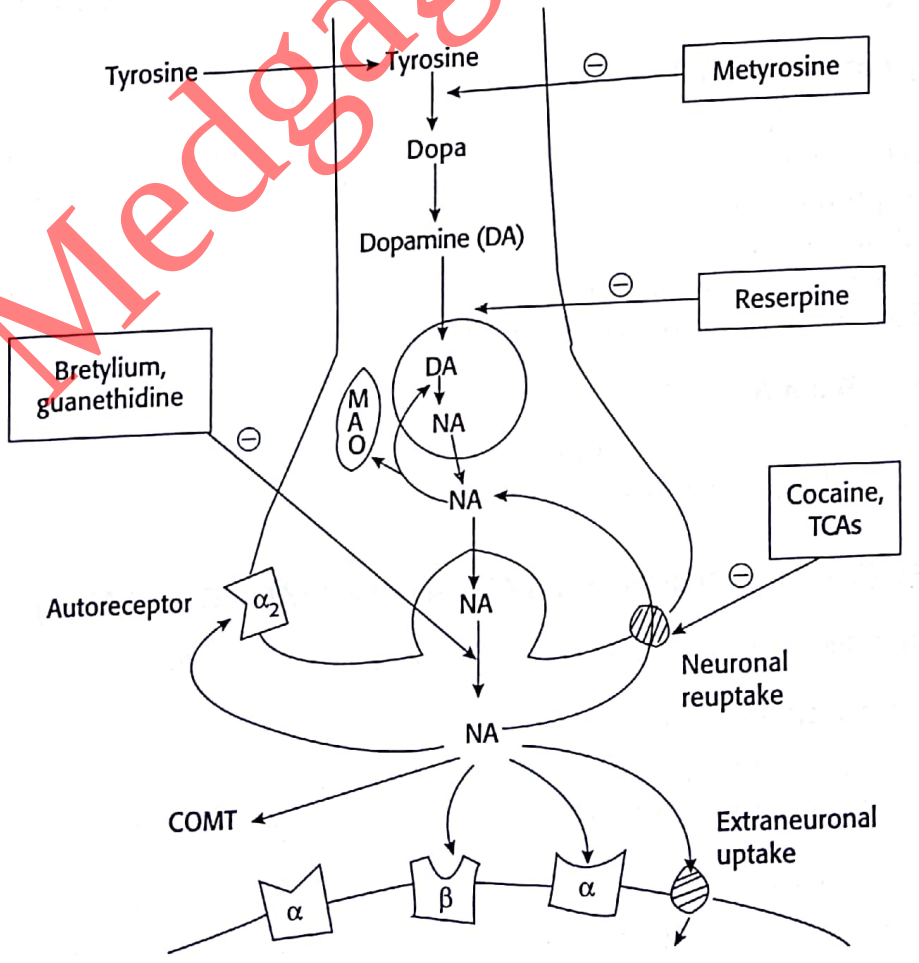

FIGURE 2.19 Synthesis and release of NA from the adrenergic neuron and various drugs affecting the pathway (Table 2.10). MAO, Monoamine oxidase; COMT, Catechol-O-methyltransferase; TCAs, Tricyclic antidepressants.

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 [a]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 102–103; 106–107
Tranylcypromine, pargyline (nonselective MAO inhibitors)	Potentiate tyramine action	As antidepressants
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

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Metabolism of Catecholamines

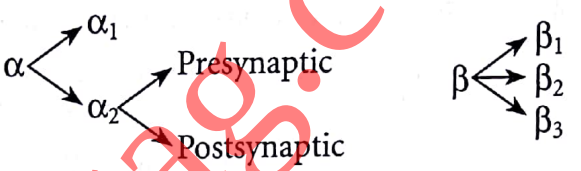
Vanillyl mandelic acid (VMA) is the main metabolite of catecholamines excreted in urine. Normal value of VMA is 4–8 mg per 24 hours urine. Its levels are raised in pheochromocytoma, a tumour of adrenal medulla and sympathetic ganglia. Estimation of the levels of catecholamines and their metabolites in blood and

urine is of great value in the diagnosis of pheochromocytoma. CT (computed tomography) and MRI (magnetic resonance imaging) scans are the important diagnostic aids.

Adrenaline, Noradrenaline → (COMT and MAO)
- Vanillyl mandelic acid (VMA)
- Metanephrine
- Normetanephrine

Types, Distribution and Functions of Adrenergic Receptors

Ahlquist divided the 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), ↑ cAMP (α_2) and ↓ cAMP (β). They are further divided into various subtypes, which are as follows:



Distribution of various adrenergic receptors is indicated in Fig. 2.20.

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 the 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.

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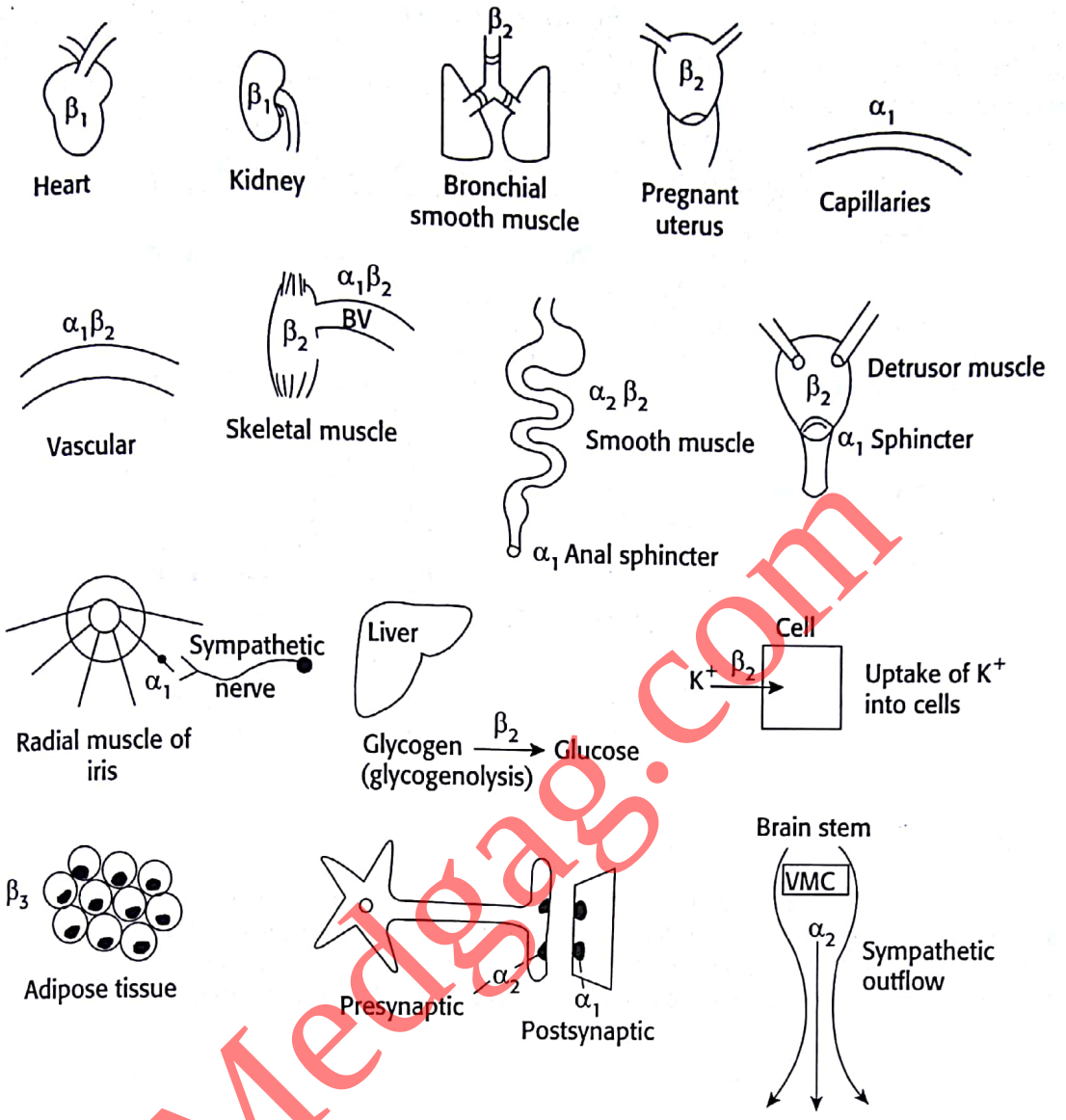

FIGURE 2.20 Distribution of various adrenergic receptors. VMC, Vasomotor centre; BV, Blood vessel.

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- 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, 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.

Adrenergic Drugs (Sympathomimetics)

The sympathomimetic drugs mimic effects of sympathetic stimulation (Fig. 2.21). They are also referred to as adrenergic agonists.

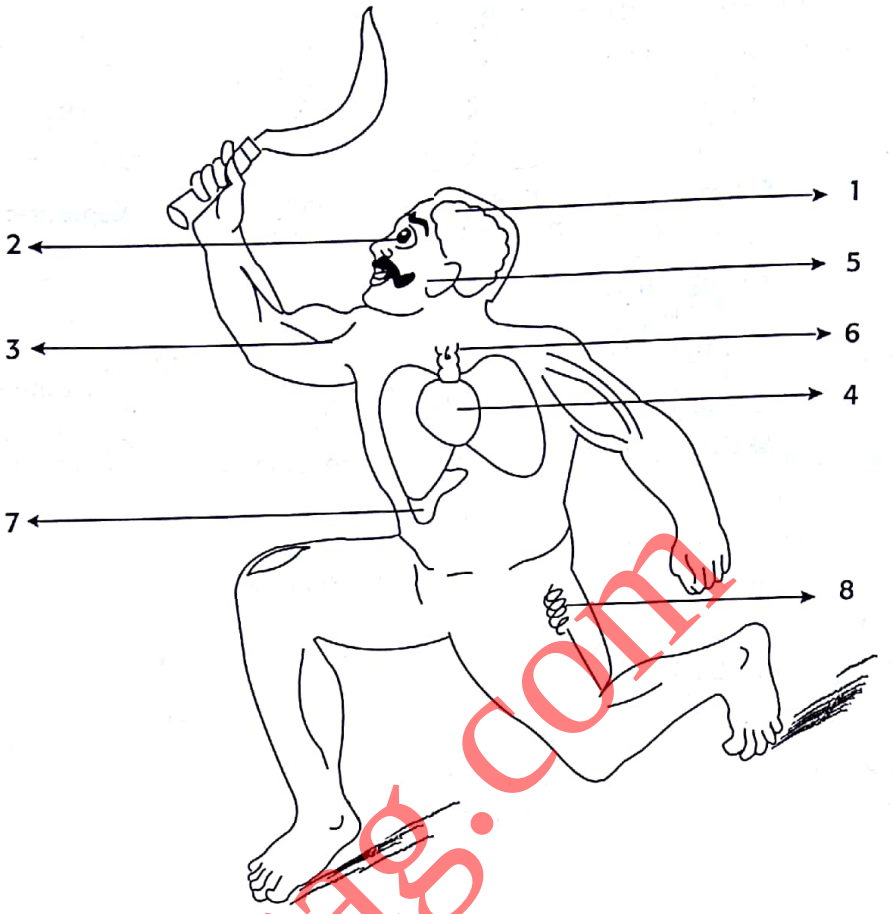

FIGURE 2.21 An angry man symbolizing the sympathetic overactivity (Fight–Fright–Flight)—1: Anger, alert, aggressive; 2: Pupillary dilatation (mydriasis); 3: Increased muscle tone, tremors; 4: Palpitation, increased cardiac output–increased blood flow to the skeletal muscles; 5: Flushing of the face; 6: Tachypnoea, bronchodilatation; 7: Liver–glycogenolysis–more energy; 8: Adipose tissue–lipolysis–energy.

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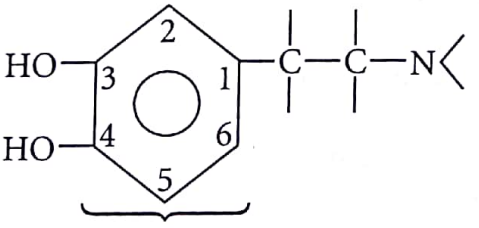
Classification of Sympathomimetics

1. **On the basis of their chemical structure**
   (a) *Catecholamines:* Sympathomimetics with catechol nucleus are called catecholamines, e.g. adrenaline, noradrenaline, dopamine, isoprenaline and dobutamine.



Catechol nucleus

   (b) *Non-catecholamines:* Sympathomimetics that lack catechol nucleus are called non-catecholamines, e.g. tyramine, ephedrine, amphetamine, phenylephrine, salbutamol, etc.

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.

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	**A**naphylactic shock, **B**ronchial asthma (acute severe), **C**ardiac arrest, to prolong **D**uration of local anaesthesia, to control **E**pistaxis and other capillary oozing **(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) • Terbutaline • Salmeterol • Formoterol	Selective β_2-agonists	Bronchial asthma, to suppress premature labour (as uterine relaxant)
• Ritodrine • Isoxsuprine	Selective β_2-agonists with 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

Continued

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Table 2.11 Summary of sympathomimetic agents—cont'd

Adrenergic agonists	Receptor action	Therapeutic uses
• 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 hyperkinetic 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 agonists + releases NA	Hypotensive states

3. **On the basis of their therapeutic use:**
   (a) *To raise blood pressure in shock:* Dopamine, noradrenaline, ephedrine, phenylephrine, methoxamine, mephentermine.
   (b) *As bronchodilator:* Salbutamol, terbutaline, bambuterol, salmeterol, formoterol.
   (c) *As cardiac stimulant:* Adrenaline, isoprenaline, dobutamine.
   (d) *As CNS stimulant:* Modafinil, amphetamine, dextroamphetamine, methamphetamine.
   (e) *For local vasoconstrictor effect:* Adrenaline.
   (f) *As nasal decongestant:* Phenylephrine, xylometazoline, pseudoephedrine, oxymetazoline, naphazoline.
   (g) *As anorexiant:* Dextroamphetamine, mazindol, phentermine, sibutramine.
   (h) *As uterine relaxant:* Isoxsuprine, terbutaline, salbutamol, ritodrine.
   (i) *As mydriatic:* Ephedrine, phenylephrine.

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.

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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 – ↑ 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 the 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 vasodilatation 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 (Fig. 2.22).
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_2 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.

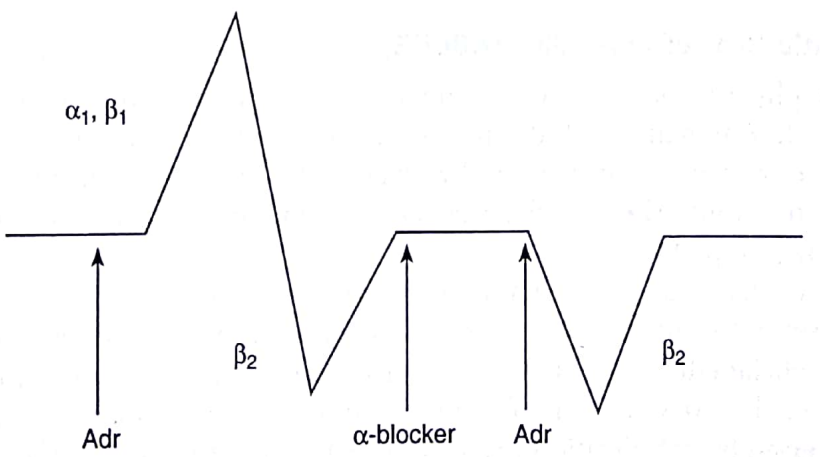

FIGURE 2.22 Biphasic effect of adrenaline (Adr) on BP and Dale's vasomotor reversal.

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5. CNS: In therapeutic doses, adrenaline does not cross the 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. 67).
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 also 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 the 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, CCF, etc. 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 in p. 93.
2. Bronchial asthma: Adrenaline is a powerful bronchodilator and has rapid onset but short duration of action. It is useful for acute severe asthma. The beneficial effects of adrenaline in bronchial asthma are shown in Fig. 2.23. Adrenaline 0.3–0.5 mL of 1:1000 solution is given subcutaneously. It can be given by nebulization (as inhalation). Its use has declined because of its dangerous cardiac stimulant effect.
3. Cardiac resuscitation: In the treatment of cardiac arrest due to drowning or electrocution, adrenaline is injected intravenously in 1:10000 (0.1 mg/mL)

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Adrenaline produces the following effects:

- β_1-mediated cardiac stimulation (↑ heart rate and ↑force of contraction) + α_1-mediated vasoconstriction → ↑ peripheral resistance. These actions help to ↑BP.
- α_1-mediated vasoconstriction → ↓ mucosal oedema (↓laryngeal oedema).
- β_2 stimulation → bronchodilation ↓ release of mediators from mast cells.
- It is physiological antagonist of histamine.

Effect of adrenaline in anaphylactic shock.

concentration along with other supportive measures such as external cardiac massage.

4. Prolongs the Duration of local anaesthesia: Adrenaline (1:1,00,000) with lignocaine. Adrenaline, by its vasoconstrictor effect (α_1) delays absorption of the local anaesthetic and prolongs the duration of local anaesthesia.
5. 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.
6. Glaucoma: Adrenaline has poor penetration when applied locally into the eye; hence it is administered as a prodrug, dipivefrine (p. 67).

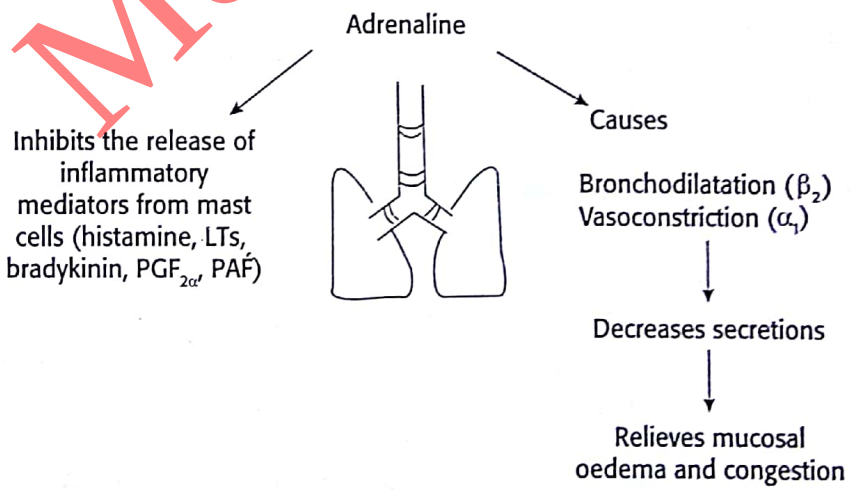

FIGURE 2.23 Effects of adrenaline in bronchial asthma. LTs, Leukotrienes; $PGF_{2\alpha}$, Prostaglandin $F_{2\alpha}$; PAF, Platelet activating factor.

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; has negligible β_2 action. The main action of NA is on cardiovascular system. It has a direct cardiac stimulant

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effect (β_1), constricts all the blood vessels (α_1) including those of the skin, mucous membrane, renal, mesenteric, pulmonary, skeletal muscle, etc. The systolic, diastolic and pulse pressure is 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 is 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. In bronchial asthma, isoprenaline has been replaced by selective β_2-agonists. 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 dopamine. It acts on β_1-, β_2- and α_1-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

The main adverse effects of non-selective β-agonist, isoprenaline, is on the heart. It can cause tachycardia, palpitation, cardiac arrhythmias and may even precipitate angina or MI. Use of isoprenaline is almost obsolete for the treatment of asthma. Selective β_2-agonists are the main drugs used in bronchial asthma, e.g. salbutamol, terbutaline, salmeterol, formoterol, etc.

Pharmacological Actions. Pharmacological actions of selective β_2-agonists are depicted in Fig. 2.24. They cause bronchodilatation, relaxation of pregnant uterus, dilatation of blood vessels supplying the skeletal muscles, 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.

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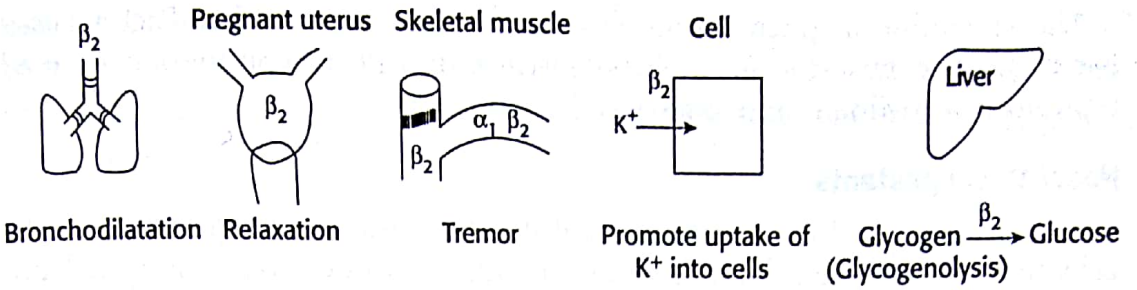

FIGURE 2.24 Pharmacological actions of selective β_2-adrenergic agonists.

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 the 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 an uterine relaxant to suppress premature labour.

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 diabetics 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

- Phenylephrine
- Methoxamine

} Directly acting α_1 agonists

- Mephentermine – Directly acting α_1 agonist + releases NA (indirect action)

↓

Cause vasoconstriction

↓

Increase peripheral vascular resistance (PVR)

↓

Increase in BP

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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. They are usually combined with antihistaminics in anticold 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. 89) and tizanidine (see p. 79, Table 2.7).

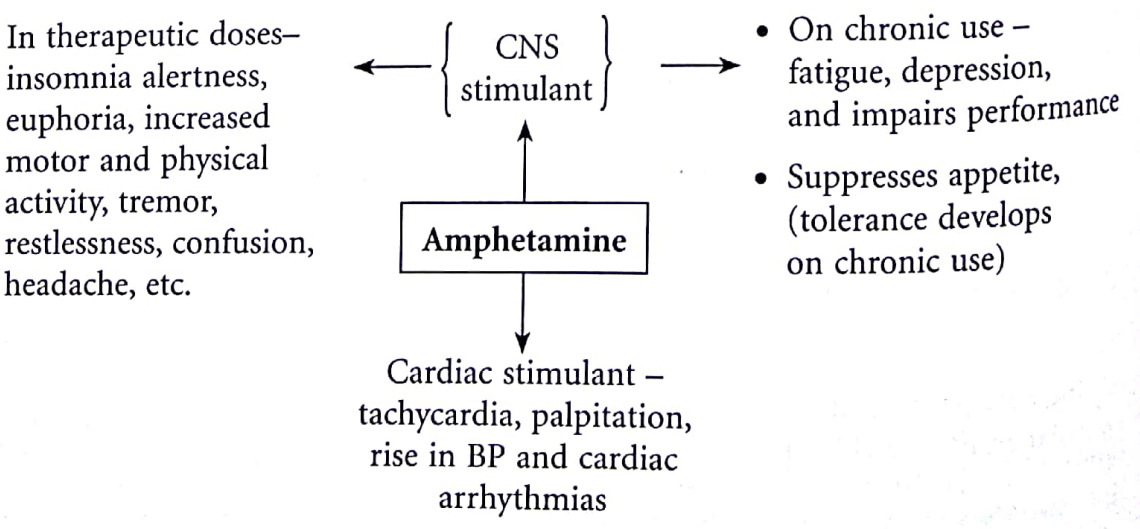
Apraclonidine and brimonidine, selective α_2-agonists, are used topically in glaucoma (see p. 66).

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



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Adverse Effects. They 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 hyperkinetic disorder: Amphetamine acts paradoxically and controls the activity in children with hyperkinetic 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.

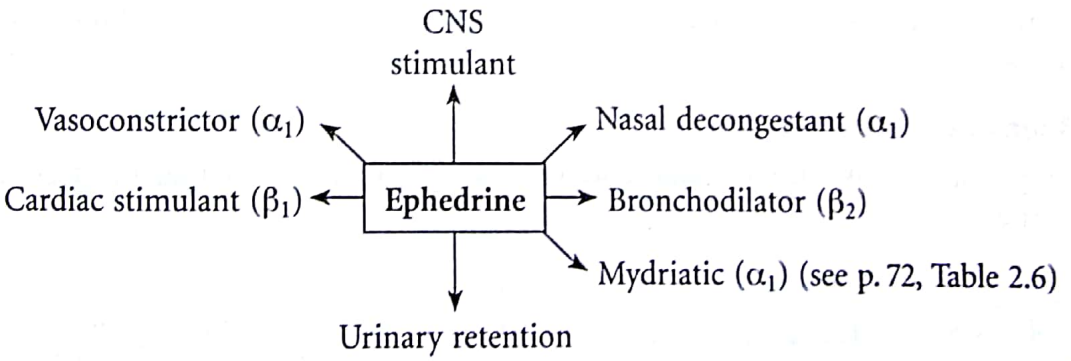
Modafinil: It is a CNS stimulant – useful in narcolepsy.

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, heart rate, cardiac output and thus BP. It was used in heart block, narcolepsy and more frequently in 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.

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Dopamine: α_1-, α_2-, β_1-, and D_1-agonist with NA Release

Dopamine (DA) is a catecholamine and the immediate metabolic precursor of NA. It acts on dopaminergic D1 receptors as well as β_1- and α_1-adrenergic receptors. DA, like adrenaline and noradrenaline, is not effective orally. DA is rapidly inactivated by COMT and MAO is administered by i.v. infusion.

Pharmacological Actions. At low doses (<2 mcg/kg/minute), 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/minute), dopamine 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/minute), 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 dopamine 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:** Dopamine 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:** Dopamine improves both cardiac and renal function.

Fenoldopam

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

Fenoldopam → D_1 agonist → Peripheral vasodilatation → ⇩ BP

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

Anorectics (Anorexiants)

Amphetamine-like drugs promote weight loss by acting on hypothalamic feeding centre.

- Mazindol, Phentermine → Inhibit reuptake of NA → Enhance noradrenergic transmission in the brain → Inhibit hypothalamic feeding centre → Suppress appetite
- Sibutramine → Inhibits NA and 5-HT reuptake → Suppresses appetite and enhances satiety
- Orlistat → Inhibits pancreatic lipase → Interferes with absorption of dietary fat → Promotes weight loss

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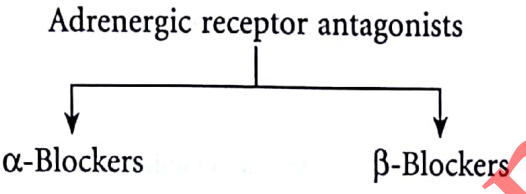
Other anti-obesity agents are leptin and rimonabant.

The main adverse effects of these agents are addiction liability, rise in BP, palpitation, sleep disturbances, depression and dry mouth.

ADRENERGIC RECEPTOR BLOCKERS

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

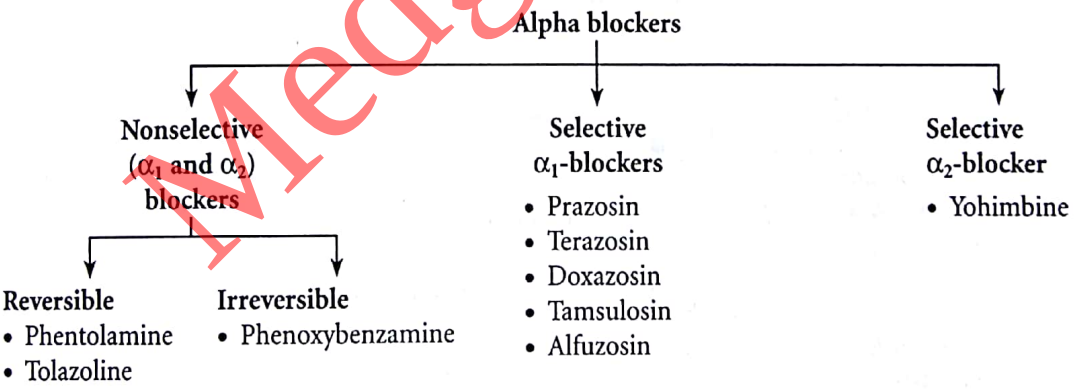


ALPHA ADRENERGIC BLOCKERS

Pharmacological Effects of α-Blockers *(Fig. 2.25, p. 100)*

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

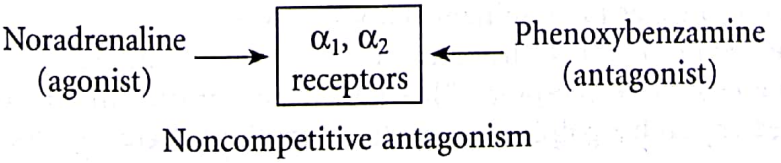
Classification



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.



Noncompetitive antagonism

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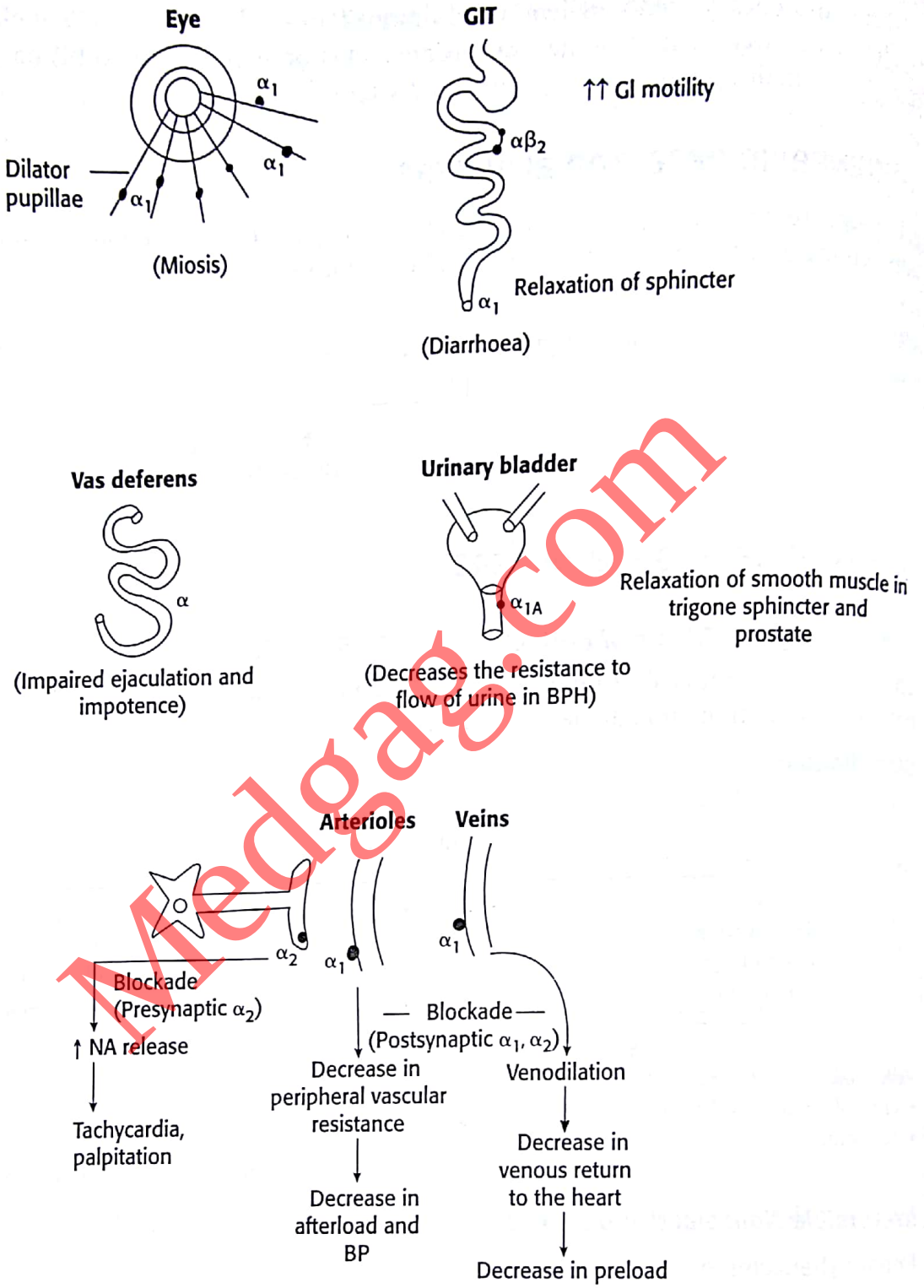

FIGURE 2.25 Effect of α-blockade at various sites. GIT, Gastrointestinal tract; BPH, Benign prostatic hyperplasia; NA, Noradrenaline. Other effects: Blockade of alpha receptors in nasal blood vessels results in nasal stuffiness.

Pharmacological Effects

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

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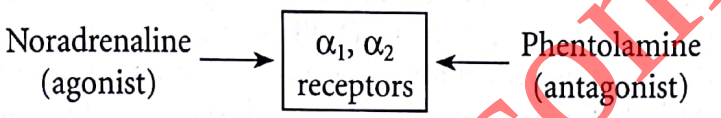
Phenoxybenzamine is given orally or through slow i.v. infusion. It has a slow onset but long duration of action because of irreversible blockade of α-receptors. Its main use is in the treatment of pheochromocytoma. The side effects are postural hypotension (mainly due to venodilatation), tachycardia, 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-HT receptors, K^+ channels; causes histamine release from mast cells.



Competitive antagonism

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.

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 the Fig. 2.25. Unlike nonselective α-blockers, selective α_1-blockers produce minimal or no tachycardia. 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.

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- *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.

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), computed tomography (CT) and magnetic resonance imaging (MRI) scans.

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

   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 in the treatment of mild-to-moderate hypertension. They cause less tachycardia and have favourable effects on lipid profile.
4. **Benign prostatic hyperplasia:** Transurethral resection of the prostate is the commonly used method to relieve urinary symptoms of BPH; however, medical therapy is helpful in many patients. Selective α_1-blockers are used in BPH; they reduce 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.

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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.
7. Other uses include congestive cardiac failure and peripheral vascular diseases.

Selective α_2-Adrenergic Antagonist

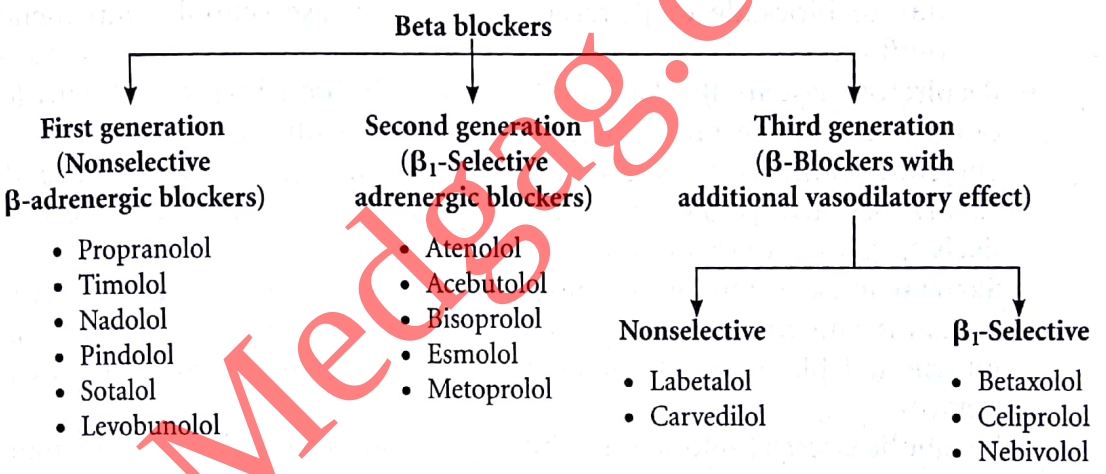
Yohimbine

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.

BETA ADRENERGIC BLOCKERS

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

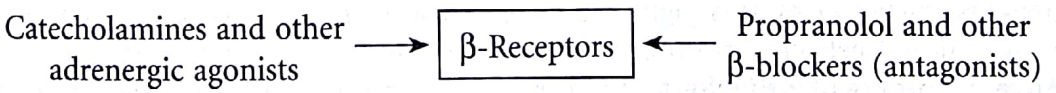
Classification



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

Propranolol, acebutolol, carvedilol, labetalol, metoprolol, pindolol 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).

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(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 peripheral vascular resistance (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, metoprolol, etc. 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 diabetics on hypoglycaemic agents. Chronic use of nonselective β-blockers decreases HDL (high-density lipoprotein) cholesterol and LDL (low-density lipoprotein) 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. 66).

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.

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- 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's angina (variant angina) due to unopposed α_1 action, hence are contraindicated (see p. 131) 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 hypoglycemia (induced by antidiabetic drugs) is delayed by beta 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 and even sudden death can occur. This is due to up-regulation (supersensitivity) of β-receptors in response to prolonged blockade (see p. 31).

Drug Interactions

1. **Propranolol × verapamil:** They produce additive cardiac depressant effects and may cause CCF, bradyarrhythmias, heart block or even cardiac arrest.
2. **Propranolol × lignocaine:** Propranolol reduces the clearance of lignocaine by decreasing hepatic blood flow.
3. **Cholestyramine and colestipol × 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. **Insulin/Sulfonylureas × β-blockers:** Nonselective β-blockers inhibit glycogenolysis and delay recovery from hypoglycaemia (Fig. 2.26).
5. **Propranolol × nonsteroidal antiinflammatory drugs (NSAIDs):** NSAIDs by inhibiting prostaglandin synthesis, promote Na^+ and water retention on chronic use. Thus, they decrease antihypertensive effect of β-blockers.
6. **Propranolol × chlorpromazine:** Propranolol interferes with the first-pass metabolism of chlorpromazine and increases its bioavailability.

Therapeutic Uses of β-Blockers

1. **Hypertension:** β-Blockers are useful for all grades of hypertension. These drugs are preferred especially in patients with angina, myocardial infarction (MI) or cardiac arrhythmias (see p. 117).
   The advantages of β-blockers are:
   - Sodium and water retention is rare.
   - Cheaper.
   - Have a long duration of action.
   - Well tolerated.
2. **Angina prophylaxis and Myocardial infarction (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

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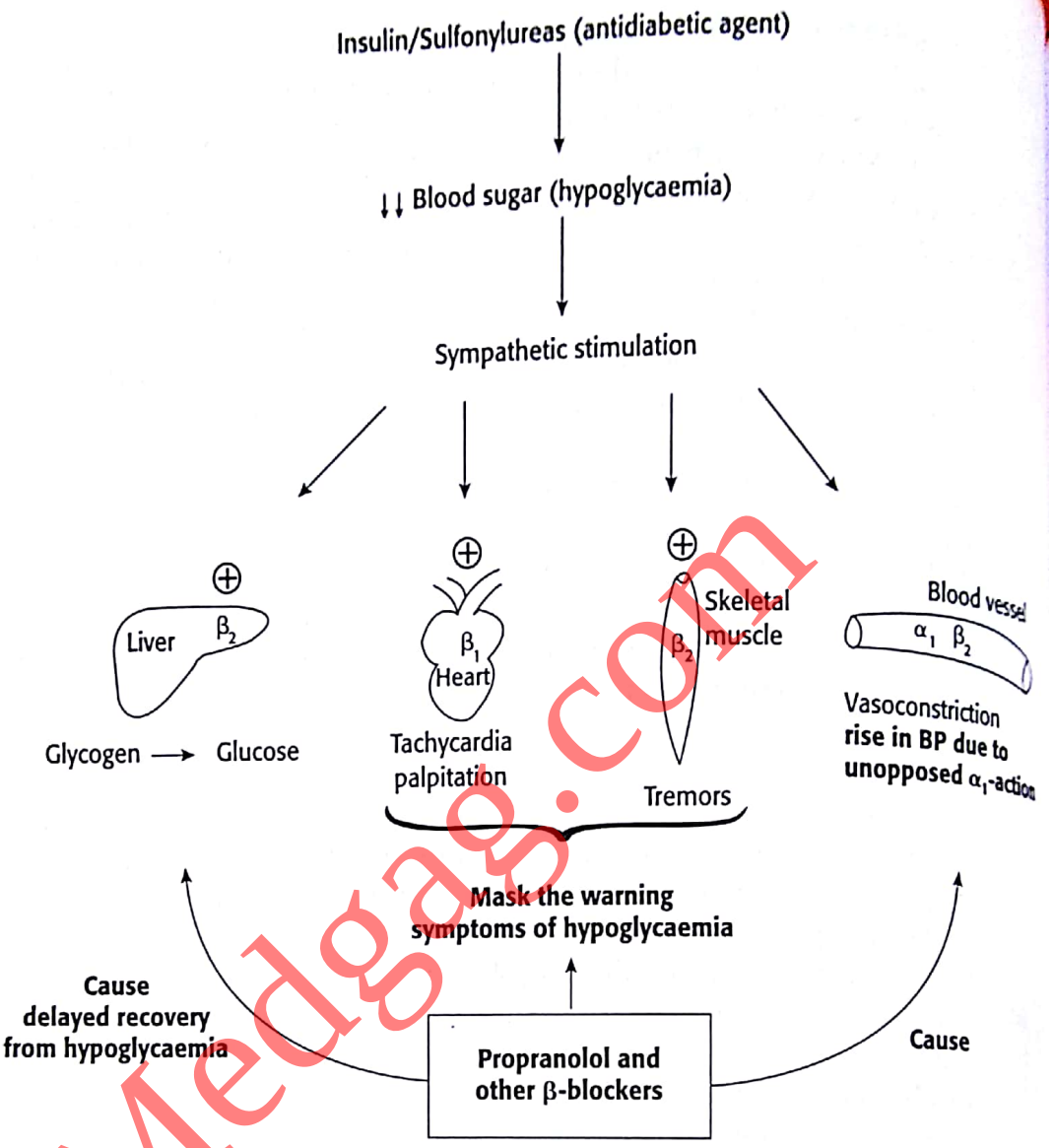

FIGURE 2.26 Interaction between insulin/sulfonylureas and β-blockers.

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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.

3. **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. 152).
4. **Congestive cardiac failure** (see p. 140): 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. 102).
6. **Glaucoma** (see p. 66): β-Blockers decrease the IOP by reducing the production of aqueous humour. They are useful in the treatment of glaucoma. 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, anxiety, etc. 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, sweating, etc.
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, p. 108.

Selective β_1-Adrenergic Blockers

Esmolol

- It is administered intravenously.
- Its $t_{1/2}$ 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 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.

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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	Intravenous	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
Labetaol	+	+	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

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.

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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	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

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 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.

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CHAPTER 3
Drugs Affecting Cardiovascular Function

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HYPERTENSION

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

The classification of blood pressure (BP) readings is shown in Table 3.1 (as per JNC: 7(2003) guidelines).

- **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 systolic and diastolic blood pressure (PP = SBP – DBP).
- **Mean arterial pressure:** DBP + 1/3 PP.

Table 3.1 Classification of blood pressure for adults

Category	Blood pressure (mmHg)	
	Systolic	Diastolic
Normal	<120	<80
Prehypertension	120–139	80–89
Hypertension		
Stage 1	140–159	90–99
Stage 2	≥160	≥100

CLASSIFICATION OF ANTIHYPERTENSIVE DRUGS (Fig. 3.1)

1. **Angiotensin converting enzyme (ACE) inhibitors:** Captopril, enalapril, lisinopril, perindopril, ramipril, benazepril, fosinopril.
2. **Angiotensin II receptor blockers (ARBs):** Losartan, candesartan, irbesartan, valsartan, telmisartan, olmesartan.
3. **Direct renin inhibitor:** Aliskiren.
4. **Calcium channel blockers (CCBs):** Diltiazem, verapamil, nifedipine, amlodipine, nicardipine, isradipine, felodipine, nitrendipine.
5. **Diuretics**
   (a) *Thiazides and related agents:* Hydrochlorothiazide, chlorthalidone, indapamide.
   (b) *Loop diuretics:* Furosemide, bumetanide, torsemide.
   (c) *Potassium-sparing diuretics:* Amiloride, triamterene, spironolactone, eplerenone.
6. **Sympatholytic agents**
   (a) *Centrally acting sympatholytics:* Clonidine, α-methyldopa.
   (b) β-*Adrenergic blockers:* Atenolol, metoprolol, esmolol, betaxolol, carteolol, propranolol, timolol.
   (c) β-*Adrenergic blockers with additional* α-*blocking activity:* Labetalol, carvedilol.

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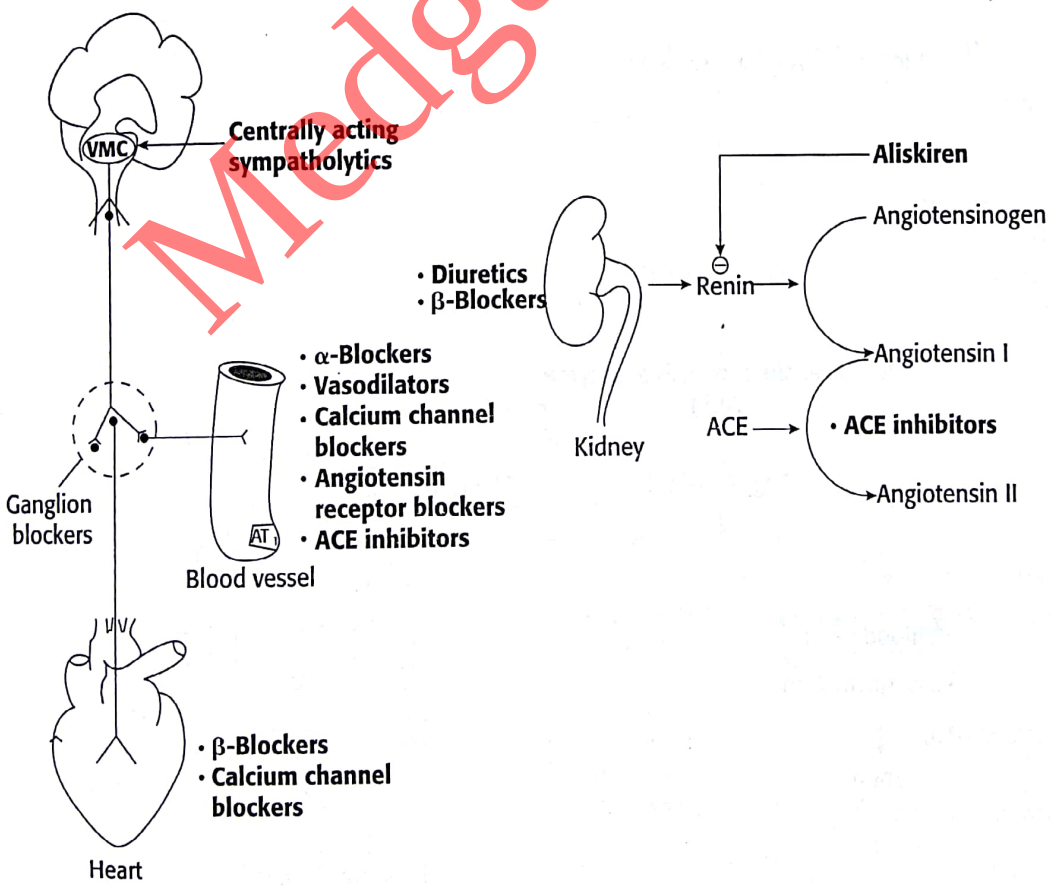

FIGURE 3.1 Sites of action of major groups of antihypertensive drugs. VMC, Vasomotor centre (medulla); ACE, Angiotensin converting enzyme; and AT_1, Angiotensin receptor. (Adapted from Katzung – *Basic and Clinical Pharmacology*, 12e.)

(d) *α-Adrenergic blockers:*
- *Selective*: Prazosin, terazosin, doxazosin.
- *Nonselective*: Phenoxybenzamine, phentolamine.

(e) *Ganglion blocker:* Trimethaphan.

(f) *Neurone blocker:* Reserpine.

7. Vasodilators
   (a) *Arteriolar-dilators:* Hydralazine, minoxidil, diazoxide, fenoldopam.
   (b) *Primarily venodilator:* Nitroglycerin.
   (c) *Arteriolar and venodilator:* Sodium nitroprusside.

Angiotensin Converting Enzyme Inhibitors (Fig. 3.2)

Angiotensin converting enzyme inhibitors (ACE inhibitors) are frequently used as first line antihypertensive drugs.

Mechanism of Action

Angiotensin converting enzyme inhibitors

1. Inhibit the generation of angiotensin II resulting in:
   - Dilatation of arterioles → ⇩ peripheral vascular resistance (PVR) → ⇩ BP.
   - Decrease in aldosterone production → decrease in Na^+ and H_2O retention → ⇩ BP
   - Decrease in sympathetic nervous system activity.

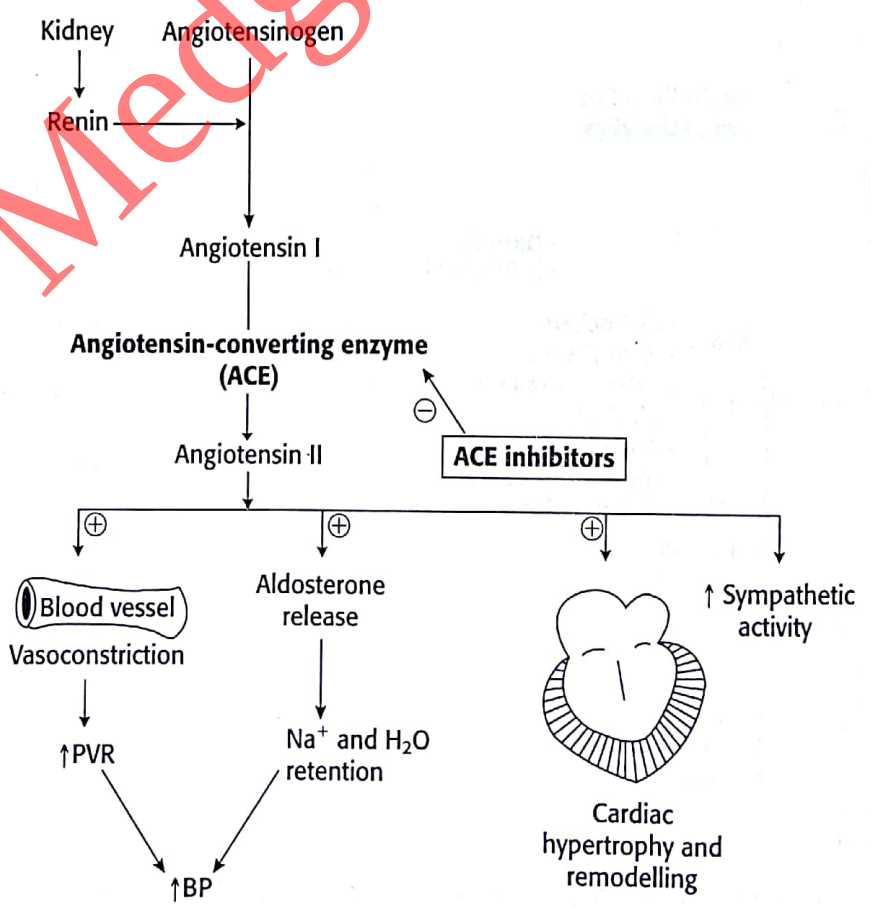

FIGURE 3.2 Site of action of ACE inhibitors. Effects of angiotensin II are prevented by ACE inhibitors. (Adapted from Katzung – *Basic and Clinical Pharmacology*, 12e.)

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Table 3.2 Pharmacokinetic features of ACE inhibitors

Drug	Captopril	Enalapril	Lisinopril	Perindopril	Ramipril
Active/ Prodrug	Active	Prodrug	Active	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
Duration of action	8–12 h	24 h	>24 h	>24 h	>24 h
Route of excretion	Kidney	Kidney	Kidney	Kidney	Kidney

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. Angiotensin converting enzyme 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 3.2).

Adverse Effects* and Contraindications

1. Cough (dry cough) is due to increased bradykinin levels in the lungs. 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.
5. Hypotension may occur following the first dose of ACE inhibitor – this can be marked in patients who are volume depleted or have CHF.
6. NeutroPenia is rare.
7. Rashes.

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

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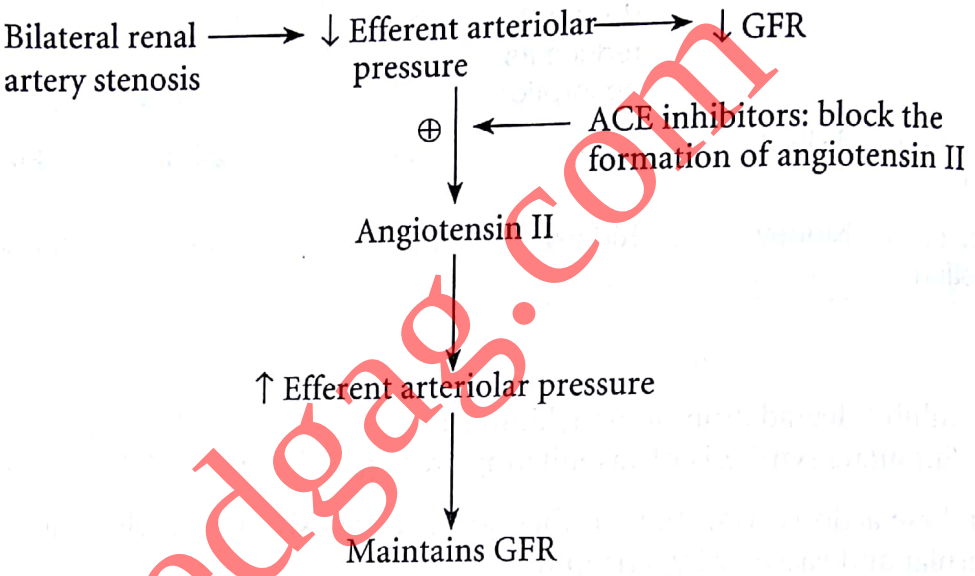
8. Itching. Discontinuation of the drug is not required.
9. Loss of taste sensation (dysgeusia).
10. Hyperkalaemia: In patients receiving ACE inhibitors, hyperkalaemia may occur in the presence of renal insufficiency or when they are combined with potassium-sparing diuretics.

Angiotensin converting enzyme inhibitors are contraindicated in patients with bilateral renal artery stenosis as acute renal failure can be precipitated. (Basis: When renal perfusion pressure is low, angiotensin II maintains glomerular filtration rate (GFR) by constriction of efferent arteriole). Angiotensin converting enzyme inhibitors are also contraindicated in patients with single kidney with renal artery stenosis as they can precipitate renal failure.



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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 the 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 above) ACE inhibitors are used in all grades of hypertension. They decrease cardiovascular and cerebrovascular morbidity and mortality (fatal and nonfatal myocardial infarction, 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 hypertrophy and peripheral vascular disease.

2. **Acute myocardial infarction (MI):** ACE inhibitors should be started within 24 hours in patients with myocardial infarction (MI). They have shown both short-term and long-term improvement in survival and decrease in reinfarction.
3. **Congestive heart failure (CHF):** ACE inhibitors should be prescribed to all patients with impaired left ventricular function (for explanation see p. 140).
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 → ↓ 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 (ARBs) or Angiotensin Receptor Antagonists

They are losartan, irbesartan, candesartan, olmesartan, valsartan and telmisartan. The two types of angiotensin II receptors are AT_1 and AT_2. Most of the effects of angiotensin II are mediated by AT_1 receptors. They are vasoconstriction, aldosterone secretion and the release of noradrenaline from sympathetic nerve endings. The role of AT_2 receptors is not known.

Angiotensin II (Agonist) → **Angiotensin receptors (AT_1) (Competitive antagonism)** ← **ARBs (Antagonists)**

Angiotensin receptor blockers competitively inhibit the binding of angiotensin II to AT_1-receptor subtype and block its effects. Angiotensin receptor blockers produce effects similar to those of ACE inhibitors. Angiotensin receptor blockers do not affect bradykinin production.

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 diabetics. 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.

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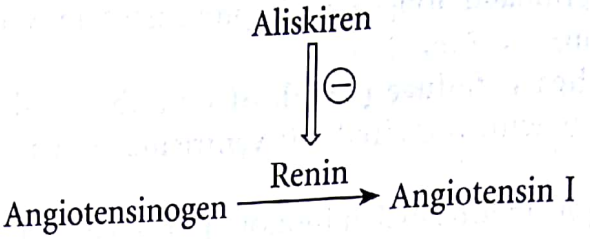
Direct renin inhibitor: Aliskiren



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.

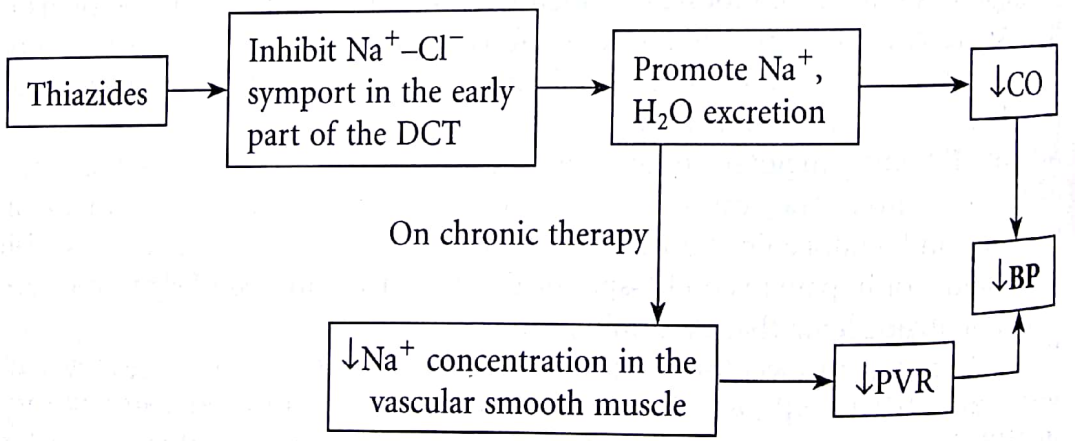
Diuretics

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.

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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 (CCBs)

Verapamil, diltiazem and dihydropyridines (nifedipine, amlodipine, felodipine, nicardipine, isradipine, etc.) are useful in all grades of hypertension.

The antihypertensive effect is mainly due to peripheral vasodilatation. Dihydropyridines (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. Calcium channel blockers are particularly useful in elderly patients and also 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 diabetic 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, betaxolol, etc.
- Nonselective β-blockers (block both β_1 and β_2), e.g. propranolol and timolol.

During initial therapy with β-blockers, cardiac output decreases but peripheral vascular resistance may increase. On chronic therapy, peripheral vascular resistance gradually decreases because of sustained reduction in cardiac output – BP

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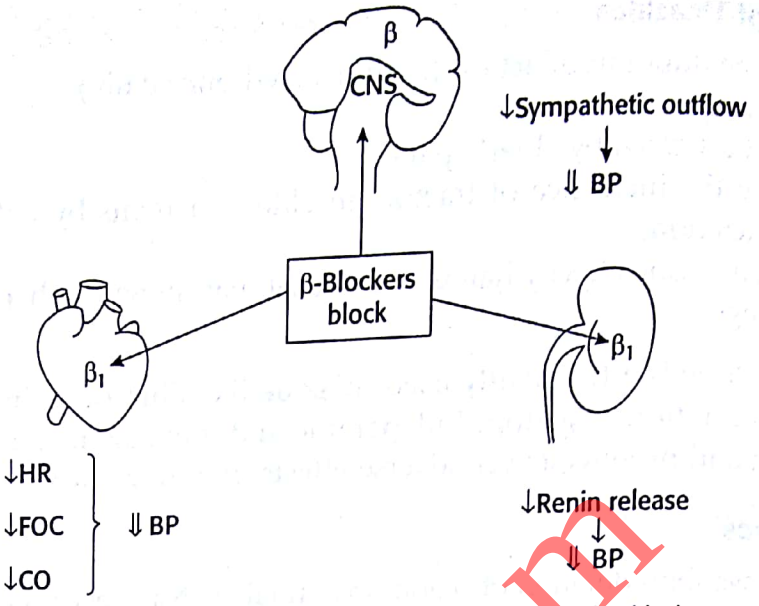

FIGURE 3.3 Mechanism of antihypertensive effect of β-blockers.

falls. Other mechanism of antihypertensive effect is 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.

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 diabetics 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.

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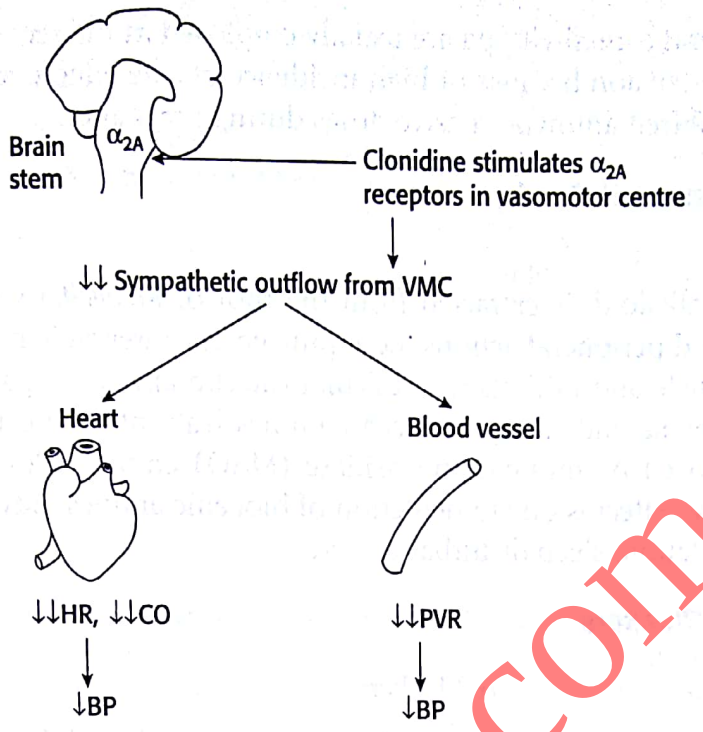

FIGURE 3.4 Mechanism of action of clonidine.

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.

α-Methyldopa

It is a centrally acting sympatholytic agent.

Mechanism of Action

α-Methyldopa → α-Methyldopamine → α-Methylnoradrenaline → Stimulates α_2–VMC → ↓↓ Central sympathetic outflow → ↓HR, ↓PVR → ↓↓BP

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, depression, dryness of mouth, bradycardia, impotence, gynaecomastia, hepatitis and rarely haemolytic anaemia.

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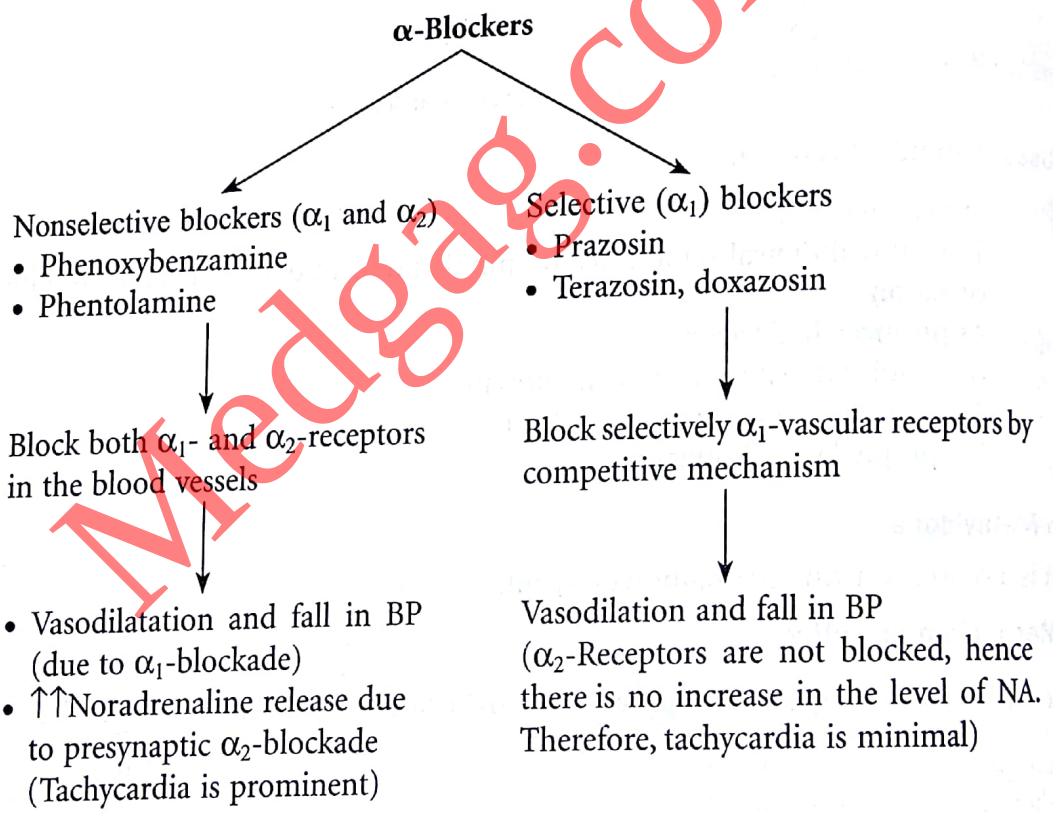
Clonidine and α-methyldopa are usually employed as the second or third line agents in hypertension because of high incidence of side effects. α-Methyldopa is one of the preferred antihypertensive drugs during pregnancy.

Adrenergic Neuronal Blocker

Reserpine

Reserpine, an alkaloid, is extracted from the root of *Rauwolfia serpentina*. It has both central and peripheral actions. Reserpine enters adrenergic neuron, binds to the storage vesicle and inhibits the vesicular catecholamine (dopamine and noradrenaline) uptake and storage. Catecholamines leak into the cytoplasm where they are destroyed by monoamine oxidase (MAO) enzyme. Reserpine-induced antihypertensive effect is due to depletion of biogenic amines. Adverse effects are depression, sedation, sleep disturbances, etc.

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 in p. 100.

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.

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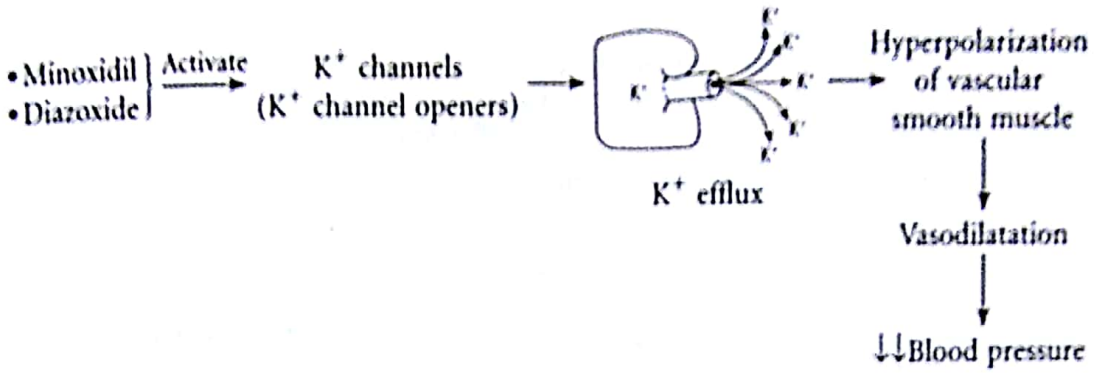
Vasodilators



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

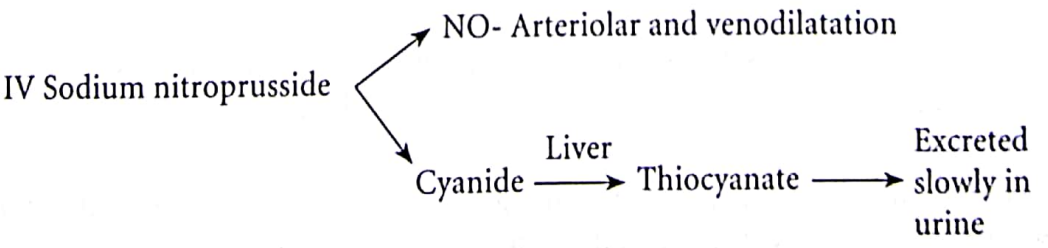
It is used in the treatment of hypertensive emergencies. It is administered intravenously and has a long duration of action (6–24 hours). It also relaxes uterine smooth muscle. Adverse effects are reflex tachycardia, hyperglycaemia, sodium and water retention.

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, myocardial infarction, 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 and tolerance does not develop to its action.



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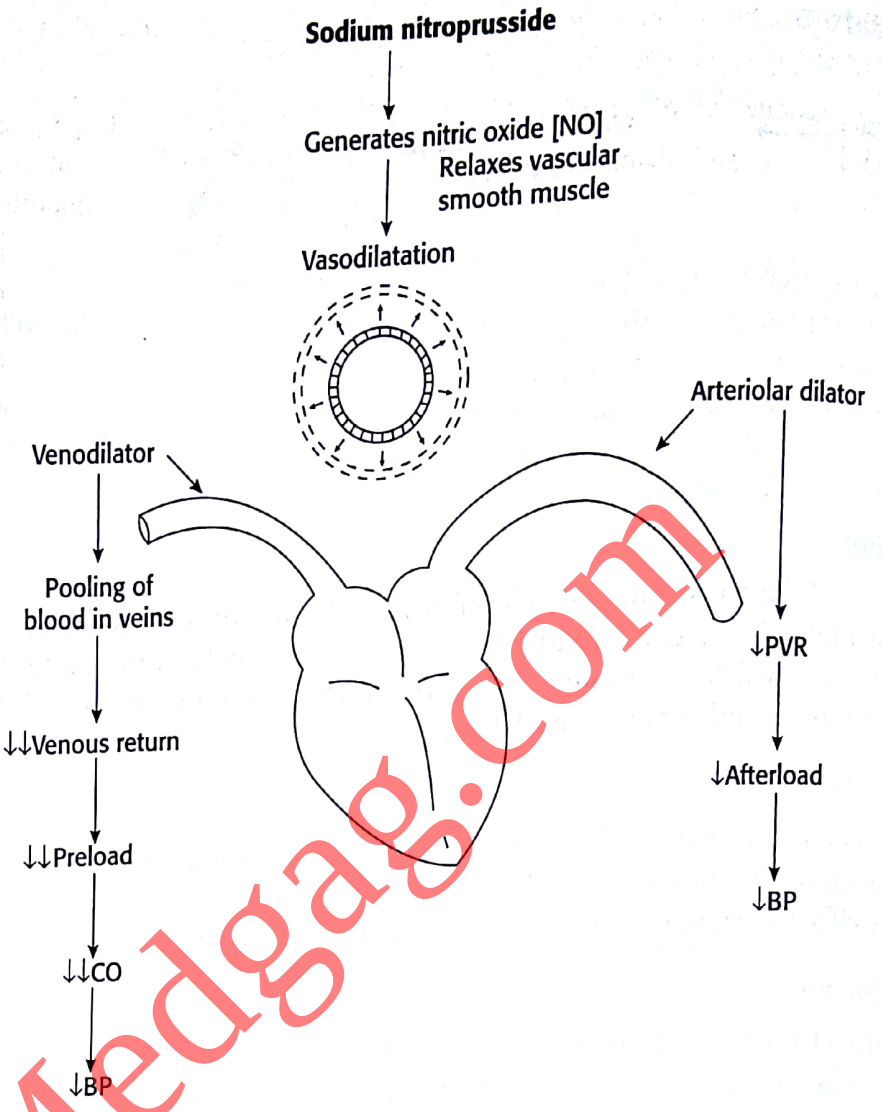

FIGURE 3.5 Mechanism of action and effects of sodium nitroprusside.

Sodium nitroprusside is the drug of choice for hypertensive crisis; can also be used to improve cardiac output in severe CCF. It is administered at a dose of 0.25-1.5 mcg/kg/minute i.v. infusion in 5% dextrose. Nitroprusside can cause severe hypotension, hence close monitoring of BP is required. Prolonged administration may cause anorexia, nausea, vomiting, fatigue, disorientation, toxic psychosis due to accumulation of cyanide, which in turn may lead to severe lactic acidosis and convulsions.

Nitroglycerine

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) → D_1 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.

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Treatment of Hypertension

1. Non-pharmacological 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 3.3 and 3.4): 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.

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Table 3.3 Dosage and indications of antihypertensive drugs

Drug	Dosage	Indications
Hydrochlorothiazide	12.5–25 mg OD oral	Mild hypertension
Chlorthalidone	12.5–25 mg OD oral	Mild hypertension
Captopril	12.5–75 mg BD oral	Mild to severe hypertension – especially in diabetics
Enalapril	2.5–40 mg OD oral	Mild to severe hypertension – especially in diabetics
Lisinopril	5–40 mg OD oral	Mild to severe hypertension – especially in diabetics
Ramipril	1.25–20 mg OD oral	Mild to severe hypertension – especially in diabetics
Losartan	25–50 mg OD or BD oral	Mild to severe hypertension – especially in diabetics
Propranolol	10–120 mg, BD or QID oral	Mild to moderate hypertension
Atenolol	25–100 mg OD oral	Mild to moderate hypertension
Prazosin	1–10 mg BD oral	Mild to moderate hypertension
Clonidine	0.05–0.6 mg BD	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 OD oral	Mild to moderate hypertension
Amlodipine	2.5–10 mg OD oral	Mild to moderate hypertension
α-Methyldopa	250 mg–2 g/day oral	Hypertension during pregnancy

Table 3.4 Commonly used drugs for hypertension associated with the following conditions

Angina/Post MI	β-Blockers
Congestive cardiac failure/Left ventricular failure	ACE inhibitors, loop diuretics and ARBs
Diabetes mellitus and diabetic nephropathy	ACE inhibitors, ARBs, CCBs
Bronchial asthma/COPD	Calcium channel blockers (CCBs)
Hypertensive emergencies	Sodium nitroprusside, labetalol, nitroglycerin
Benign prostatic hyperplasia (BPH)	Selective α_1-blockers
Pregnancy	α-Methyldopa, hydralazine, labetalol

- 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/DHPs. If response is not satisfactory, other antihypertensives can be added, e.g. thiazides/DHPs with beta blockers. ACE inhibitors are not to be combined with ARBs.

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 Emergencies)

It is characterized by a very high blood pressure (systolic > 220 and/or diastolic >120 mmHg) with progressive end organ damage such as retinopathy, renal dysfunction and/or hypertensive encephalopathy. It is a medical emergency. The BP should be reduced by not more than 25% within minutes to 2 hours and then to 160/100 mmHg within 2–6 hours. The drugs used as i.v. infusion are labetalol, nitroglycerin, sodium nitroprusside, nicardipine, clevidipine, esmolol, hydralazine, fenoldopam, enalaprilat and furosemide, etc.

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ANTIANGINAL DRUGS

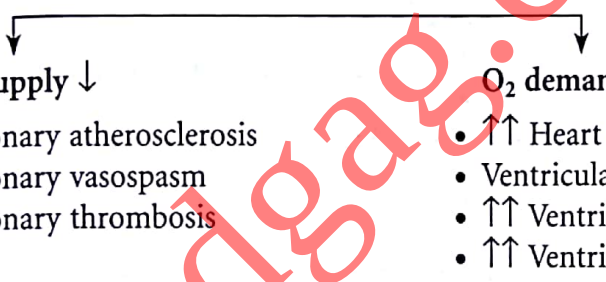
Angina and Myocardial Infarction

Angina pectoris is a symptom of ischaemic heart disease.

Types of angina pectoris

1. **Stable angina (classical angina):** It is characterised 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's 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.



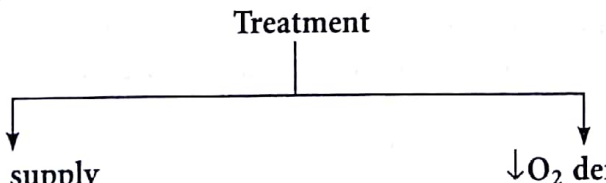
O_2 supply ↓

- Coronary atherosclerosis
- Coronary vasospasm
- Coronary thrombosis

O_2 demand ↑

- ↑↑ Heart rate
- Ventricular hypertrophy
- ↑↑ Ventricular contractility
- ↑↑ Ventricular wall tension

Treatment. Treatment is aimed at maintaining the balance between O_2 supply and demand.



Treatment

↑O_2 supply

1. Restore the coronary blood flow by:
   (a) Percutaneous intervention (PCI) including stenting
   (b) Coronary artery bypass graft (CABG)
2. Relieve the vasospasm by drugs: CCB/nitrates
3. Break the thrombi using thrombolytic agents: streptokinase/urokinase
4. Prevent thrombus formation by using antiplatelet drugs

↓O_2 demand

By reducing work load on the heart:

(a) Decrease preload (mainly): Nitrates
(b) Decrease afterload: CCBs, K^+ channel openers
(c) Decrease heart rate and contractility: β-adrenergic blockers

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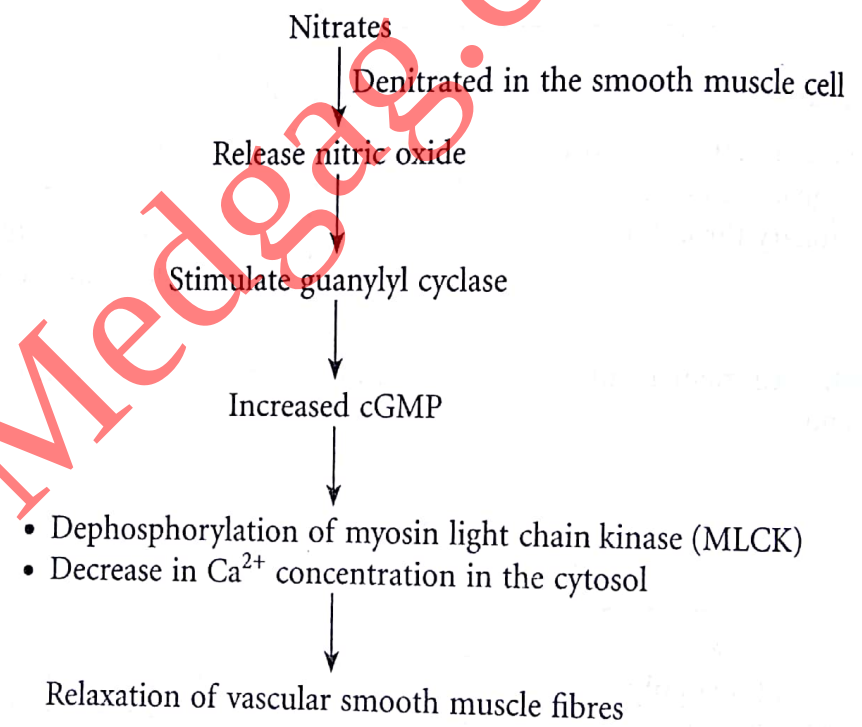
Classification

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

Organic Nitrates

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

*Mnemonic: STAIR.

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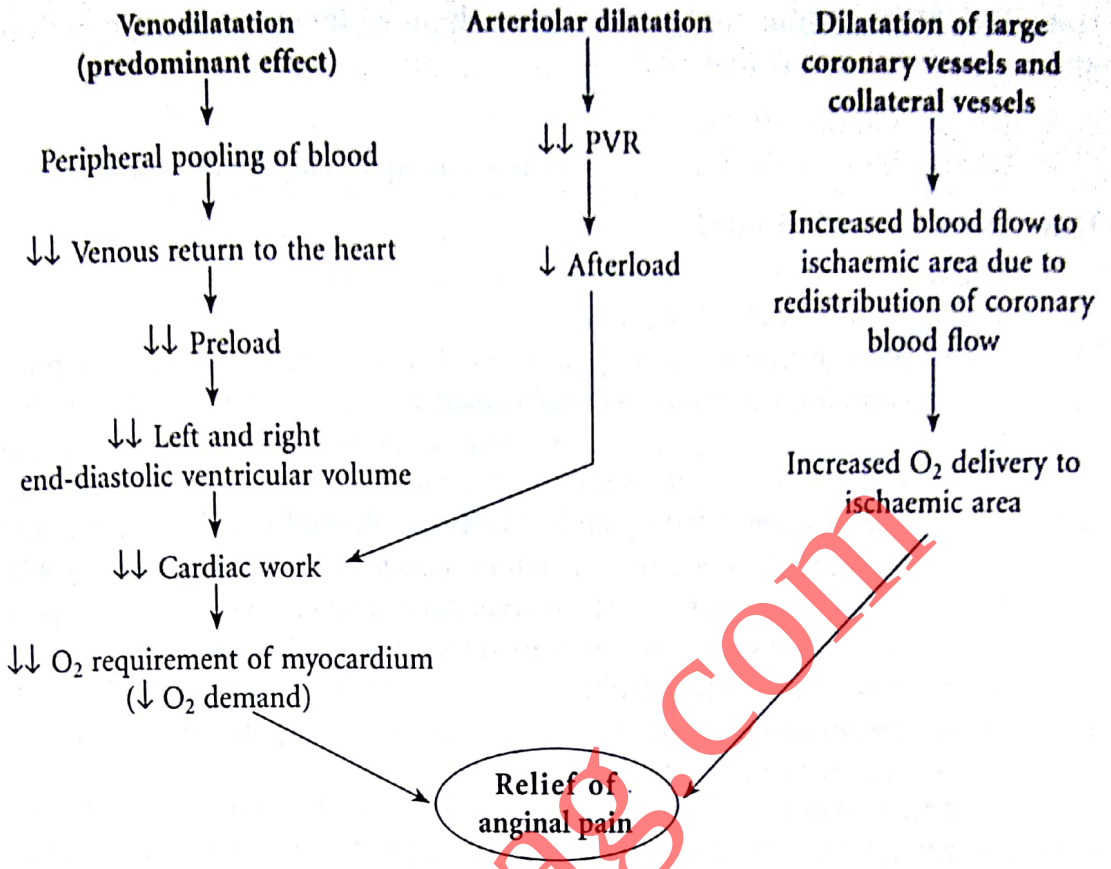

2. **On other smooth muscles:** Smooth muscles of the bronchi, oesophagus, biliary tract, etc. are relaxed by nitrates.

Pharmacokinetics. Organic nitrates are readily absorbed through the buccal mucous membrane, the 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/IV infusion. Development of tolerance is rare following intermittent exposure (e.g. sublingual GTN). Tolerance is due to decreased NO generation, depletion of sulfhydryl 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 h) 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.

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Isosorbide Mononitrate: It is preferred over dinitrate for chronic prophylaxis of angina, because it has (Table 3.5):

- 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). 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,

Table 3.5 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	• 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
Erythrityl tetranitrate	20–40 mg oral	4–6 hours
Pentaerythritol tetranitrate	80 mg oral	10–12 hours

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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's angina): It is due to coronary vasospasm. Episodes of coronary vasospasm are treated with nitrates; for prophylaxis, nitrates and calcium channel blockers (amlodipine, nifedipine SR and diltiazem) are effective. Addition of a CCB with nitrate produces better efficacy in variant angina and also reduces the incidence of MI.
3. **Unstable angina:** It requires treatment with multiple drugs.
   (a) ***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.
   (b) ***Anticoagulants:*** Low-molecular-weight heparin, unfractioned heparin or fondaparinux.
   (c) ***Nitrates:*** Nitroglycerin (sublingual) is usually effective. Intravenous nitroglycerin is administered if pain persists or recurs. They reduce myocardial oxygen consumption and relieve coronary vasospasm (BP should be monitored during i.v. infusion of nitroglycerin).
   (d) ***β-Blockers:*** They (atenolol, metoprolol) are routinely administered in unstable angina unless contraindicated.
   (e) ***Calcium channel blockers:*** Amlodipine, nifedipine SR, diltiazem or verapamil are used if symptoms persist in patients on nitrates and β-blockers or if β-blockers are contraindicated.
   (f) ***Statins:*** They have been shown to improve outcome in unstable angina.
4. **Myocardial infarction:** For management of acute MI, intravenous infusion of nitroglycerin is useful for persistent or recurrent ischaemic pain and treatment of left ventricular failure. It should be avoided if there is hypotension and in patients who received sildenafil or tadalafil in the past 24 hours.
5. **Congestive cardiac failure:** The role of nitrates in CCF is discussed in p. 139. 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.
6. **Hypertensive emergency:** Intravenous infusion of nitroglycerin is used because of rapid onset of action, but the disadvantage is development of tolerance.
7. **Biliary colic:** Sublingual nitroglycerin can be used to relieve biliary spasm and associated pain.
8. **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).

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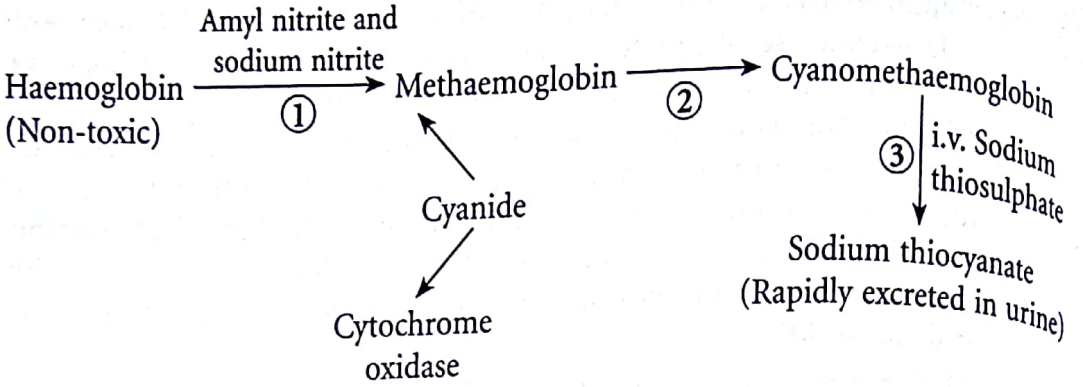


Treatment of cyanide poisoning:

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.

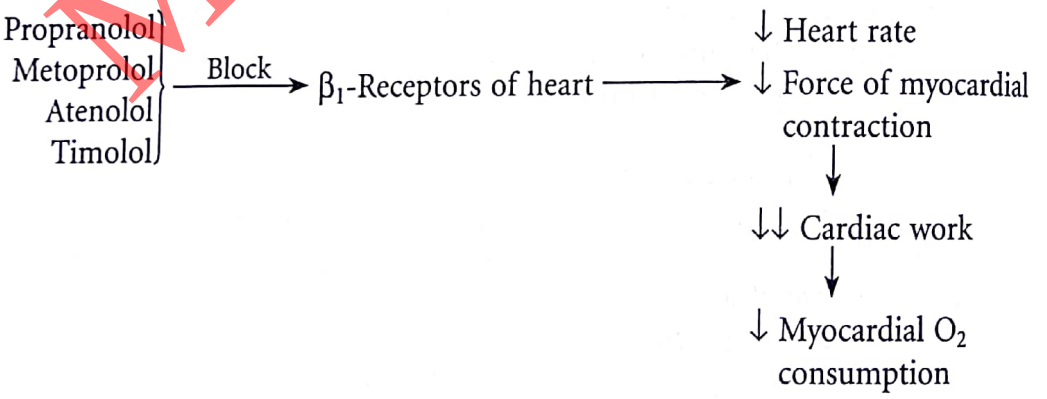
Step 2: Methaemoglobin combines with cyanide to form non-toxic cyanomethaemoglobin.

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. Cardioselective β-blockers are preferred. β-Blockers with intrinsic sympathomimetic activity (e.g. pindolol) should be avoided as they may worsen angina.

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

β-Blockers can increase left ventricular end diastolic volume.

β-Blockers → ↓ Heart rate, ↓ Myocardial contractility → ↓ Cardiac output → Increase left ventricular 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 myocardial infarction.

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:** Nifedipine, amlodipine, nicardipine, felodipine, isradipine, nisoldipine.

Mechanism of Action. Voltage-sensitive Ca^{2+} channels are of five subtypes. They are L, N, T, P and R subtypes. 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. Calcium channel blockers 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.

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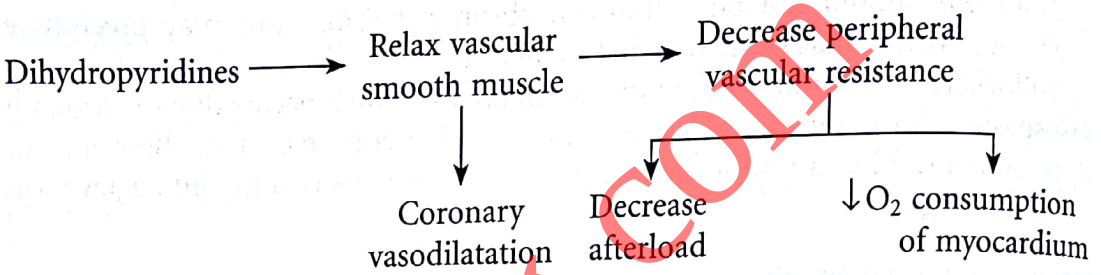
- depresses SA node and slows AV conduction (negative dromotropic effect) by prolonging effective refractory period.
  Verapamil is a less potent coronary and peripheral vasodilator than the DHPs.

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. **Dihydropyridines (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 as well as 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 →↑ hydrostatic pressure → 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.

(d) **Felodipine:** It has greater vascular selectivity than nifedipine and amlodipine. Like nifedipine, it can also produce tachycardia and palpitation.

(e) **Isradipine and nisoldipine:** They are peripheral vasodilators.

(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.

Pharmacokinetics. All calcium channel blockers 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 3.6.

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Table 3.6 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 • A–V block and headache, rarely	• Headache • Hypotension • Bradycardia • Oedema • A–V block occurs rarely

Uses of CCBs

1. **Exertional angina** (for detailed explanation, see pharmacological action): The beneficial effect in angina pectoris with CCBs is mainly due to a decrease in myocardial O_2 consumption (following ↓HR, ↓force of contraction or ↓afterload) and also due to 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 over verapamil as it has fewer side effects. Dihydropyridines like nifedipine and felodipine may aggravate anginal symptoms because of reflex tachycardia, which can be counteracted by combining them with β-blockers.
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 have shown increased efficacy in patients with variant angina.
3. **Unstable angina:** Calcium channel blockers are used mainly when symptoms are not relieved by nitrates and β-blockers or if these drugs are contraindicated.
4. **Supraventricular arrhythmias:** Verapamil is the 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 calcium channel blocker 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.

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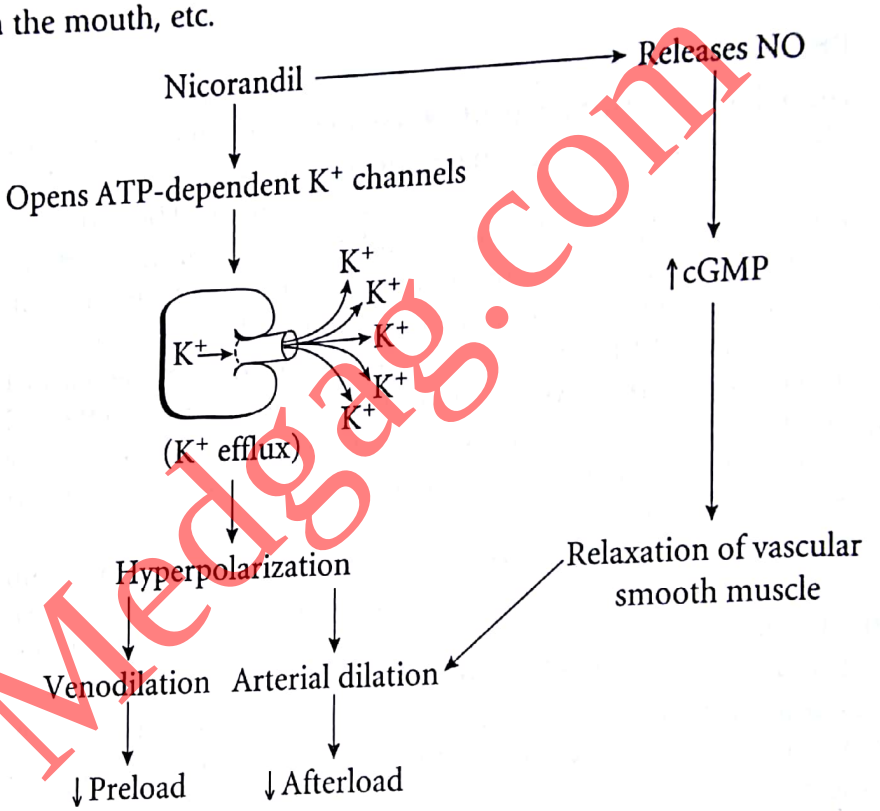
8. **Raynaud's phenomenon:** It is a peripheral vasospastic condition. Nifedipine, amlodipine, felodipine or diltiazem are used to treat this condition.
9. Nifedipine is used as uterine relaxant in premature labour.
10. Nimodipine is used for prevention and treatment of cerebral vasospasm and subsequent neurological defects in patients with subarachnoid haemorrhage.

Potassium Channel Openers (Potassium Channel Activator)

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



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Other Drugs

Antiplatelet Agents: Antiplatelet agent, aspirin 162 mg or 325 mg, is administered orally in 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.

Statins: See p. 129.

Ranolazine

- Ischaemia increases the late inward sodium current in myocardium resulting in calcium influx and overload. Ranolazine inhibits late inward Na^+ current → ⇩ 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 → fatty acid oxidation inhibitor → partial inhibition of fatty acid oxidation in myocardium → increased use of glucose for energy → ⇩ 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 → ⇩ myocardial O_2 demand.
- Decreases frequency of anginal episodes. It can also be used in sinus tachycardia.

Combination Therapy

1. **Nitrates × β-blockers (Propranolol):** This combination (used in exertional angina) increases the effectiveness and reduces the incidence of adverse effects (Fig. 3.6).

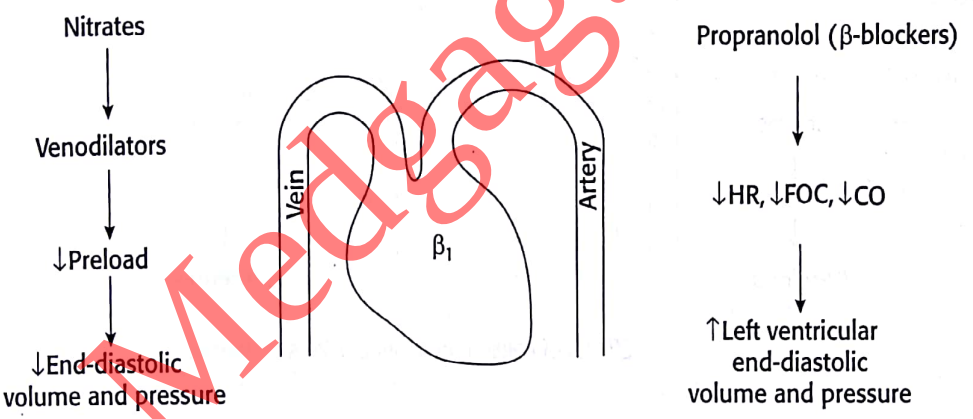

FIGURE 3.6 Effects of nitrates × β-blockers (propranolol).

(a) Nitrates can counteract the increase in left ventricular end-diastolic volume associated with propranolol.

(b) Nitrates → arteriolar dilatation → ↓ PVR → reflex tachycardia. Propranolol can block the reflex tachycardia that is associated with nitrates.

(c) Blockade of β_2 receptors → Coronary artery (α_1 β_2) → Unopposed α_1 action → Coronary spasm

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

2. **Nifedipine (DHPs) × 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 beta blockers. The combination is useful in classical angina with associated coronary vasospasm.

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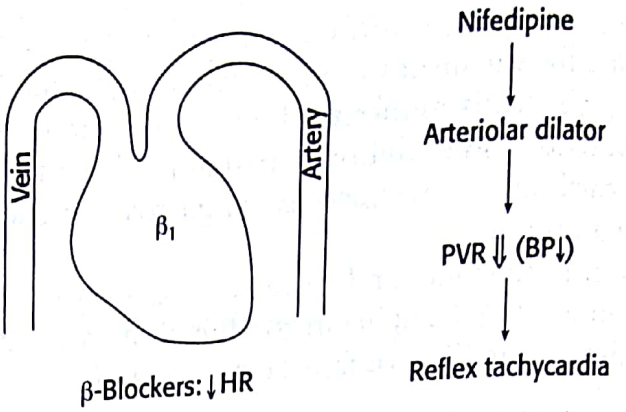

FIGURE 3.7 Effects of nifedipine (DHPs) × β-blockers.

3. **β-blockers × 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. **Calcium channel blockers × 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.

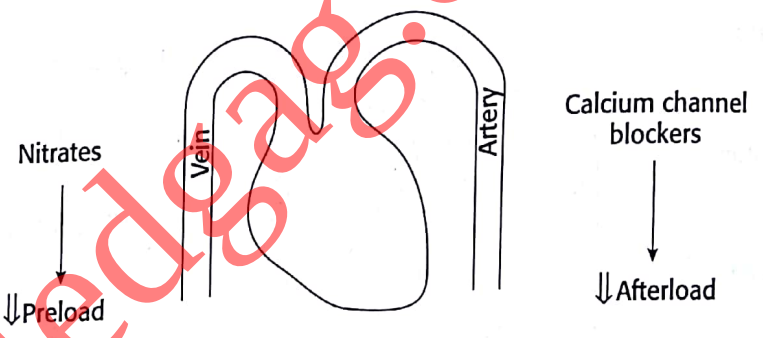

FIGURE 3.8 Effects of calcium channel blockers + nitrates.

5. **Nitrates × β-blockers × CCBs:** This combination is especially useful in severe and resistant cases of exertional angina and also in unstable angina (Fig. 3.9).

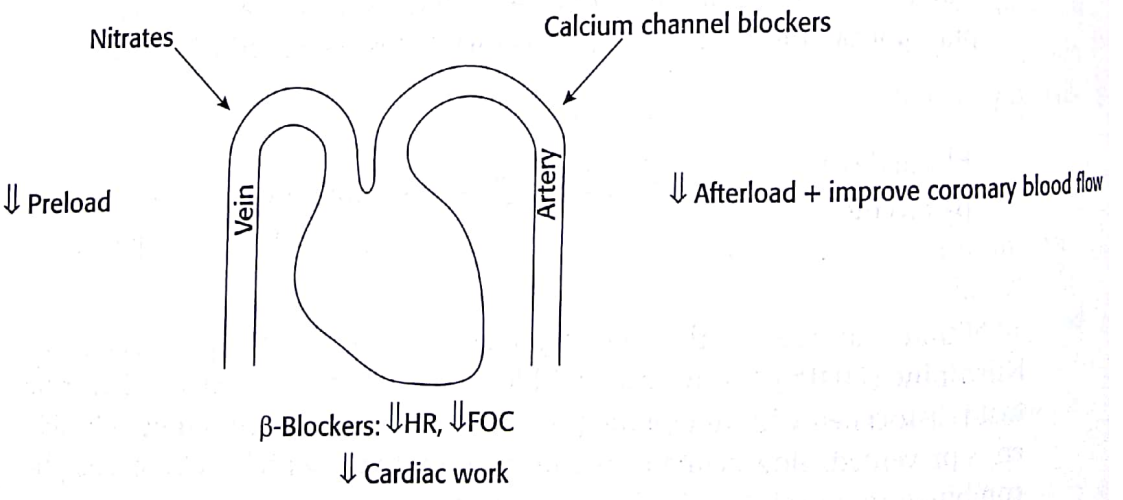

FIGURE 3.9 Effects of nitrates + β-blockers + CCBs.

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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 or pethidine 50–75 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 left ventricular failure.
4. Low flow oxygen therapy (2–4 L/min) if there is decreased oxygen saturation.
5. Reperfusion therapy: Primary percutaneous coronary intervention (PCI) or thrombolytic therapy.
   - Primary percutaneous coronary intervention (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

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 cardiac output (CO). In initial stages of CCF, the compensatory mechanisms that try to maintain the cardiac output (Fig. 3.10) are:

- 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 congestive cardiac failure are:

- Increased pulmonary capillary pressure termed as backward failure, which is characterised by dyspnoea and orthopnoea.
- Decreased cardiac output termed as forward failure, leading to decreased oxygen supply to the peripheral tissues (tissue hypoxia).

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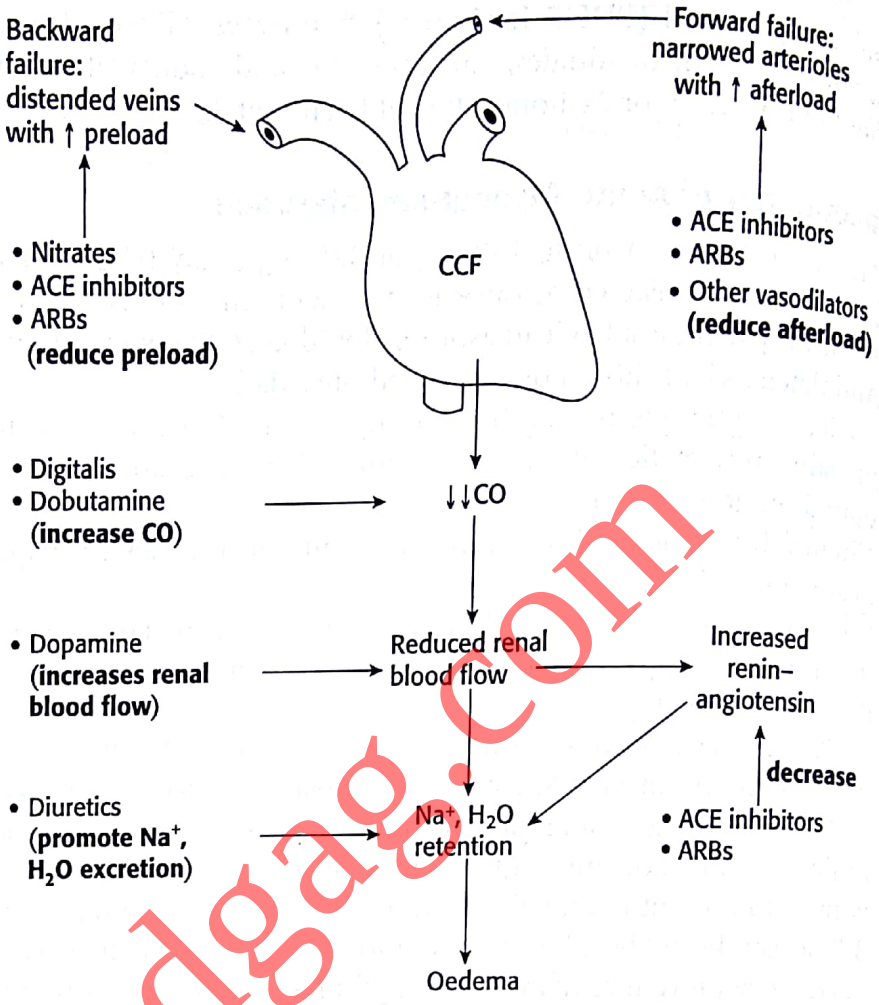

FIGURE 3.10 Pathophysiology of CCF and mechanism of action of some drugs used in its treatment. ARBs, Angiotensin receptor blockers; CCF, Congestive cardiac failure; CO, Cardiac output.

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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.

Classification

1. **Diuretics**
   (a) *Loop diuretics:* Furosemide, bumetanide, torsemide.
   (b) *Thiazide diuretics:* Chlorothiazide, hydrochlorothiazide, metolazone.
   (c) *Aldosterone antagonists:* Spironolactone, eplerenone.
2. **Vasodilators:**
   (a) *Arteriolar and venodilators:*
      - ACE inhibitors: Enalapril, lisinopril, ramipril, fosinopril, trandolapril.
      - Angiotensin receptor blockers (ARBs): Losartan, candesartan.
      - Direct renin inhibitor: Aliskiren.
      - Sodium nitroprusside.
   (b) *Venodilators*: Nitroglycerin, isosorbide dinitrate.
   (c) *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. **Brain natriuretic peptide (BNP):** Nesiritide.

Diuretics

A majority of patients with CHF are started on diuretics.

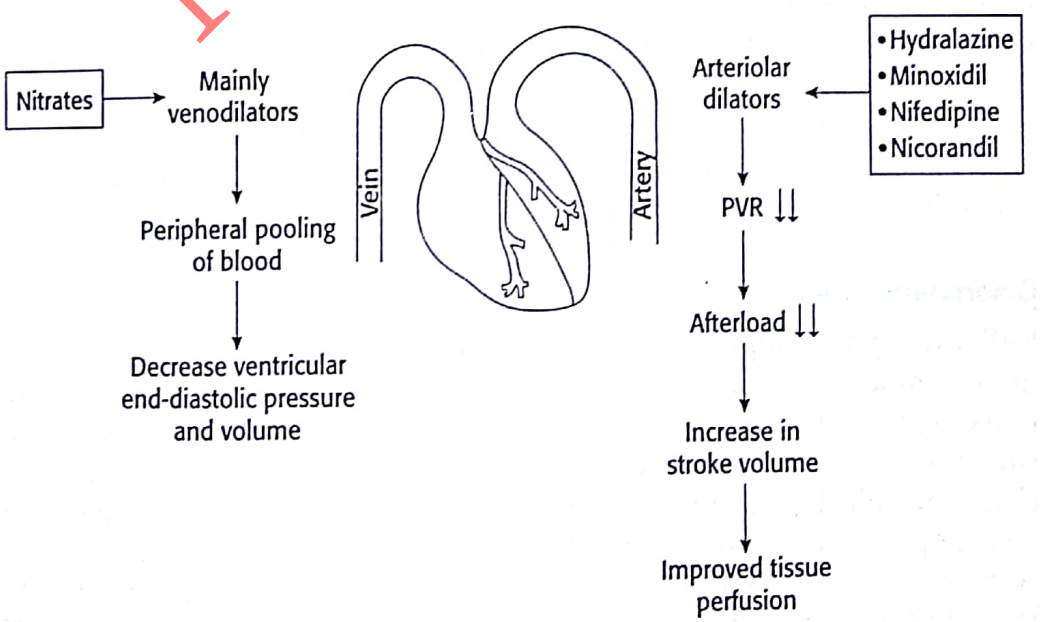
Diuretics → Promote salt and water excretion → ↓Circulating volume → ↓Preload → • Improve cardiac function • Decrease dyspnea and peripheral oedema

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, but 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.

FIGURE 3.11 Effects of vasodilators in congestive cardiac failure.

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ACE Inhibitors

They are the standard therapy for all grades of congestive heart failure 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 AII 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. 112-114).

Angiotensin Receptor Blockers (ARBs) (p. 115)

Losartan, candesartan, etc. competitively block AT_1-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, left ventricular 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 cardiac output 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 left ventricular (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.

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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.

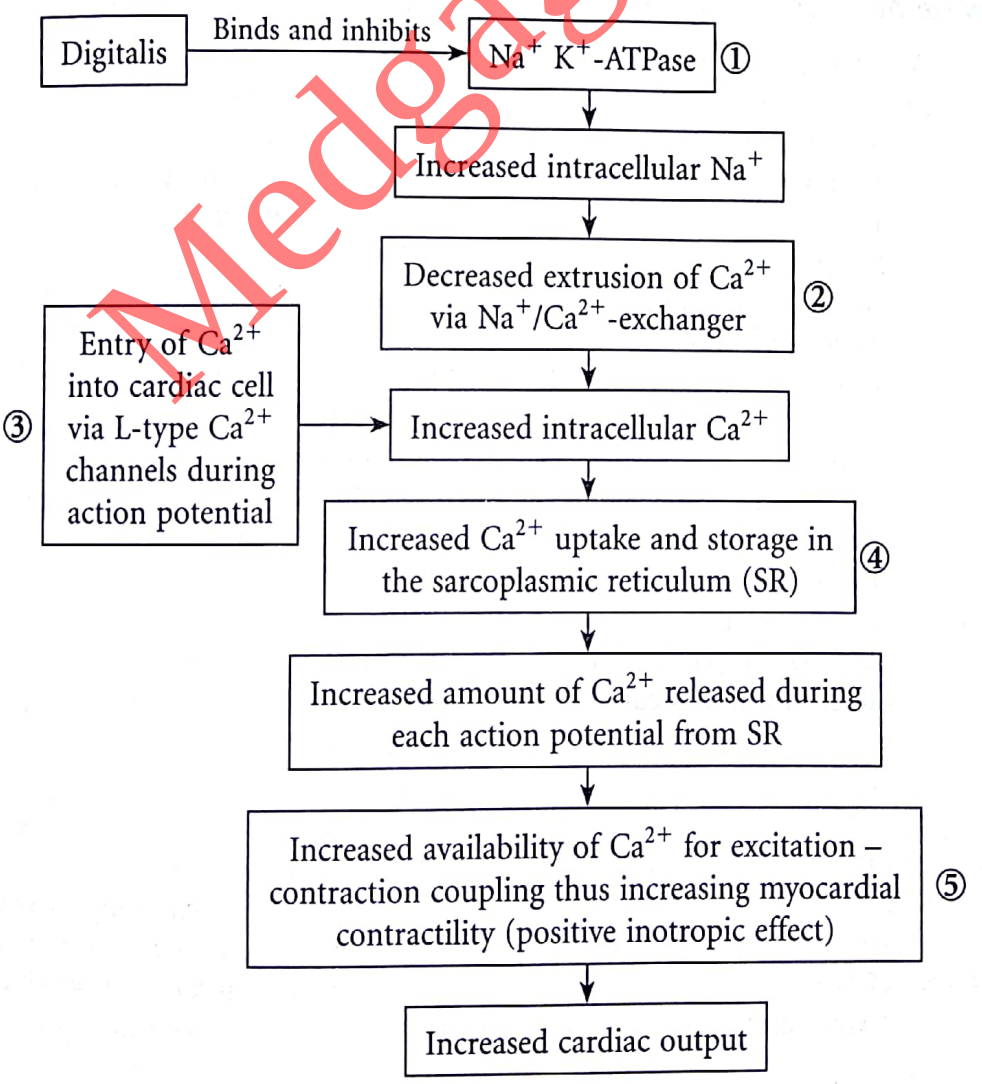
Sources

Source	Glycosides
Digitalis purpurea (leaf)	Digitoxin
Digitalis lanata (leaf)	Digoxin, digitoxin
Strophanthus gratus (seed)	Strophanthin-G (ouabain)

The utility of digitalis in the treatment of heart failure was shown by William Withering.

Mechanism of Action of Cardiac Glycosides (Digitalis; Fig. 3.12)

Na^+ K^+-ATPase is a membrane-bound enzyme which is called digitalis receptor. It is also called sodium pump.



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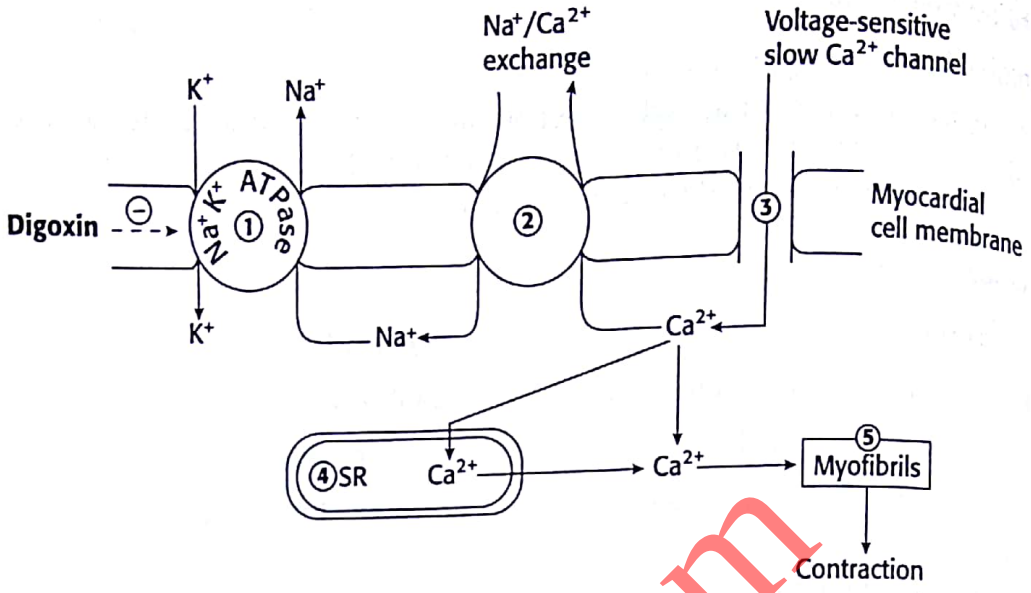

FIGURE 3.12 Mechanism of action of cardiac glycosides: SR, Sarcoplasmic reticulum.

Pharmacological Actions

1. Cardiac.
2. Extracardiac.

Cardiac Actions: Digitalis has direct and indirect actions on the heart.

- Direct action by inhibiting Na^+ K^+-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. Digitalised heart contracts more forcibly and completely. The positive inotropic effect causes complete emptying of the ventricles during systole and increases the cardiac output. 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, decreasing the oxygen requirement of myocardium. The digitalised heart, thus, can do more work for the same energy. Therefore, digitalis is called a 'cardiotonic'.
2. **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.
3. **Electrophysiological actions:** At therapeutic concentrations, digoxin decreases automaticity and increases resting membrane potential by vagal action in atria and AV node. It also prolongs effective refractory period (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.
4. ECG: Digitalis produces prolongation of P-R interval, inversion of T wave and depression of ST segment.

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Extracardiac Actions

1. **Gastrointestinal tract (GIT):** Digitalis can produce anorexia, nausea, vomiting and occasionally diarrhoea. Nausea and vomiting is due to stimulation of chemoreceptor trigger zone (CTZ) and a direct action on the gut.
2. **Kidney:** In patients with CCF, digitalis causes diuresis (increased urine output).
3. **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 the 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
   (a) 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 functions.
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.

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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 neutralises 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.

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 (Fig. 3.13):
   - Myocardium (positive inotropic effect): for explanation, see under pharmacological actions.
   - Venous system.
   - Kidney.
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

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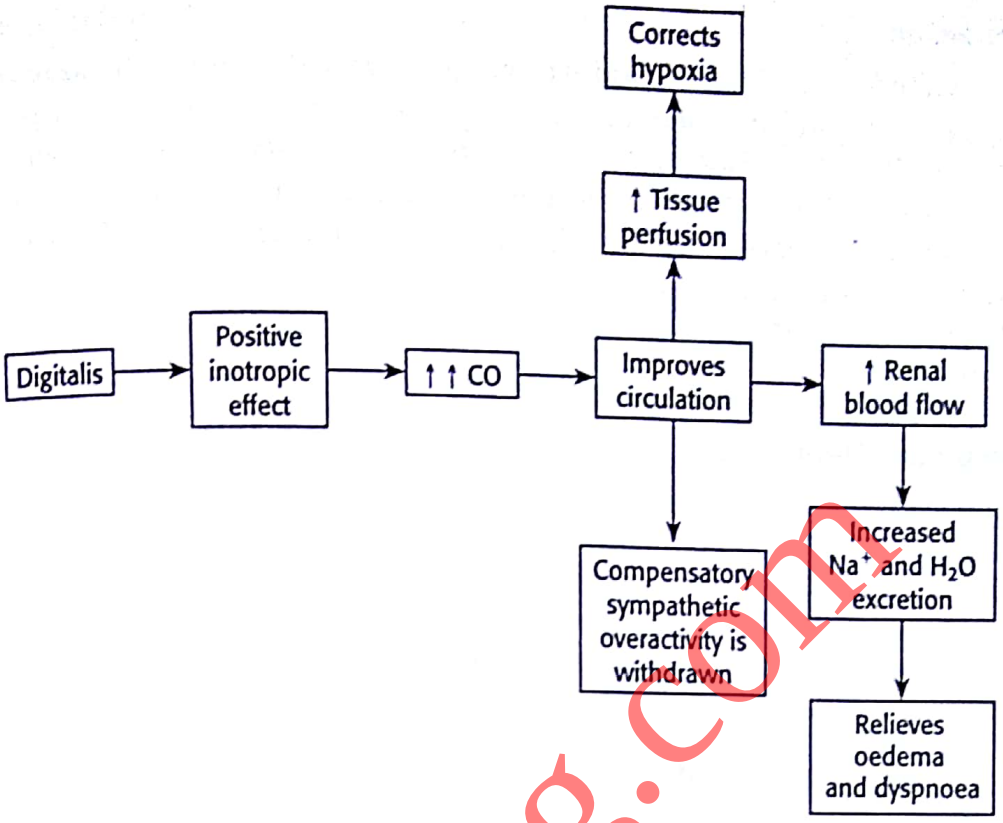

FIGURE 3.13 Beneficial effects of digitalis in CCF. CO, Cardiac output.

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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/min) 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 (2–5 mcg/kg/min), dopamine stimulates β_1-receptors of heart, increases myocardial contractility and cardiac output 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 (> 5 mcg/kg/min), it causes generalised 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 cardiac output. 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 → increased preload; potassium excretion can cause hypokalaemia → increased risk of arrhythmias. Aldosterone also causes ventricular remodeling and hypertrophy. Spironolactone/eplerenone block action of aldosterone on its receptor and block 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 cardiac output 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 hyponatremia.

Natriuretic Peptide

Nesiritide, recombinant form of brain natriuretic peptide (BNP), is useful in acute decompensated heart failure. Dyspnea is reduced. It is a vasodilator and is administered intravenously. Hypotension is a common adverse effect.

Management of congestive cardiac failure include Diet (salt restriction), Diuretics, Dilators (vasodilators), Digoxin, Dopamine, Dobutamine, β-blockers, PDE-3 inhibitors, etc. (Note the 'D's)

ANTIARRHYTHMIC DRUGS

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.

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Ionic Distribution

Normally

- K^+ is more in the intracellular fluid (ICF) than extracellular fluid (ECF).
- Na^+, Ca^{2+} and Cl^- are more in the extracellular fluid (ECF).

Cardiac Action Potential

Normally, an impulse is generated in the SA node. From SA node → atria → AV node (slowly) → bundle of His → 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 nodes, phase 0 is due to slow inflow of Ca^{2+} ions through activated Ca^{2+} channels (Fig. 3.15a). 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.

In atria and ventricles, the membrane potential is steady during diastole. The duration of atrial action potential is shorter than that of ventricles (Fig. 3.15b).

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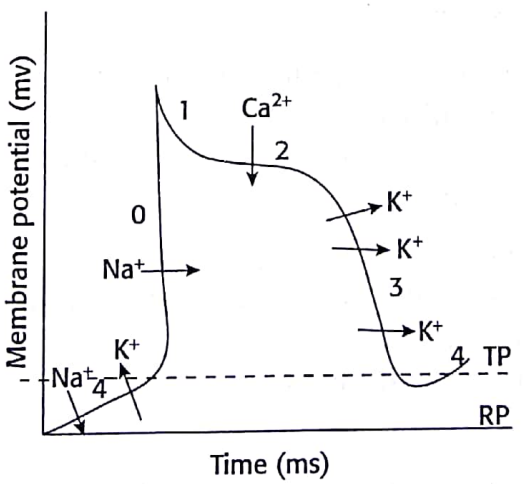

FIGURE 3.14 Cardiac action potential. TP, Threshold potential; RP, Resting potential; PHASE 0, Rapid depolarization; PHASE 1, Early fast repolarization; PHASE 2, Plateau phase; PHASE 3, Repolarization; PHASE 4, Spontaneous depolarization.

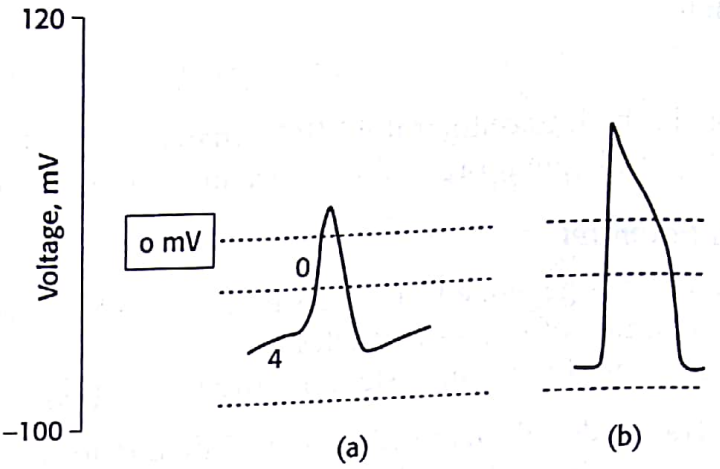

FIGURE 3.15 Cardiac action potential: (a) Nodal and (b) atrial.

Properties of a Cardiac Cell

- **Automaticity:** It is the ability of the cardiac cell to undergo spontaneous depolarization. Normally, the rate of spontaneous depolarisation is fastest in the SA node, hence, it is the pacemaker of the heart.
- **Excitability:** It is the ability of a cell to undergo depolarisation 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:** 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 depolarisation or re-entry of an impulse.

Various cardiac arrhythmias are atrial flutter, atrial fibrillation, paroxysmal supraventricular tachycardia (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 stabilising agents)**
  - IA: Drugs that moderately depress phase 0 depolarization – Quinidine, procainamide, disopyramide.

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- 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 (Calcium channel blockers): Verapamil, diltiazem.

Other antiarrhythmic agents are digoxin, adenosine, atropine, isoprenaline.

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 the Na^+ channels in the open state → decreases automaticity, excitability, rate of phase 0 depolarization and conduction velocity.
   - Blocks potassium channels → increases duration of action potential.
   - Prolongs effective refractory period 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 the 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 × β-blockers/verapamil/potassium salts:** Additive cardiac depressant effect may lead to cardiac arrest.

Therapeutic 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

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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 the 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 has more marked anticholinergic actions.

Pharmacokinetics. Disopyramide is well absorbed after oral administration. It is partly metabolized in the 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 include effects like 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

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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 the liver and has short plasma $t^{1}/_{2}$ 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 doses 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 also 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 congestive cardiac failure. Other adverse effects seen with propafenone are metallic taste, constipation, bradycardia and bronchospasm. Blurring of vision is common with flecainide.

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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. 104-107.

Esmolol

A cardioselective β_1-blocker has 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 effective refractory period (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 → increases duration of action potential → prolongs refractory period and suppresses abnormal automaticity (Fig. 3.16).
- Blocks sodium channels in the inactivated state → 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.

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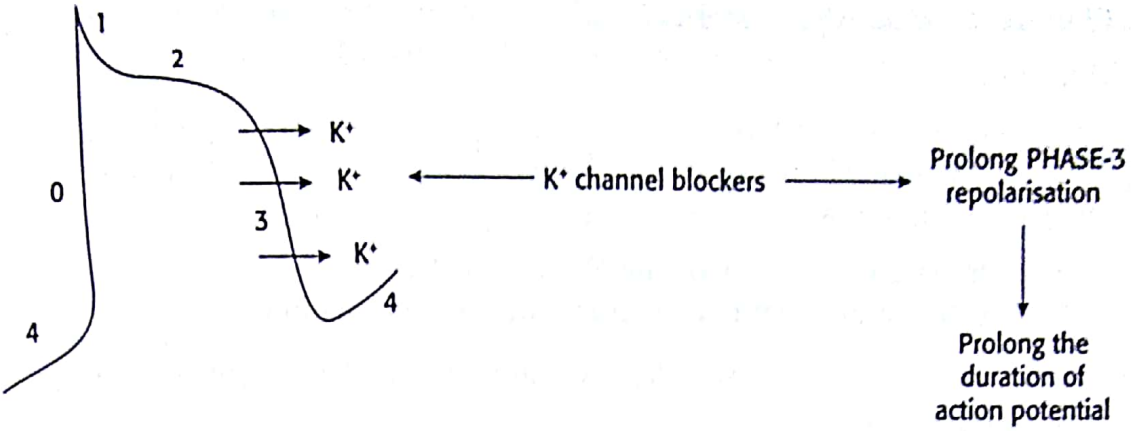

FIGURE 3.16 Mechanism of action of amiodarone.

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, T_3 and T_4 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 nodes 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 $t_{1/2}$, 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.

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Class IV: Calcium Channel Blockers

Verapamil

It blocks both activated and inactivated L-type Ca^{2+} channels – depresses calcium-mediated depolarization. Verapamil decreases conduction velocity and increases refractory period of AV node; useful in

- terminating reentry 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 in pp. 131-134.

Diltiazem

All features are similar to verapamil but 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 paroxysmal supraventricular tachycardia (PSVT). The duration of action of adenosine is less than one minute because it is rapidly transported into RBCs and endothelial cells.

Mechanism of Action

Intravenous adenosine

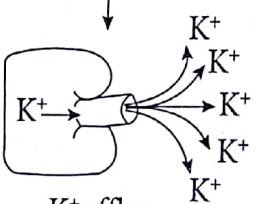
↓

Binds to specific G-protein-coupled adenosine (A_1)-receptors

↓

Activates ACh-sensitive K^+ channels in the atrium, SA and AV nodes

↓



K^+ efflux

↓

- 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 actions 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:

(1) has high efficacy.
(2) has a short duration of action – adverse effects last for brief period.
(3) has minimal negative inotropic action.

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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 myocardial infarction, digitalis toxicity, etc). It has vagolytic action.

Isoprenaline

Intravenous isoprenaline can be used in second degree or complete heart block following acute myocardial infarction.

Some of the important drugs used in different types of cardiac arrhythmias are listed in Table 3.7.

Table 3.7 Drugs used in cardiac arrhythmias

Type of arrhythmia	Drugs used
Paroxysmal supraventricular tachycardia (PSVT)	• Adenosine • Verapamil • Esmolol • Digoxin
Atrial fibrillation	• Esmolol • Verapamil • Amiodarone • Propafenone • Digoxin
Atrial flutter	• Esmolol • Verapamil • Amiodarone • Propafenone
Ventricular tachycardia	• Amiodarone • Lignocaine • Procainamide • Propranolol
Ventricular fibrillation	• Lignocaine • Amiodarone • Procainamide

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HYPOLIPIDAEMIC DRUGS

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. **Others:** Gugulipid, omega-3 fatty acids.

HMG–CoA Reductase Inhibitors (Statins; Fig. 3.17)

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 $t_{1/2}$)

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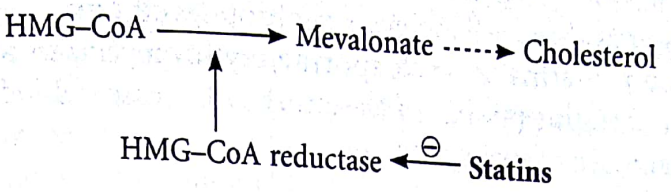
are usually given once daily in the evening because cholesterol biosynthesis occurs mainly at night. Atorvastatin and rosuvastatin have long $t_{1/2}$.



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 (Fig. 3.17). Pitavastatin is the most potent statin.

Other actions of statins – atherosclerotic plaque stability, antioxidant and antiinflammatory actions; decrease platelet aggregation; increase production of nitric oxide 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.

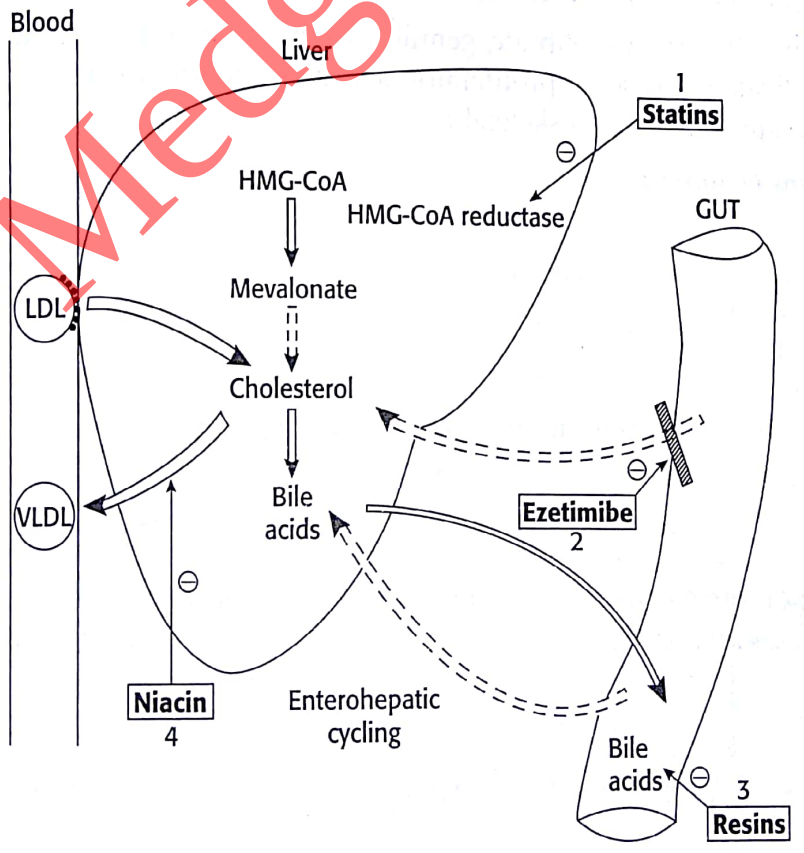


FIGURE 3.17 Site and mechanism of action of hypolipidaemic drugs. 1 = Statins: Inhibit HMG-CoA reductase. 2 = Ezetimibe: Inhibits cholesterol absorption in the gut. 3 = Resins: Interrupt enterohepatic cycling of bile acids. 4 = Niacin: Inhibits VLDL secretion, ⊖ : Inhibits.

*Mnemonic for adverse effects of statins-HMG.

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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; Fig. 3.17)

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 hypercholesterolaemias. Resins should be taken orally with water or fruit juice before meals. They are also useful to relieve itching of obstructive jaundice.

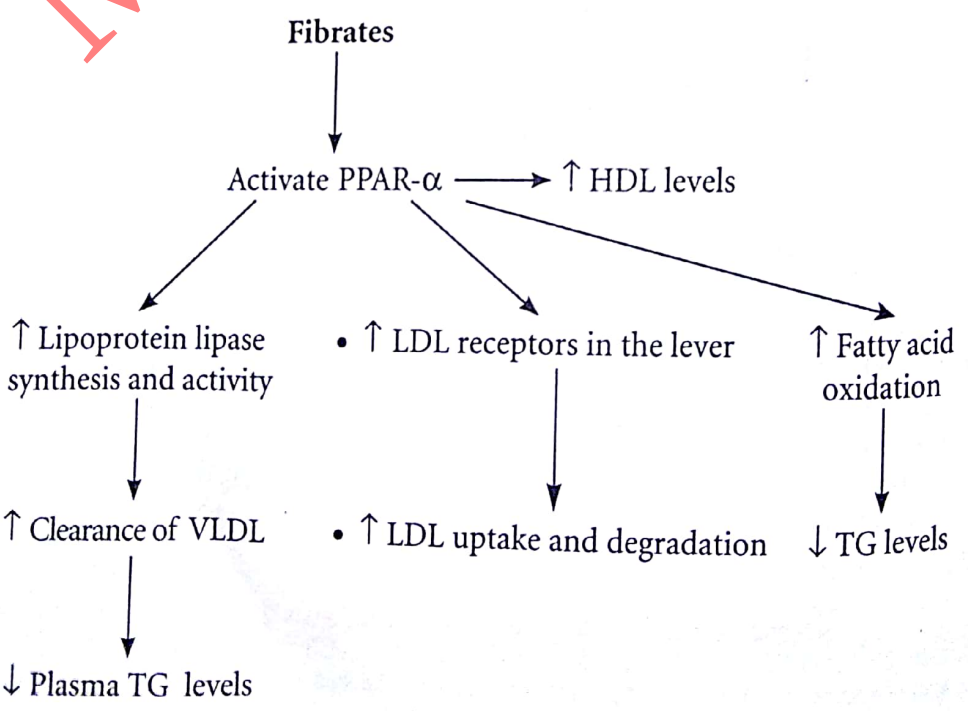
Adverse Effects Since resins are not absorbed through the gut, systemic adverse effects are not seen. The common adverse effects are unpalatability, bloating, nausea, flatulence and constipation. They also bind to other drugs (thiazides, digitalis, anticoagulants, propranolol, thyroxine, fat-soluble 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



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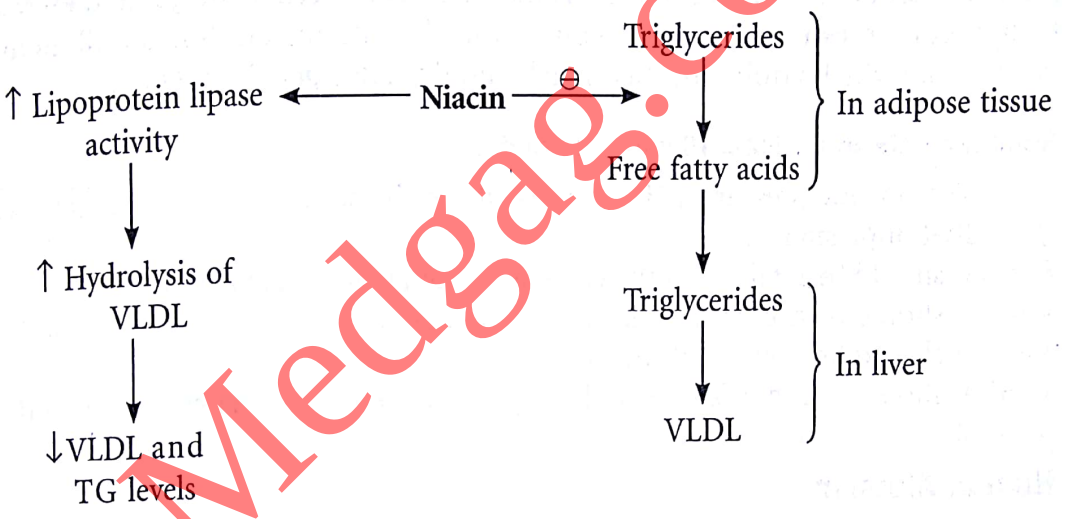
Fibrates also inhibits TG synthesis in liver. Fibrates are well absorbed after oral administration, widely distributed and concentrated in liver, kidney and intestine; metabolized in liver and excreted in urine.

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 gall stones 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/benzafibrate can be combined with statins.) Fibrates are contraindicated in pregnancy.

Nicotinic Acid (Niacin, Fig. 3.17)

Niacin is a B-complex vitamin. In larger doses, it has hypolipidaemic effect; it reduces plasma TGs, VLDL, LDL, and increases HDL levels. Lipoprotein (a) is decreased.



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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; Fig. 3.17)

It inhibits the absorption of dietary and biliary cholesterol in the intestine. It reduces LDL cholesterol (Fig. 3.17).

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.

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

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 non-pyrogenic and non-antigenic.
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 red blood corpuscles (RBCs) in small blood vessels. It also improves microcirculation.

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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 leukopheresis 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 hypersensitivity: 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, congestive heart failure, renal failure and hepatic failure.

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CHAPTER 4
Renal Pharmacology

Kidney is mainly a regulatory organ; it also has excretory function. The functional unit of the kidney is nephron. Each kidney contains about 1 million nephrons. The functions of kidney are:

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

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 the 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 Na^+–K^+–$2Cl^-$ cotransporter. This is selectively blocked by loop diuretics. Ca^{2+} and Mg^{2+} are also reabsorbed at this site. The tubular fluid becomes hypotonic.

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.

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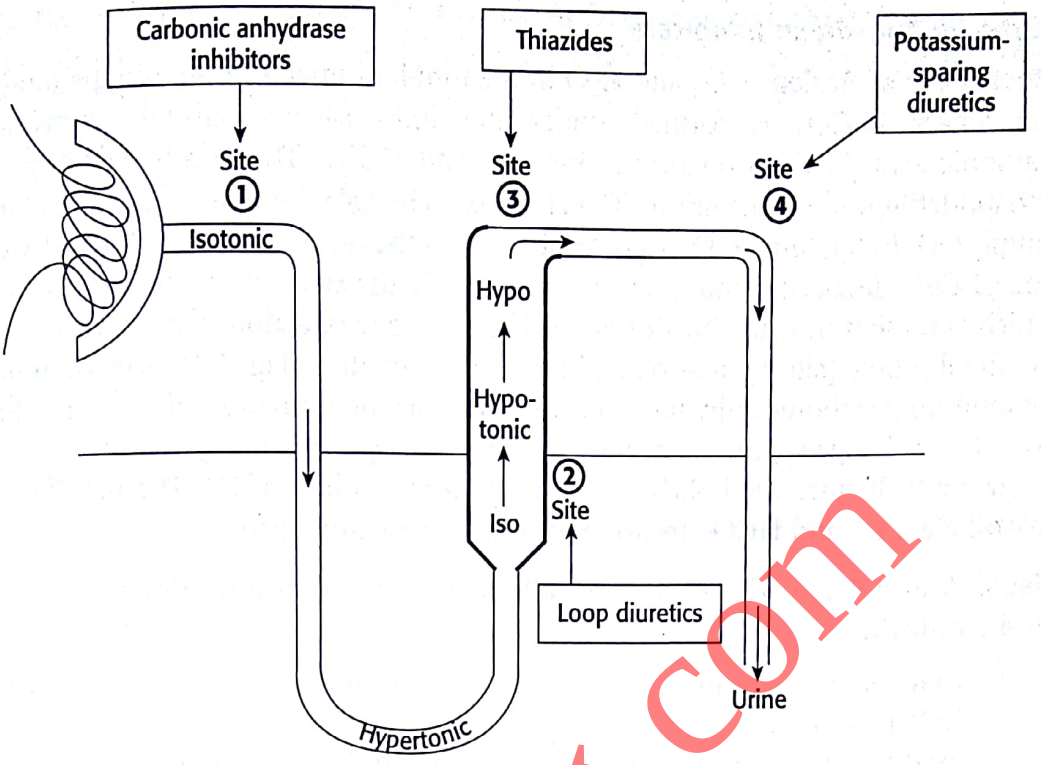

FIGURE 4.1 Nephron showing various sites of action of diuretics.

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 the 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

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 proximal convoluted tubule (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 collecting duct (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.

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Carbonic Anhydrase Inhibitors

Mechanism of Action. CO_2 and H_2O in the tubular lumen diffuse into the tubular cell where H_2CO_3 is formed under the influence of carbonic anhydrase. 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 collecting duct (Fig. 4.2). 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. 65).
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.
4. Miscellaneous: As an adjuvant in epilepsy; familial periodic paralysis – benefit results from lowering of pH.

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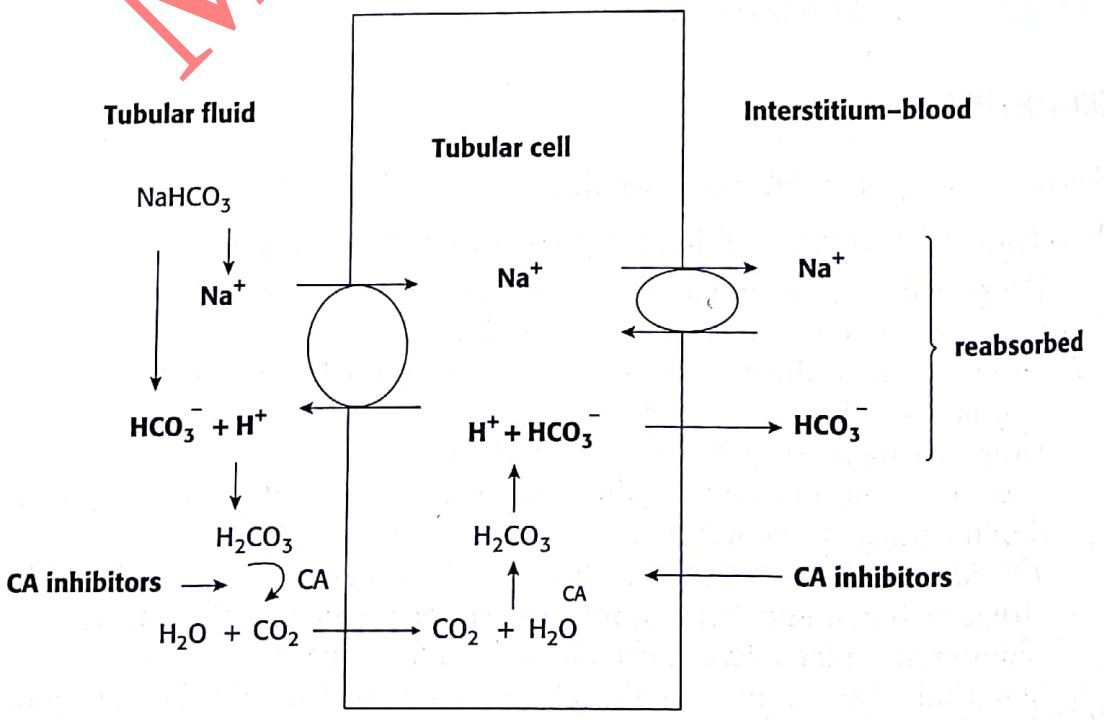


FIGURE 4.2 Mechanism of action of carbonic anhydrase (CA) inhibitors.

Adverse Effects. These include hypersensitivity reactions (skin rashes, fever, nephritis, etc.), drowsiness, paraesthesia, hypokalaemia, metabolic acidosis, headache and renal stones.

Contraindications

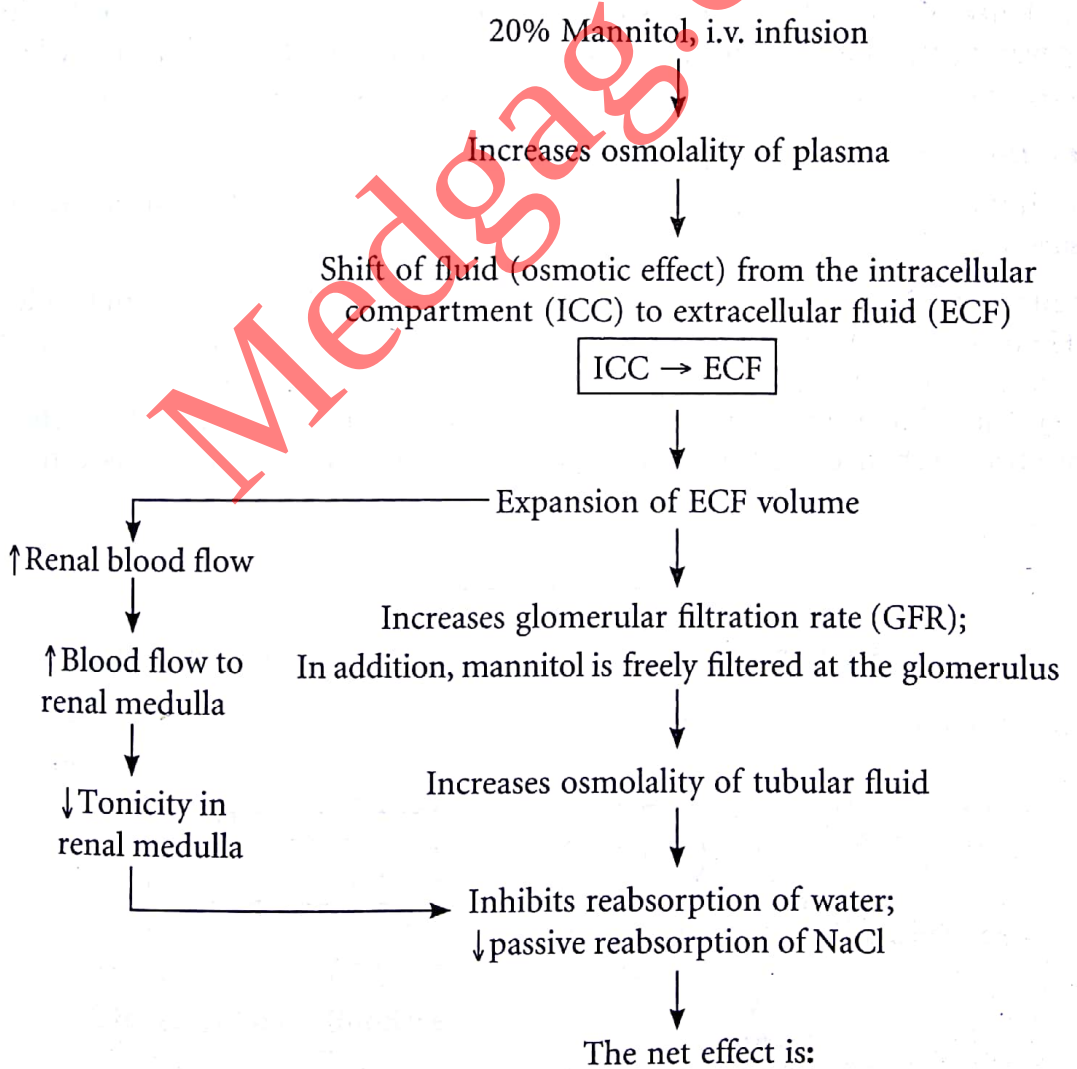
1. **Liver disease:** Hepatic coma may be precipitated in patients with cirrhosis due to decreased excretion of NH_3 in alkaline urine.
2. **Chronic obstructive pulmonary disease (COPD):** Worsening of metabolic acidosis is seen in patients with chronic obstructive pulmonary disease.

Osmotic Diuretics

These include mannitol, glycerol and isosorbide.

Mannitol. Mannitol is administered intravenously. It is neither metabolized in the body nor is significantly reabsorbed from the renal tubules. It is pharmacologically inert and is freely filtered at the glomerulus.

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-}

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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, torsemide and ethacrynic acid.

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 $Na^+-K^+-2Cl^-$ cotransporter and block its function. There is an increased excretion of Na^+ and Cl^- in urine. The tubular fluid reaching the DCT contains large amount of Na^+. Hence, more Na^+ exchanges with K^+ leading to K^+ loss. Furosemide has weak carbonic

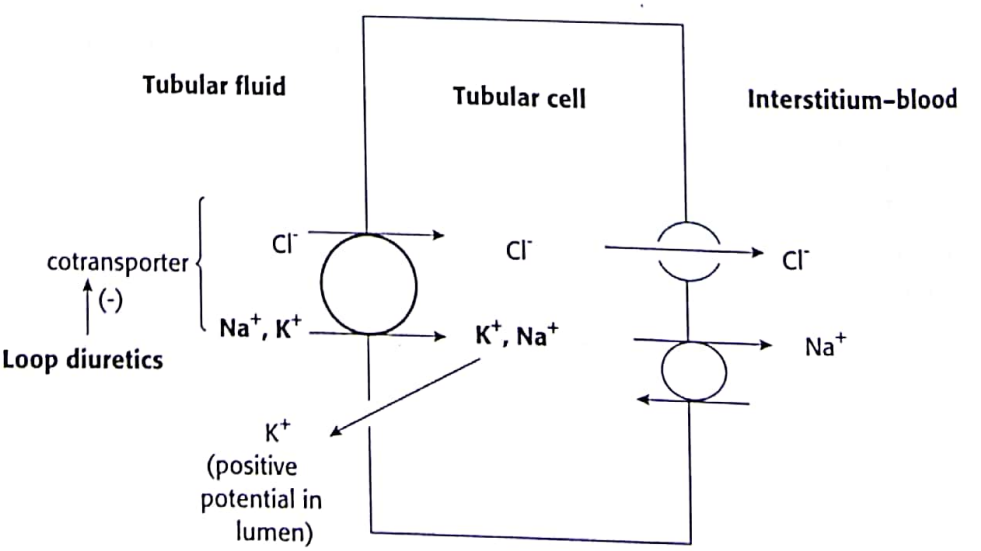

FIGURE 4.3 $Na^+-K^+-2Cl^-$ cotransport system in thick ascending limb and the mechanism of action of loop diuretics.

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anhydrase-inhibiting activity, hence, increases the excretion of HCO_3^-. Loop diuretics also increase the excretion of Ca^{2+} and Mg^{2+}.

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.

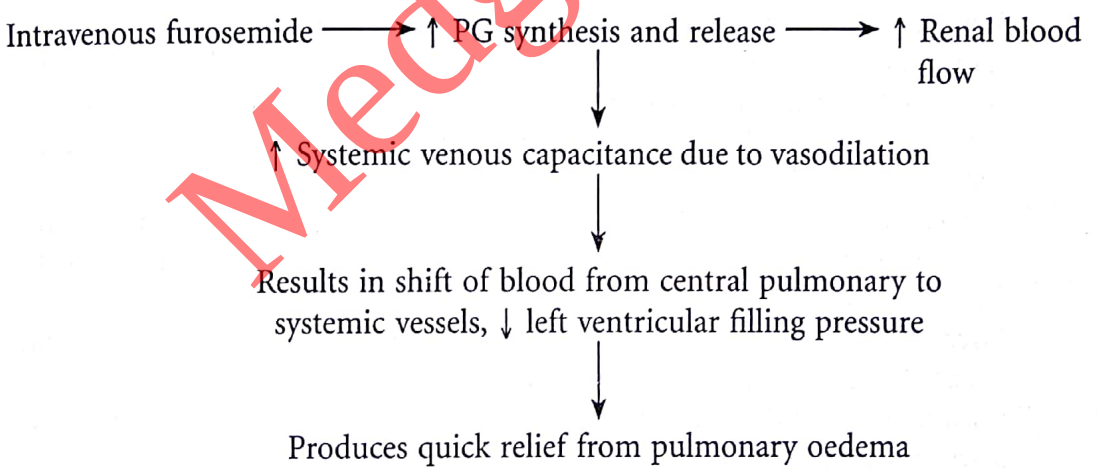
The loop diuretics are rapidly absorbed through the gastrointestinal tract. Furosemide and bumetanide are administered by oral, i.v. and i.m. routes. Torsemide is given orally and intramuscularly. Furosemide has a rapid onset of action within 2–5 min of i.v.; 10–20 min after i.m. and 30–40 min after 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 $t_{1/2}$ 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:
   (a) *Hypokalaemia:* It is the most important adverse effect. It can cause fatigue, muscular weakness and cardiac arrhythmias. Hypokalaemia

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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. Hypomagnesemia can predispose to 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, aminoglycosides, etc.
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 antiinflammatory drugs:** Nonsteroidal antiinflammatory drugs (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 the plasma potassium levels and also improves diuretic response—synergistic effect.

Thiazides (Benzothiadiazides) and Thiazide-Like 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. There is increased delivery of Na^+ to the 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 (Fig. 4.4).

Pharmacokinetics. Thiazides are administered orally. They have long duration of action and are excreted in urine.

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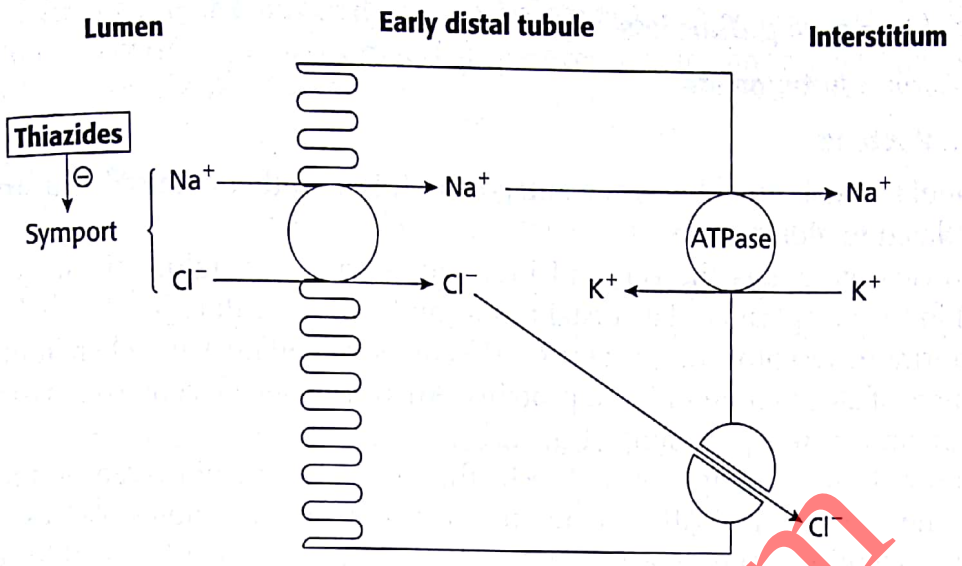

FIGURE 4.4 NaCl reabsorption in early distal tubule and mechanism of action of thiazides. (Adapted from *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12e.)

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Uses

1. **Hypertension:** Thiazides are used in the treatment of essential hypertension (see p. 116).
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 GFR (glomerular filtration rate) is low.
3. **Hypercalciuria:** Thiazides are used in calcium nephrolithiasis as they reduce the urinary excretion of calcium.
4. **Diabetes insipidus** (see p. 174).

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, diarrhoea, etc. can occur. Diuretics should be avoided in pregnancy as they reduce placental perfusion by decreasing blood volume which can cause fetal death.

Thiazide-Like Diuretics

Chlorthalidone is a frequently used thiazide-like 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.

Potassium-Sparing Diuretics

Aldosterone Antagonists

Spironolactone

Spironolactone 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 collecting duct (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).

Spironolactone competitively blocks the mineralocorticoid receptor and prevents the formation of AIPs. Therefore, spironolactone promotes Na^+ excretion and K^+ retention. Spironolactone 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 (congestive cardiac failure, hepatic cirrhosis and nephrotic syndrome).
2. Congestive cardiac failure: 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.

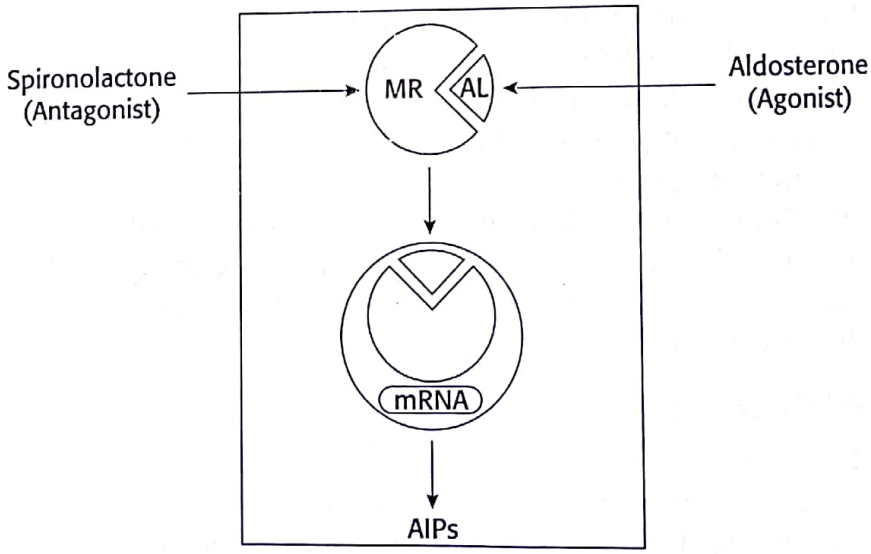

FIGURE 4.5 The mechanism of action of spironolactone. MR, Mineralocorticoid receptor; AL, Aldosterone; AIP, Aldosterone-induced proteins.

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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 × Spironolactone:** Dangerous hyperkalaemia can occur.

Eplerenone, an **aldosterone antagonist**, is more selective for mineralocorticoid receptor. 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 the Na^+ channels in the luminal membrane of the cells of the late DCT and CD. The net effect of these drugs is to increase Na^+ excretion and retain potassium, hence these are called K^+-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 the diuretic and antihypertensive 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 diabetes insipidus. It blocks lithium transport through Na^+ channels in the cells of the collecting duct.
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.

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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

Continued

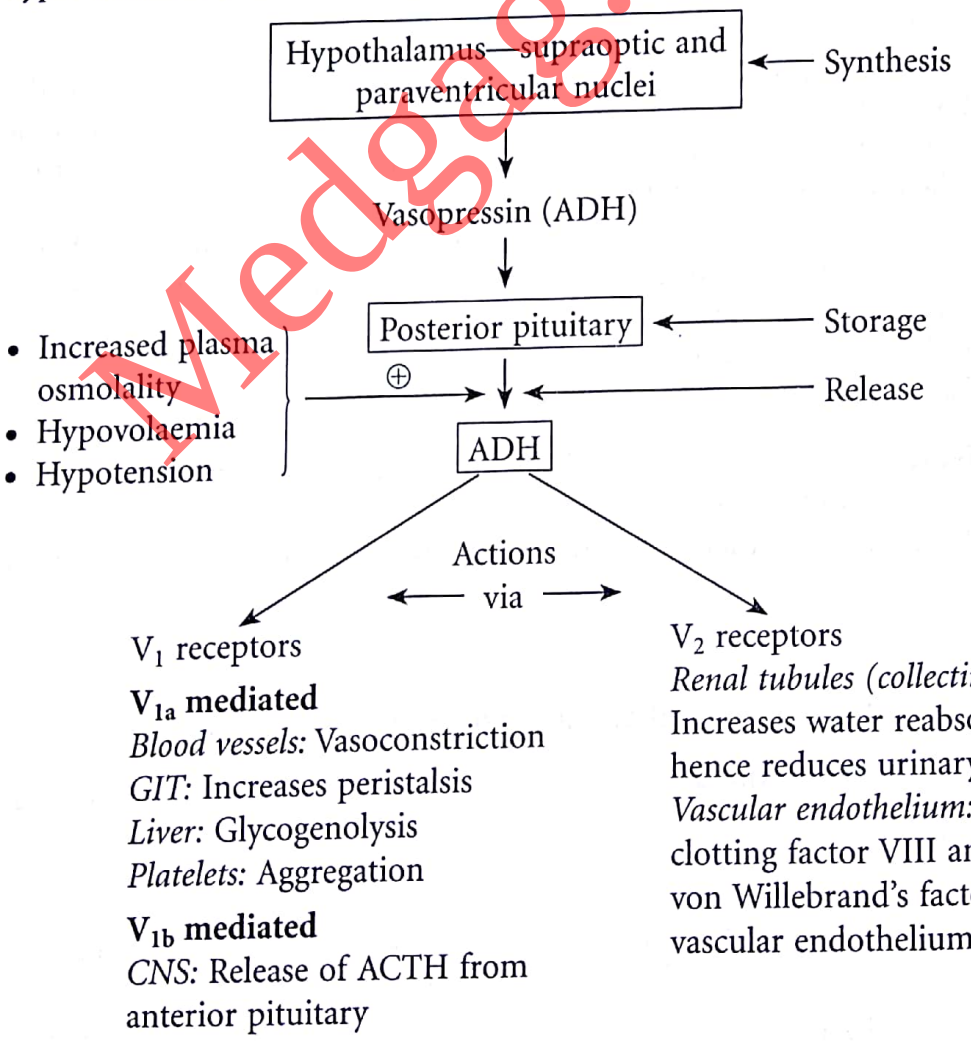
Table 4.1 Diuretics with their site and mechanism of action—cont'd

Diuretics	Site of action	Mechanism of action	Efficacy
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

ANTIDIURETICS

Vasopressin

Vasopressin (AVP or arginine vasopressin; antidiuretic hormone or ADH) is a peptide hormone synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and stored in posterior pituitary.



Uterus: Contraction of the smooth muscle by vasopressin is mediated through *oxytocin* receptors.

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Both V_1 and V_2 are G-protein-coupled Receptors

Synthetic AVP (arginine vasopressin) 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).

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

Vasopressin analogues

Desmopressin: It is a selective V_2 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.

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. **Due to V_1 receptor-mediated actions**
   (a) For emergency control of bleeding oesophageal varices: Terlipressin is preferred over vasopressin because it is safer. It constricts mesenteric blood vessels → decreases blood flow to portal vessels → reduces pressure in the varices → stops bleeding.
   (b) Vasopressin may be used before abdominal radiography to expel intestinal gas.
2. **Due to V_2 receptor-mediated actions**
   (a) Central (neurogenic) diabetes insipidus—desmopressin is the drug of choice (see Table 4.3). It is not effective in nephrogenic diabetes insipidus.
   (b) Haemophilia and von Willebrand's disease—Desmopressin, administered intravenously, controls bleeding by promoting release of factor VIII and von Willebrand's factor.
   (c) Primary nocturnal enuresis—Administration of desmopressin at bedtime reduces nocturnal urine volume.

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Diabetes insipidus (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).

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 *Desmopressin* has more selective action on V_2 receptors, hence preferred in central DI. Its action on V_2 receptors in the cells of the collecting duct results in a decrease in urine volume Other drugs (if patient does not tolerate desmopressin) *Chlorpropamide* (oral antidiabetic): Increases antidiuretic effect of ADH on kidney *Carbamazepine* (antiepileptic): Decreases urine volume in high doses *Thiazides* are also useful in central DI as they decrease urine volume	• ADH levels are normal, but renal tubules (CD) fail to respond to ADH • Drugs: *Thiazides:* 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 *Amiloride* is the preferred drug for lithium-induced nephrogenic DI *Indomethacin* reduces urine volume in nephrogenic DI by inhibiting renal prostaglandin synthesis

Adverse Effects of Vasopressin Analogs

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 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.

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Treatment

1. Restricted water intake.
2. Drugs
   Demeclocycline is useful in the treatment of SIADH. It inhibits the action of ADH in the collecting duct.
   Vasopressin receptor antagonists like conivaptan (V_{1a}/V_2) and tolvaptan (V_2 selective) are useful in the treatment of SIADH. They are non-peptides which are administered intravenously and orally, respectively.

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Inhibitory
neurotransmission

Table 5.1

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Pharmacological Ac

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Table 5.2 Impor

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BZD inverse ag

FIGUR

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Table 5.4

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Table 5.5 C
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Ketamine

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Respiratory depres
CNS: Convulsions
GIT: Nausea, vom

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Mechanism of Act

Sodium channels e
inactivated state). T
ing state before the

The LAs in 'unio
Within the axoplasm
Na^+ channels

through th
fore, LAs a
- Diameter
fibres.
- Myelinated
same diam
- Sensory fib
firing rate a
- Fibres in th

Pharmacological A

1. Nervous sys
   (a) *Peripher*
   fibres. S
   touch, p
   (b) *CNS*: M
   they cau
   cause ex
   doses ca
2. Cardiovasc

c, e.g. lignocaine

ne reuptake of NA in both
nd peripheral nerves
achycardia, rise in BP,
and euphoria
ed

---

ely used local anaes-
so used in ventricular

Lignocaine

It is a prototype a
for topical applic
It is also available
neuralgias.

Tetracaine

An ester type of L
spinal anaesthesia
surface anaesthetic

Benoxinate

It is a surface anaest

Benzocaine and Bu

Surface anaesthetics
lozenges; used for h

Oxethazaine

It is a topical anaest

burns, fissures, et
benzocaine 1–2%
available as soluti

Addition of ad
because of poor p
procedures like to

EMLA is used
subcutaneous tiss

Infiltration Anae

Uses: Spinal anaes
umbilicus, i.e. lowe
tectomy, surgery on
Advantages of Spin
ation and good an
tolerate spinal anae

Complications

1. Headache is d
2. Hypotension

- Diuresis due to inhibition of ADH release

- Fatty degener
- Alcoholic hep and cirrhosis

Treatment of alcohol

- Benzodiazep
  anxiety, trem
  associated w
- Psychologica

Treatment of Chro

- *Psychotherap*
- *Drug treatme*

of toxic m
unchanged

Met

Forma

Partial Seizures

1. Simple partia
cortex involve
aesthesia (sen
2. Complex pa
epilepsy): It
automatism

Chemical Classifica

Mechanism of Ac

- Phenyt
- Fosphe
- Carbam
- Oxcarb
- Sodium
- Lamotri
- Topiram

Voltage dep
Na^+ channe

– Resting st

– Activated

– Inactivate

4. Hyperglyca
5. Megalobla
6. Osteomala
7. Hypocalca
8. Fetal Hyda
   due to use

At high concentr

1. CNS: Vest

2. Carbamazepine is
gias. It inhibits hi
nytoin, gabapenti
Other treatmer
alcohol or pheno
for diabetic neuro
3. It is used in the tr

Oxcarbazepine (Iminos

Oxcarbazepine is an a

3. Increases the
   (a) Increase
   boxylase
   (b) Decreas
   transam

Pharmacokinetics
the GI tract, highly
and excreted in uri

Adverse Effects (

NEWER ANTIEP

These are lamotrigin
lin, tiagabine, vigaba
tant features are give

Table 5.10

Table 5.10

Drugs
Gabapentin

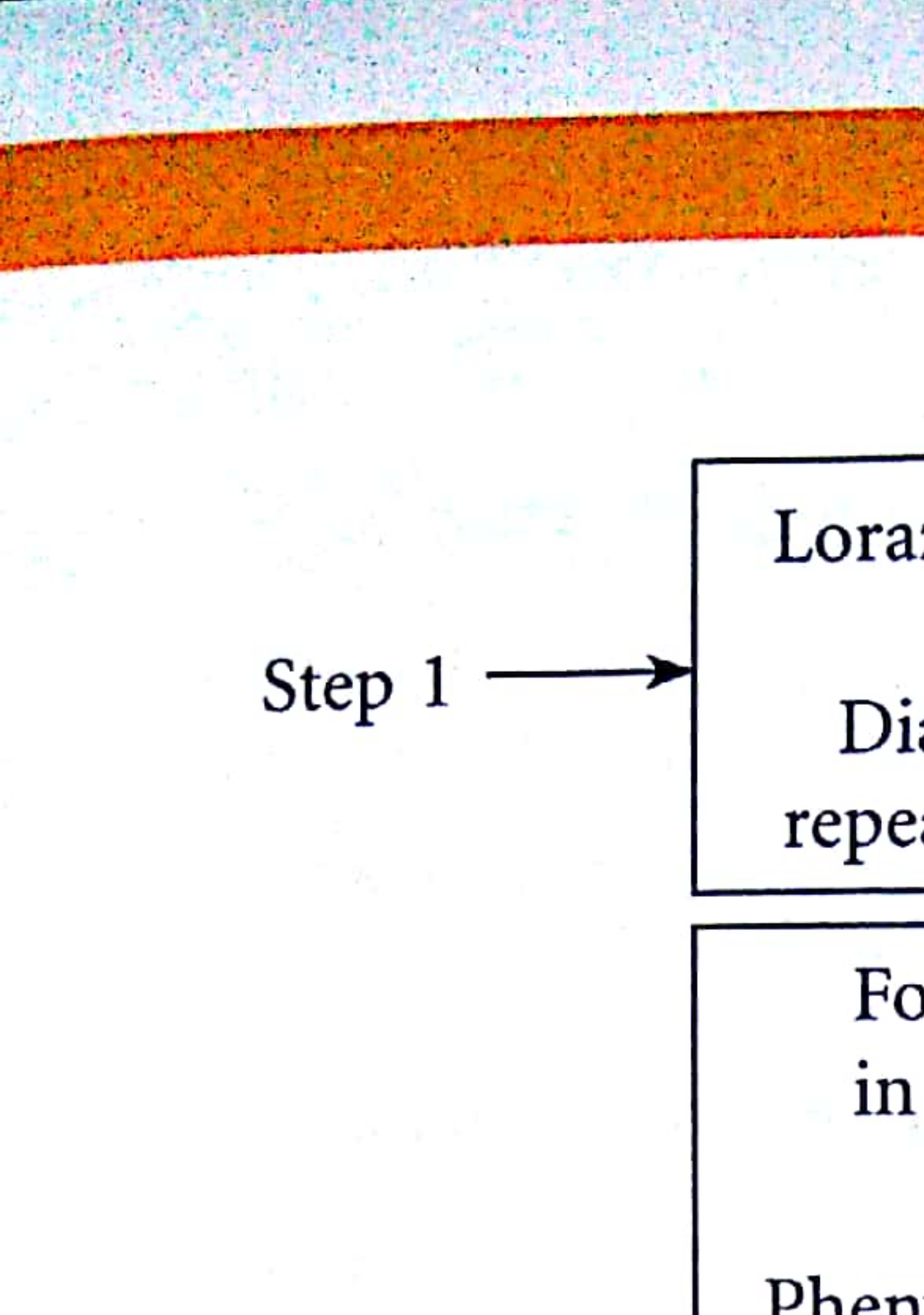

Step 1
Lora
Di
repe
Fo
in
Phen

Table 5.11

Drug
Carbamazepine

OPIOID ANALGE

Morphine is the m
tained from the ca
other alkaloids, e.g
refers to drugs deriv
to any substance (
phine-like analgesia

Classification of Op

ne
pa
lat
cit
ho
pr
m
ve
ge
ne

(b) **The stim**

(i) Mio
stim
to t
mor
mor

(ii) Nau
the
opic

3. Hypotensio
4. Drowsiness
5. Itching (du
6. Difficulty i
7. Respiratory
   the mother
8. Drug tolera
   ance develo
9. Drug depe

Naloxone is a pure a
reverses the respirato
is short, hence repea

Mo
(A

Pholcodine: see

Pethidine (Meper

Pethidine can be
sorbed from the
effect; widely dis
lized in liver. The

Adverse Effects.

phine. It can cau
sions due to its

If pain persists

If pain is

Start

Adjuvants – a

Table 5.13

Opioid
Codeine (po) metabolised to morphine

Table 5.13 Imp

Opioid
Buprenorphine (im, iv, sublingual) • Thebaine congener • Slow onset • Longer acting

Fentanyl

It is a synthetic
than morphine a

Pharmacologi
remifentanil are
dures where inte

Methadone

It is a synthetic o

Buprenorphine

It is a partial μ-recep
potent than morphi
similar to morphine
It can be administer

Nalmefene

- It is adminis
- It is longer a
- Useful in th

Endogenous Opio

Endorphins, enke
present in the bra
ates because they

Dopamine Precurs

Levodopa (L-Dopa)
Dopamine does not
used. It is converted
rons of the striatum.
ganglia to produce a
is almost complete.
parkinsonism impro
amount of the drug

Brain L

The advantages o

1. Increased bi
   Hence, the d
2. Prolongation
3. Reduction in
4. Cardiovascul
   arrhythmias
5. Better patien

inhibits COMT only
to levodopa-carbido
vodopa + carbidop
Adverse Effects. Th
and hallucinations. T
avoided in patients v

MAO-B Inhibitors:

They selectively and i
administered orally T

2. **Levodopa ×** sion of levod levodopa.
3. **Levodopa × a**
4. **Levodopa × r** the D_2 recepto ism (i.e. inter done poorly c effect of levod

Table 5.14 C

Piracetam	Ora
Citicoline	Ora

Table 5.15 CN

Drug	Route admini
Amphet-amine Dextroam-phetamine	Oral

ANTIPSYCHOTI

Antipsychotic drug
drugs. Neuroleptic
acute psychotic stat

Classification

1. **Phenothiazi**
   ridazine, flup
2. **Thioxanthen**
3. **Butyrophen**

(c) Suppresses
(d) Relieves an
(e) Corrects di
(f) Does not a

- Endocrine: Pro
factor (PRF) ar
hence the bloc
duction of pro
in females; gyn
- Other actions

6. Preferred ag
Huntington

Atypical Antipsyc

These drugs exert a
D_2 blocking effects

Clozapine and Olan

1. Atypical antip
2. Mainly block
3. Have weak D
4. Also block α_1
5. Cause sedatio
6. Rarely cause

Adverse Effects (Ta
seizures, weight gai

ANTIANXIETY A

1. **Benzodiazep**

Chlordiazepo
pam, flurazep
tem and fac
mainly usefu
most commo
ment of men
lytic effect o

3. Serotonin a
venlafaxine.
4. Atypical anti
atomoxetine.
5. MAO-A inhil

Tricyclic Antidepre

Pharmacokinetics

bound to plasma p

2. α_1-adrenerg
   arrhythmias
3. H_1-blocking
4. Other effect
   sions (seizu

Tricyclic antidep
ischaemic heart di
Other antidepr

Table 5.18 C

Drug
4. Atypical anti-depressants • Bupropion

Drug Interactions

(a) Involving TC

- Hypertensive crisis
- Hyperpyrexia
- Convulsions

MAO inh

Inhibition of

Drugs used in bi
olanzapine, risperic

Lithium

Lithium was the firs
such as carbamazep
the treatment of M

Actions and Mech

2. **CNS:** Tremor, ata
   speech.
3. **Renal:** Polyuria, p
4. **Goitre** with hypo
5. **Acute lithium tox**
   mias, coma and d

Treatment

1. Lithium shou
   estimated.

mania. Co
are also us
- Lamotrigin
prophylaxi
lithium.
- **Benzodiaze**
patient is a

- AG:AB reaction
- Food (crab, fish)
- Bile salts
- Drugs: Morphine
  dextran, hydrala

3. They have anti
constipation, u

Pharmacokinetics. H
administration. They
extensively in liver an

Adverse Effects

1. The common a

7. Cinnarizine
vertigo in M
minic and a
8. **Sedative an**
hydramine)
surgical pro

Second-generat

Cetirizine, levocet

Cetirizine is one o
addition to H_1-blocki
minimal/or no drows
arrhythmias is rare wi

Uses. Second-generati
dermatitis, conjunctivit
or hay fever, fexofenadi
tine is used as nasal sp

Table 6.2

Receptor	Loca
5-HT_1	CNS, cranial vesse

Table 6.3 Ergo

Drug	Action recept
Ergotamine (natural alkaloid)	Partial antago 5-HT_1 and 5- recept

Antiemetics (Ora

They are used t
They also impro
e.g. metoclopram
hydramine, etc.

Ergot Preparation

Ergotamine: Oral

Adverse Effects and

sia, tightness in the c
the site of injection
vasospasm. Triptans a
heart disease, periph
factor for coronary a
be coadministered; n
ergot derivative.

analogue) is us
drug (NSAID)-i
2. **Cardiovascular**
constricts pulm
(a) PGE_1 (alpro
before surge
(b) Prostacyclin
sistance. PG
Other PGI_2 a
3. **Platelets:** PGI_2

(c) Cervical
make the
(d) Postpartu
of uterin
control p

6. **Male reprod**
erectile dysfu

Therapeutic Uses

1. **Abortion:** Pr
of the cervix,

Mechanism of Action. prostaglandins (PGs). COX-2. COX-1 is cons and kidney. PGs have i COX-2 is induced duri sible for the productio

Aspirin and most hibit both COX-1 an synthesis. The anti-in

Aspirin
(2–3 g/day)

7. **CVS:** Prolonged u
retention. They m
They may also dec
8. **Urate excretion:**
into the renal tub
salicylates inhibit
produce uricosuri

Pharmacokinetics. Sali
are highly bound to pla

5. **Reye's syndr**
hepatic dam
Hence, salicy
6. **Pregnancy:**
and increase
tion of PG s
7. **Analgesic n**
chronic use
stoppage of

Clinical Uses of NSA
Pharmacological Act

1. **As analgesic:**
   bodyache, mus
2. **As antipyretic:**
   is preferred bec
   (a) Gastrointes
   (b) It does not
3. **Osteoarthritis:**

Table 6.5

Drug
1. Ibuprofen

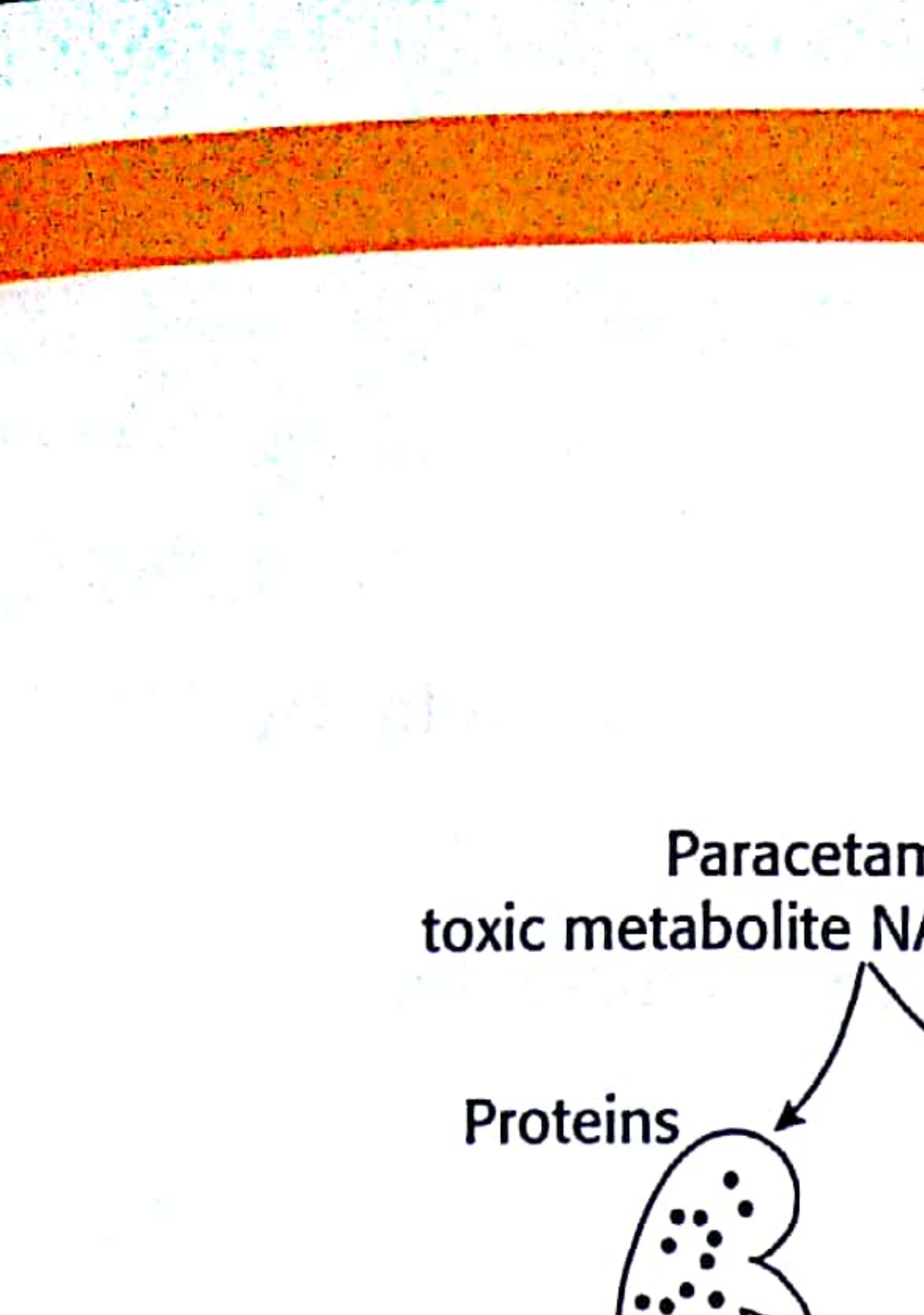
Table 6.5 Nor fea

Drug	Re fo wi
6. Mefenamic acid	Or De Th

Table 6.6

Nonselective CO

Analgesic effect
Antipyretic effect
Anti-inflammatory
Antiplatelet effect
GI side effects ar


Paracetam
toxic metabolite NA
Proteins

Classification

1. Acute gout
   (a) NSAIDs
   etoricox
   (b) Colchic
   (c) Glucoc
2. Long-term
   (a) Uricosu
   (b) Uric ac

- **Allopurinol**
- **Febuxostat**

Uric Acid Synthes

Allopurinol. Allopu
zyme xanthine oxi
alloxanthine, is a n
urate crystals in the
of xanthine and hy

Allopurinol is a
gout. It is used in
chemotherapy, rad

DRUGS USED IN T

Rheumatoid arthritis i
cause. Although there a
istic feature is persisten
course of the disease i
swelling of the joints ar
progressive damage to

Drugs used in the tr

Methotrexate

It is the preferred DM
more rapid onset of
methotrexate used i
cancer chemotherap
neutrophils and dec
T-cells. Methotrexate
once weekly and inc
can also be used in

Leflunomide

Its active metabolite inh
synthesis. It inhibits T c
with methotrexate for t
trexate. It is completely
about 2–3 weeks. Henc
(diarrhoea), loss of hai
is contraindicated in ch

Gold Compounds

Prolonged use n
infection and urina

Glucocorticoids

These are adjuvant
suppress inflamma
cal (intraarticular)
manifestations or

4. **Dextromethorpl**
analgesic proper
function in respi
hallucinations.
5. **Antihistamines:**
are useful in co
actions. They pro
allergic conditio
6. **Prenoxdiazine:**

DRUGS USED

In bronchial asthr
chial smooth mus
oedema) and incr
hyperresponsivene

Several factors
They include aller
in asthma is main

Table 6.9 Se

Salbutamol and ter

Selective β_2*-agonists*

tion, they have a rap
(within 1–5 minutes)
duration of action. T
ferred for acute attac

Route and dose: Inh

Pharmacokinetics.
administration; foo
distributed all over
metabolized in the

1. **Theophyllin**
   is available f
2. **Aminophylli**
   tered orally c
3. **Etophylline:**

Methylxanthines po

(a) Bronchodila

(b) Cardiac stim

2. **Phenytoin/rifam** inducers, hence crease its effect.

3. **Cimetidine/cipr** inhibitors; hence its metabolism.

Mast Cell Stabiliz

Sodium cromogly
chodilators. They
PAF, etc. by stabili
chial hyperreactivi
of action is slow.

Sodium cromogly

In bronchial asthr

Glucocorticoids

1. **Systemic:** Hydro
2. **Inhalational:** Be

Glucocorticoids ind
A_2 and thereby preven
SRS-A, etc. Glucocortic
pressant effects. They:

1. Suppress inflam

Treatment of Acut

1. Humidified
2. Nebulized β
   anticholiner
3. Systemic glu
   by i.v. hydr
   depending c
4. Intravenous
5. Potassium

Cerebellum

Table 7.1 Antiem

Drugs	Use
1. Anticholinergics (Scopolamine)	Mot
2. Antihistamines	Mot ness indu

5. Neuroleptics
6. Neurokinin
7. Cannabinoi
8. Adjuvant an
   (a) *Glucocor*
   (b) *Benzodia*

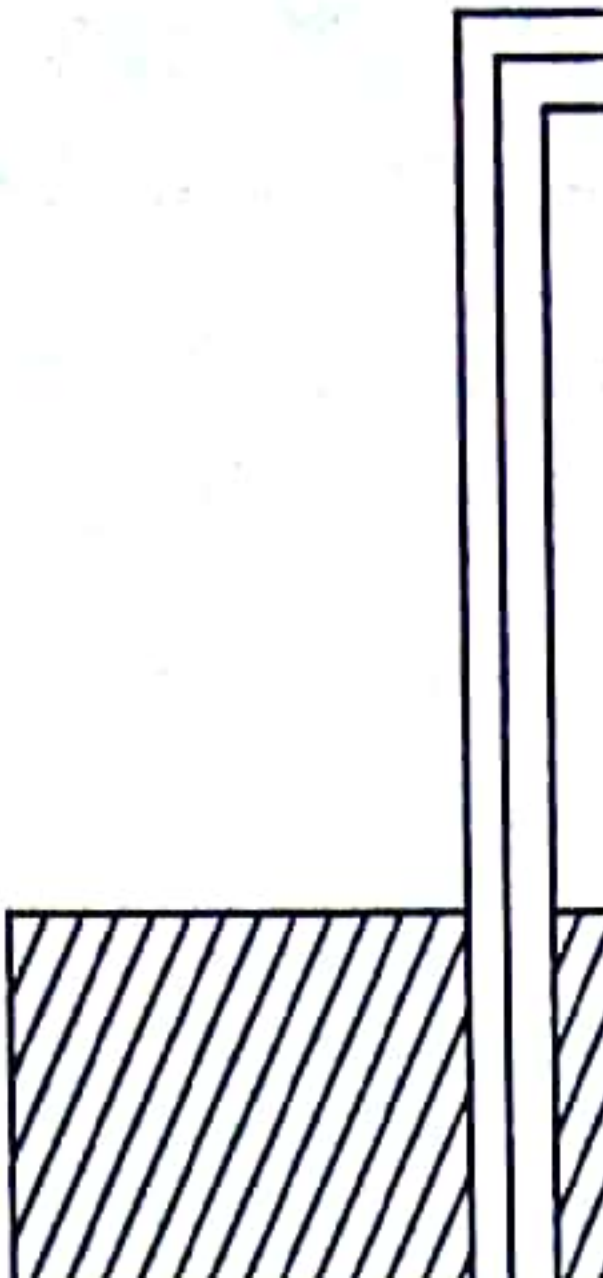
Anticholinergics

Scopolamine (hyos

Pharmacokinetics. 5-HT
The metabolites are excret
intravenous administratio
larly. Granisetron is more
patch of granisetron is av
vomiting. Palonosetron h
5-HT_3 antagonists.

Uses

1. 5-HT_3 antagonists



half an hour after oral
a short half-life of 4 ho
barrier. The drug is par

Uses

1. As an antiemetic:
   (a) Disease-assc
   (b) Drug-induce
   (c) Postoperativ
   (d) Cancer chem

that of domperidon
is low because of
metabolites are exc
children, as it rarely
or bromocriptine w
crosses BBB. Henc
induced by these dr
dryness of mouth, d
irregularities.

antiemetics. It is effectiv
central sympathomimet
hallucinations, disorien
antiemetic.

Adjuvant Antiemetics

Glucocorticoids. Gluco
methylprednisolone are
used in combination w
of anticancer drug-indu

and glucose is low
of water from the s
the losses. Sodiu
cotransporter in th
stool volume and
heat stroke and m
diarrhoea with de
oral rehydration so
instead of glucose.

Diphenoxylate: It is r
hence is usually availa
courage abuse or overd
drug addiction. This dr
Loperamide: It is an
fect than morphine. I
amide reduces GI mo
secretion induced by
orally effective and ha
has no abuse potentia

Aminosalicylates (F

Sulphasalazine

It is a prodrug and
(5-ASA). On oral ac
broken down by co
5-ASA acts locally
Sulphapyridine gets
headache. Allergic si
monitis, etc. To avoi

(oral, parenteral), hydr
Prolonged use of glucc
effects like osteoporosi

Antibiotics

Metronidazole, ciproflo
with active Crohn's dis

Immunosuppressants

Azathioprine, 6-merca

acids, increase their
be encouraged in pa
in those with mega
discomfort and flatu

Stool Softeners

Docusates

Common docusate
calcium sulphosucci

Bisacodyl is used in
surgery and radiologi
inflammation.

Sodium Picosulfate

It is a stimulant purga
bowel before surgery c

Anthraquinone Deriva

The popular anthracen

Lactulose

Lactulose is a disacc
uid and powder. On
Colonic bacteria con
fluid into the lumen
treat constipation in
coma to reduce bloo

It produces soft to
and flatulence.

PHARMACOTHER
AND GASTROESO

PHYSIOLOGY OF G

The stomach secrete
or peptic cells secrete
Parietal or oxyntic cel
cells secrete alkaline

2. **Ulcer protec**
   Sucralfate an
3. **Drugs that r**
   (a) *Non-syste*
   aluminu
   (b) *Systemic*
4. **Anti-*H. pylo***
   Amoxicillin,
   subsalicylate,

about 80–98%. PPIs are
sodium bicarbonate to pr
pantoprazole and lansop
Parenteral (i.v.) formulati
zole and rabeprazole. The
lized in liver and metabo

Therapeutic Uses

1. **Peptic ulcer:** PPIs
hibit all phases of

H_2-Receptor Antag

Histamine
(Agonist)

Therapeutic Uses

1. **Peptic ulcer dis**
   peptic ulcer. H_2-
   healing within
   4–6 weeks. Gast
   PPIs are more fi
   well tolerated.
   - *H. pylori-assoc*
     bial agents to

Sucralfate is give
reduces the absorp
fluoroquinolones,
istration of antacic
common side effec
with renal failure.

After the introdu
fate is effective for
of aspiration pneu

Sodium bicarbonate
should be avoided in p
(CCF) as it causes sodiu
Non-Systemic Antacids
num hydroxide, calciu
stomach. When this re
bonate, so HCO_3^- is n
alkalosis.

Combination of anta

Drugs Useful in Gastr

1. Proton pump i
   secretion → pH
   of esophageal le
   affect LES tone.
2. Antacids are use
3. Prokinetic drugs
   of LES, enhance

patients with hypertensio
disease and uncontrolled h
(MI) or aggravate the exist
Thrombin: It is a freeze-d
used topically to control
reactions. Thrombin shou
Fibrin: It consists of fibr
components. It is used to
on bleeding surface.

Deficiency:

Vitamin K deficiency
loss of vitamin (chr
otics (suppression o
tendency to bleed-
operative bleeding.

Preparations

Phytonadione (Vita
cular (i.m.) and intr

Anticoagulants

Anticoagulants are drugs

Classification

1. Used in vitro:
   (a) Heparin
   (b) Sodium citrat
   (c) Sodium oxala
   (d) Sodium edeta
2. Used *in vivo*:

Intrinsic sy

XI —

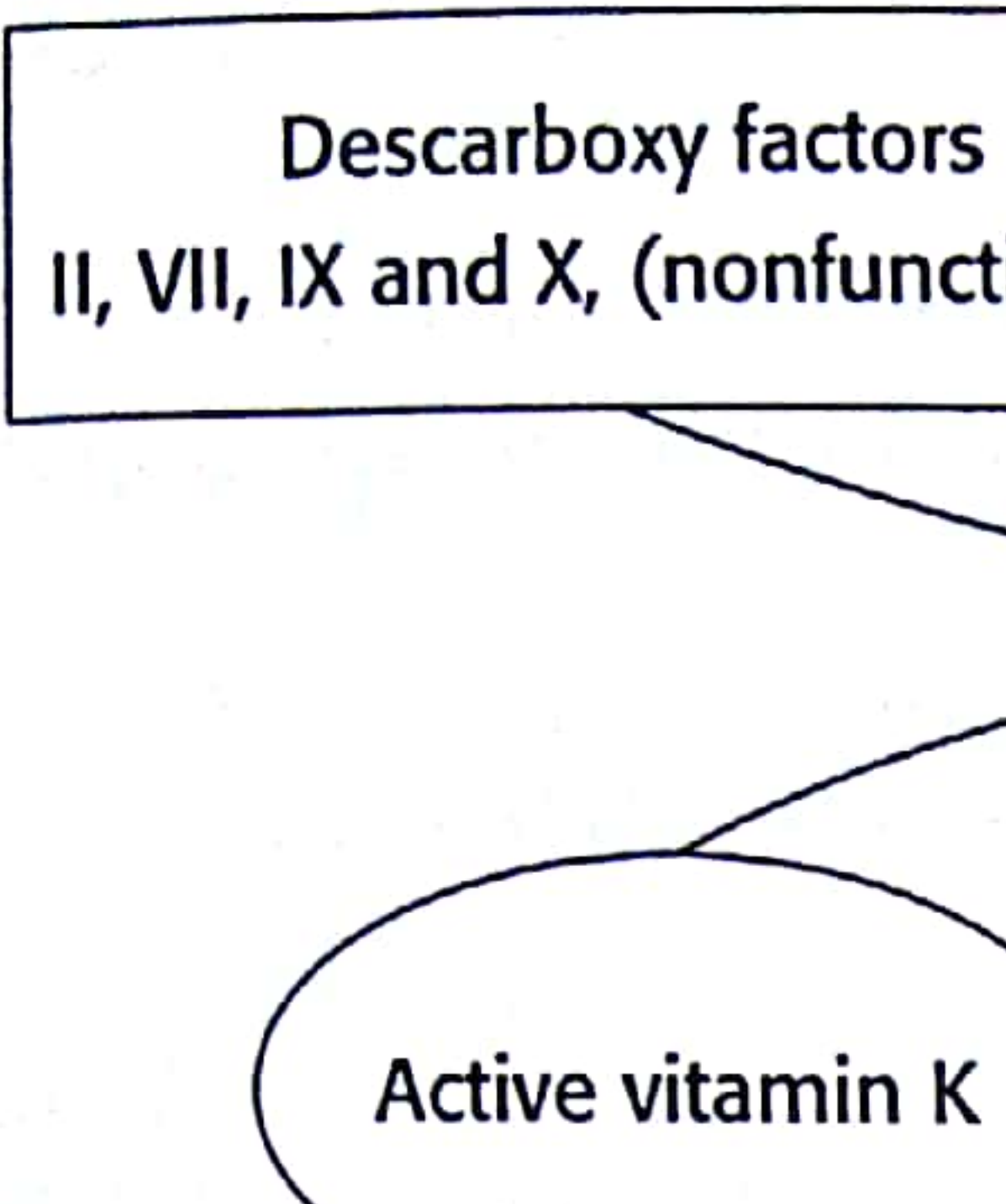
Protamine sulp
from fish sperm. C
tralizes 100 units
itself may cause b
maximum dose m

2. **Heparin-induced t**
cytopaenia,. It is c
heparin complex le
tions can occur. Th
with LMWHs. Hep

require routine lab
sulfate. Fondaparin

Parenteral Direct

They bind directly t
Lepirudin: It is a re
with heparin-indu
and requires aPTT
Argatroban: Argatr
intravenous infusi


Descarboxy factors
II, VII, IX and X, (nonfunct
Active vitamin K

PT_{ref} = Proth
ISI = Interna
Measuremen
nationally b
the standard
2. *Teratogenic e*
cause nasal h
intrauterine
3. *Skin necrosis:*

is not required. It can
thromboembolism foll
bleeding.

Factor Xa Inhibitor

Rivaroxaban, orally effe
treatment of venous th
It does not require aPT
as LMWHs. The adverse
in BP.

Therapeutic Uses of An

Fibrinolytics (Th

In response to stim
leased from vascu
converts it to plas
thrombi rapidly b
degrades fibrin and

Streptokinase, u
activators (Table 8

Reteplase and t

Table 8.2 Pharm

Streptokinase

1. It is a protein derived β-haemolytic streptococci

2. Streptokinase binds circulating plasminog form a complex that vates plasminogen to

ANTIPLATELET

Drugs that inhibit

Classification

1. Thromboxa
2. Phosphodie
3. Purinergic (
   rel, cangrelo

Dipyridamole (Phospho

It is a vasodilator. It in
of cyclic adenosine mo
gation. It is occasionall
period in patients with

Ticlopidine, Clopidogre

They are prodrugs an
phate (ADP)-mediated

possible after
the reperfusi
thrombolytic

Aspirin +
ment with fi
dergoing PCI
In unstable a
shown to sign
stroke as com

2. Coronary art

Dietary iron [mostly Fe

In the stomach [Fe

In the intestinal m

2. *Ferrous glucona*
3. *Ferrous fumara*
4. *Colloidal ferric*
5. *Carbonyl iron*

Other oral prepar*citrate, etc.*

Adverse effects of sia, metallic taste, c preparation).

Parenteral preparation

It can be used t

Ferric carboxy

preparation which
shell. It can be giv
treatment is rapid
cause pain at injec

Adverse effects

The injections are painful,
site of injection. The syste

General measures

Supportive measure
should be maintain

Vomiting can be
sodium bicarbonate

Intravenous diaz

Specific therapy

Desferrioxamine (d
by i.v. infusion or

Pharmacokinetics (Fig. 8
factor (IF) in the stomach,
B_{12}: IF complex reaches te
vitamin B_{12} gets absorbed
balamin-II and is transpo
is transported to liver for
enterohepatic cycling.

In tobacco amb
lactic therapy with
deficiency, e.g. pat

Folic Acid

Folic acid is a com
nucleus. It is abun
fruits, etc. Much o
adult is 50–100 m

Administration o
the megaloblastic a
abnormalities. This
present in the body

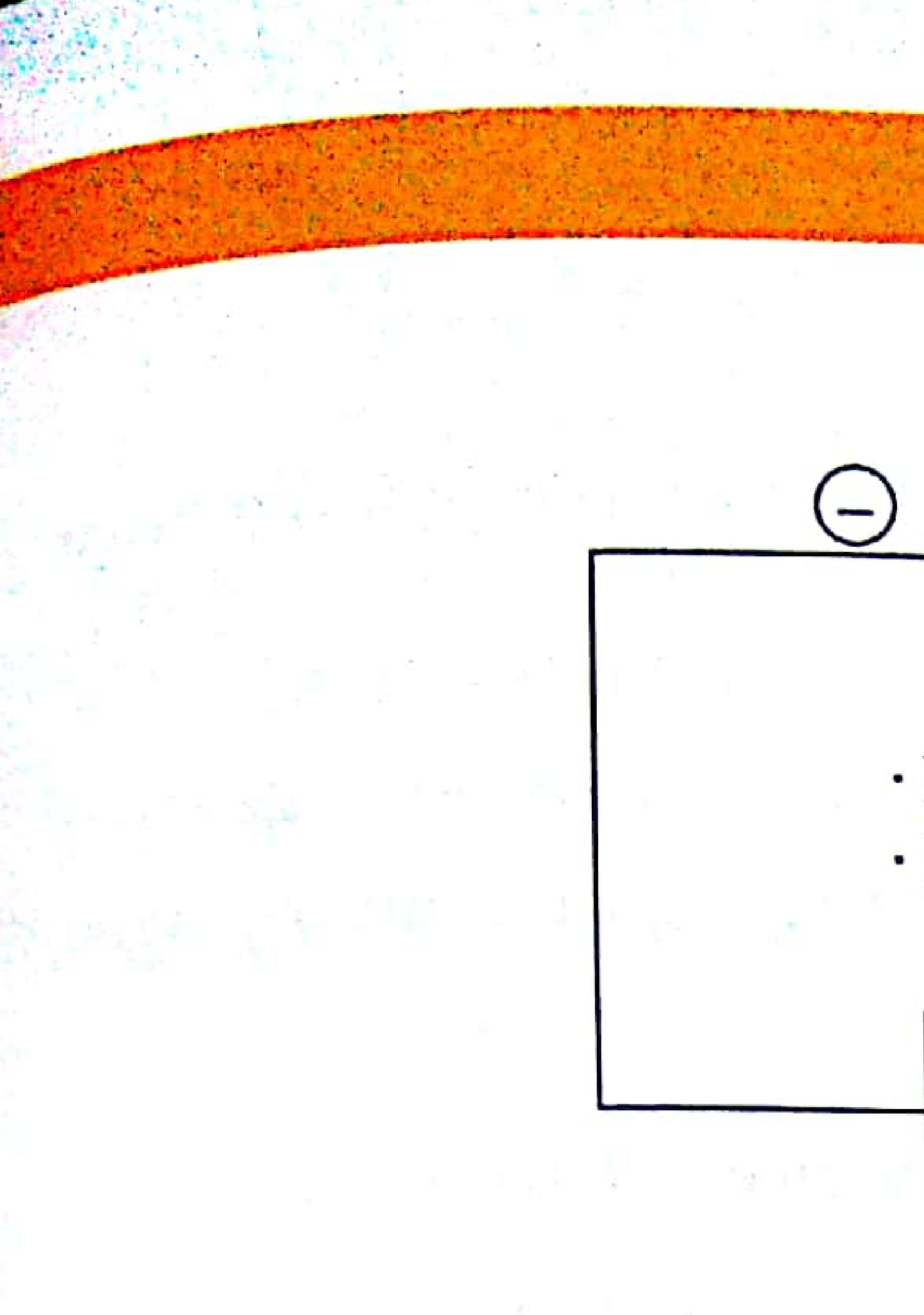
2. **Prophylactic therap**
0.5 mg/day is given
3. **Methotrexate toxici**
antagonize methotre
4. To increase the antic
tered with it.

Table 8.3 F

Drug
Erythropoietin Analogues: *Epoeti* *alfa*

2. In the cytopl

S



Octreotide. It is m
ministered subcuta

Uses of octreotide

1. Acromegaly.
2. Symptomati
   noid syndro
3. Diarrhoea as
4. Acute contro
   blood vessel

Preparations of FSH:

Urofollitropin – obtained

Follitropin alfa and follit

Luteinizing Hormone (LH

In females – ovarian ste

– ovulation.

In males – testosteron

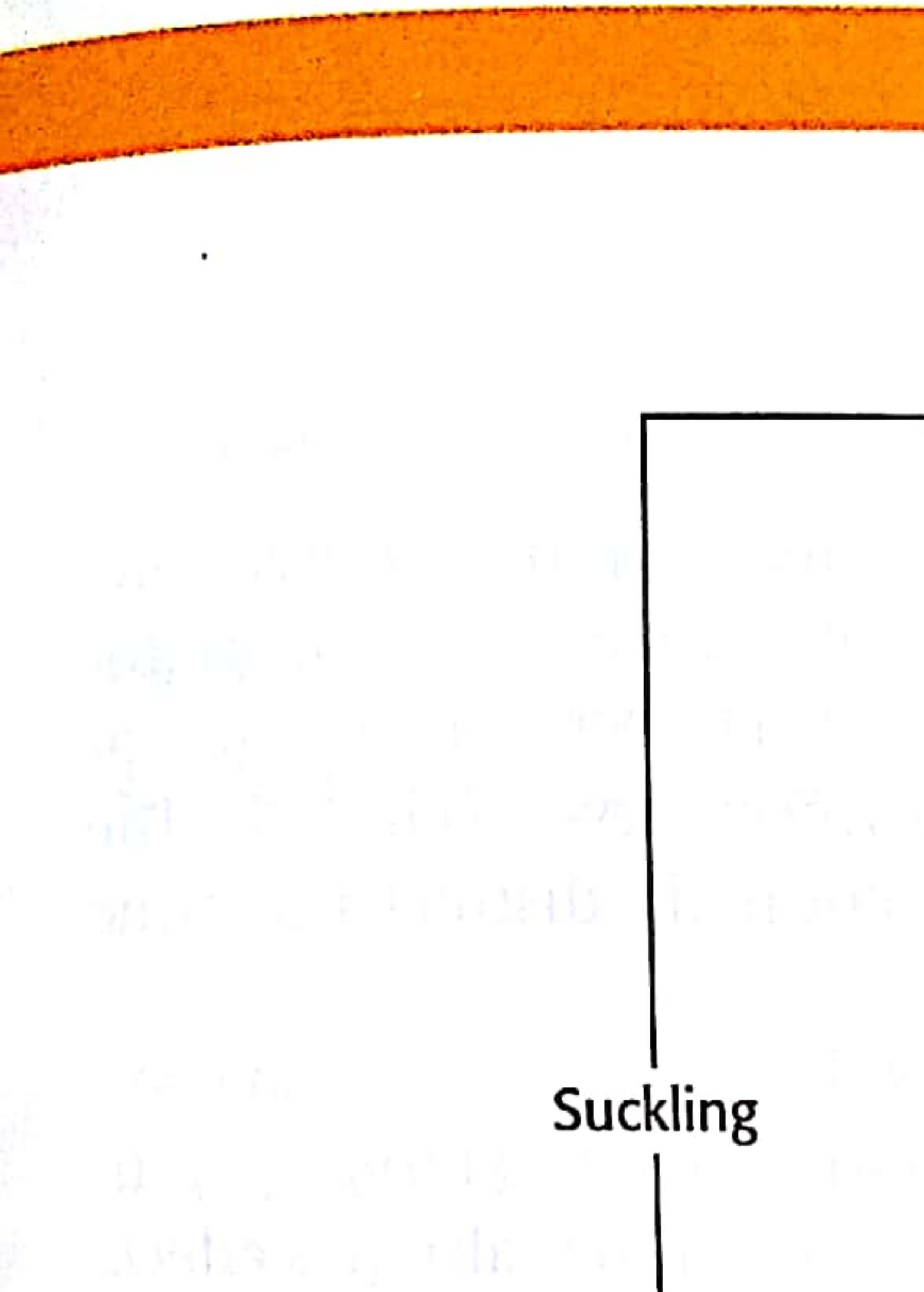
Preparations of LH:

Uses of GnRH analogu

- Prostatic carci
- Precocious pul
- Breast cancer i
- Uterine fibroi
- Polycystic ova
- Controlled ov

Adverse effects: Hot fl

GnRH Antagonists


Suckling

THYROID AND ANTIT

The hormones secreted by
(T_3) and calcitonin. The t
synthesis of thyroid horm
pituitary, which, in turn, is
'C' cells of thyroid secrete
regulating calcium metabo

The deficiency of thyro
ized by mental retardation
adults, it results in myxoed
on various organ systems

Table 9.1 Feature

System	Hyp (Thy
1. Metabolic	Incr rate
• Lipid	Dec trigl
• Carbohydrate	Incr and

thyroglobulin
proteolysis is i

5. **Peripheral co**
thyroid is T_4,
periphery is in
glucocorticoid

Differences Betwee

T_3 (Triiodothyronin	
Formed by DIT+MI	

ischaemia and myocar
ism, full replacement d
(50–100 mcg daily as
stomach). The goal of
TSH to normal levels; t

2. **Myxoedema coma:** Th
long standing untreate
fection or other forms

Diagnosis

- Clinical features
cardial effusion

Thioamides (Thiourea

Propylthiouracil, methi
hyperthyroidism. Impo
given on page 345. The

Mechanism of action o

1. They inhibit thyr
2. They inhibit iodi
3. They inhibit cou

Propylthiouracil als
thioamides do not ha
trimester of pregnancy

Important Features of P

Propylthiouracil
Less potent
Highly bound to plasma
Has short duration of ac
Inhibits peripheral conv
No active metabolite

Preparations and Use

1. Lugol's iodine
2. Ipodate sodiu

   The above prep
   before thyroide
   vascular and d
   bleeding and c
3. As an expecto

   enhances expec
4. As an antisepti

Uses

1. To control sympto
2. In thyrotoxic crisi
3. Preoperatively bef

Thyrotoxic Crisis (thyroi

state due to very high le
tures of hyperthyroidism
(e.g. atrial fibrillation),
It is usually precipitated

Hy

Anabolic Steroids (Synth

Anabolic steroids promot
ing in weight gain. They
lesser androgenic activity.
not be used because of it
androgenic activity with
bolic steroids are Nandro
ate (i.m.), Oxandrolone
Methandienone (oral, i.m

Mnemonic: NOSE.

Uses

1. In chronic ill

Testostero

2. **Synthetic oestroge**
   (a) Steroidal: Ethin
   (b) Nonsteroidal: I

Oestrogen has negativ
Progesterone has negative
pituitary (Fig. 9.8).

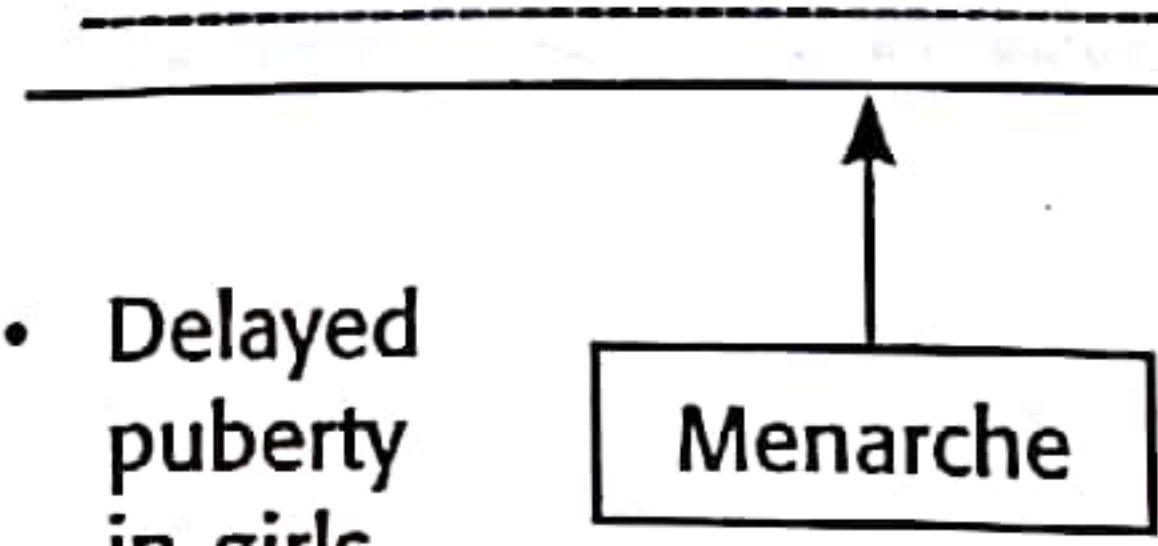
Mechanism of Action (Fig.
ERs are ERα and ERβ. Ma
uterus, vagina, ovary, breas
in prostate and ovaries.

deconjugation with t
enterohepatic cycling

Actions of Oestrogen

Therapeutic uses of

1. **Oral contracep**
   contraception, c
2. **Postmenopaus**
   in postmenop
   tion. They are
   and osteoporo
   disease is mor



FIGURE

Short-term oestr
such as hot flushes,
The main objectiv

ANTIOESTROGENS MODULATORS

Antioestrogens compete
They include clomiphen

Clomiphene Citrate

It is a nonsteroidal comp

Mechanism of Action

Fulvestrant

- Pure oestrogen anta
- Useful in breast can

Selective Oestrogen Rec

Tamoxifen, raloxifene an
and have tissue-selective
antagonistic actions in oth

Tamoxifen

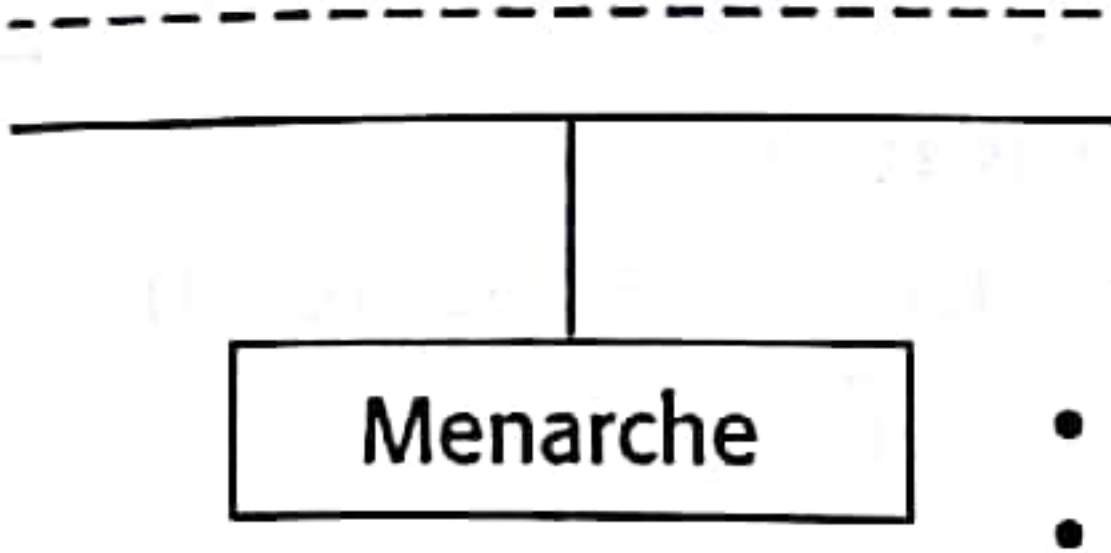
It is a nonsteroidal compo

Actions

Raloxifene is rapi
ability due to exten
ment of osteoporo
flushes, leg cramps,
embolism. It does n

Ormeloxifene

Ormeloxifene, a sele
breast and uterus. It
Adverse effects inclu



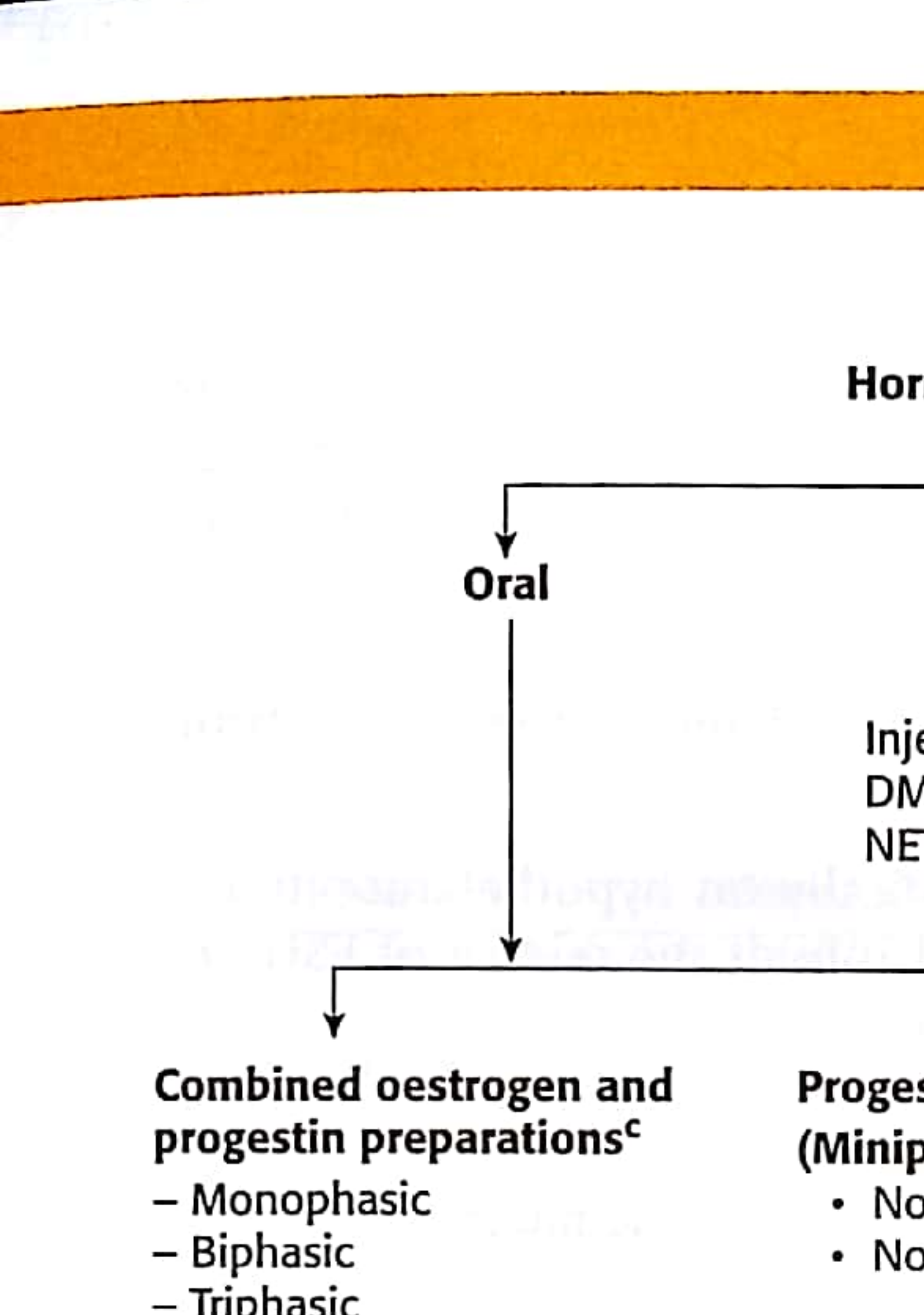
2. Dysfunctional uteri

2. *Contraception*: It
sloughing and sh
3. Used for the indu
4. For cervical riper

Adverse Effects These
uterine bleeding and ter

Aromatase Inhibitor

- *Exemestane* (ste
and anastrozole (


Hor
Oral
Inje
DM
NE
Combined oestrogen and progestin preparations[c]
– Monophasic
– Biphasic
– Triphasic
Proges
(Minip
• No
• No

gestodene and norgestimat
duce atherogenic risk. Dros
ronolactone. It is devoid o
adverse effects like weight g

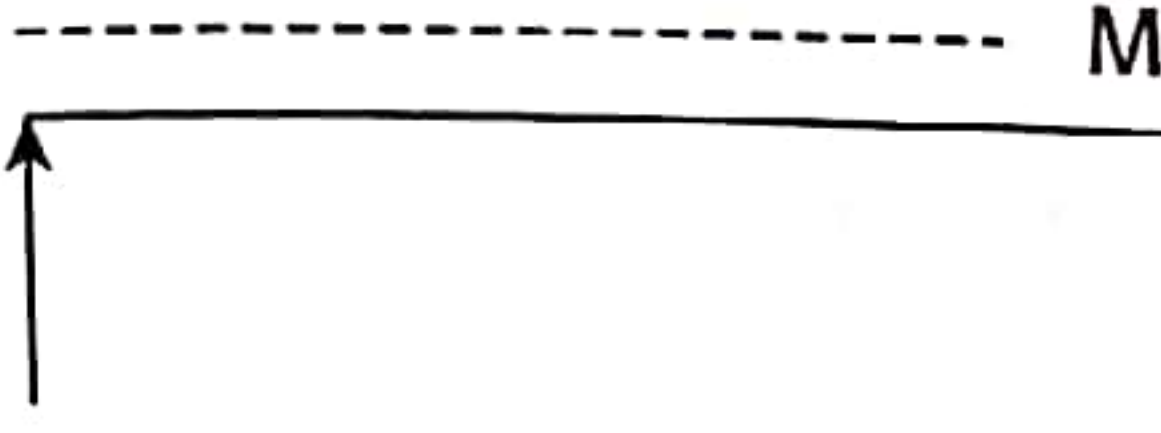
Mechanism of Action of

action of contraceptives (F
are described in the follow

1. Both oestrogen and
   axis by negative fee
   LH, which leads to
2. Cause tubal and ute
3. Make the endometr

Progestin Only Pill (Minip

Minipill contains very low
The schedule for use of m
Mechanism of action of
with implantation and inh
and there is increased risk



- Reduce incider
- Protect against
- Reduce incider

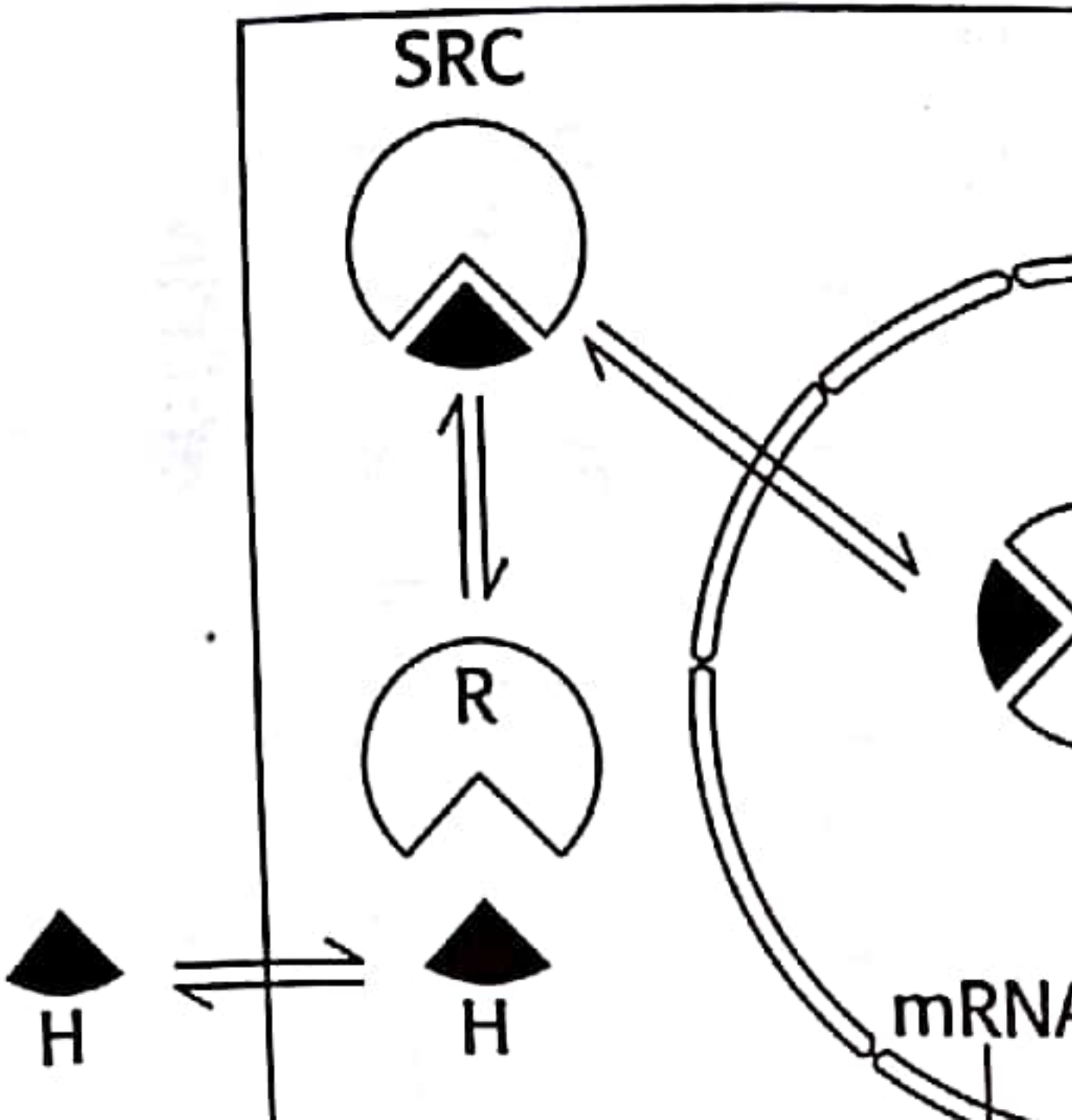
Contraindications of

1. Thromboembo
2. Hypertension a
3. Chronic liver d
4. Diabetes melli
5. Epilepsy.

2. Weight gain, fluid
3. Impaired glucose
high-dose contrac
4. Blood pressure m
with low-dose pre
5. Long-term adverse
embolic disease e
lism like smoking
coexisting diabete
6. Increased risk of
long-term use.

Table 9.5 **Ar**

	Z
Hormones secreted	M A D
Main actions	R e


SRC
R
H
H
mRNA

route of administration

oid onset but short duration of
the drug of choice for replace-
py in acute adrenal insuffi-

d relatively more toxic
ne. It has no mineralocor-

m., intra-articular and

ve highly potent antiin-
immunosuppressant
o mineralocorticoid

e of administration

nalation for asthma and

Protein Metabolism

Protein breakd
lymph

Muscle wasting, lympholy
and growth retardat

Muscle weakness
and fatigue

Prolonged use o
(steroid myopathy).

Central Nervous Sy

Corticosteroids have

1. Glucocorticoids indu
   lipase A_2; hence PGs
2. Production of cytok
   inflammation is inh
3. Glucocorticoids sta
   inflammatory media
4. Glucocorticoids inh
   endothelial cells and

Immunosuppressant Effec

7. **Growth retardatio**
   and betamethasone
8. Eye: Glaucoma and
9. **Central nervous s**
   somnia, mood cha
10. **Long-term therap**
    makes the patient
    didiasis, cryptococ
    vation of latent tu
    irritation and fung
    prevented by the u

turn reduces adre
methasone is pref

Nonendocrine diseases

Corticosteroids are an i
diseases. Because of the
Nonendocrinal diseases
cial effects of glucocort
immunosuppressant effe

1. **Rheumatoid arth**
tomatic relief in

10. **Skin diseases**
flammation in
topical steroid
conditions lik
Psoriasis, kelo
sional injectio
11. **Haematologi**
respond to glu
ticoids are us
Hodgkin's dis

Type 2 diabetes mell
DM. It is the common
and ageing are the ma
hepatic production of
insulin.

Hormones of pancr
β (B) cells secrete insul
tostatin and F (PP) cells

Insulin

Pr

Am

Alimentary absorption of glucose

soluble insulin is r
about 6 minutes.

Insulin Preparatio

Conventional Insul

1. Bovine (bee
residues and
2. Porcine (pig
acid residue

Table 9.7 Insulin

Class	Type
I. Rapid acting insulins	1. Insulin 2. Insulin 3. Insulin glulisi
II. Short-acting insulin	Regular s insulin (c line)

- Cannot be mi
- Lower risk of
- Fasting blood
- Should be avo

Insulin Detemir

- On s.c. inject action.
- Minimal peak
- Usually given

Long-acting insulin an
with regular insulins or ra
istered separately.

Insulin Administration

- Insulin syringes and
- Pen devices: They
  subcutaneously.
- Insulin pumps are
  Short-acting insulin,
  grammed to deliver

3. Lipodystrophy (e
jection. It may be
ing the injection
4. Insulin resistance
insulin per day.
tions like traum
regular insulin i
5. Oedema due to

Diabetic Ketoacidosis

Diabetic ketoacidosis
Type-2 diabetes mell

Drug Interactions

1. β-Blockers × insuli
2. Salicylates × insul
   the sensitivity of
   secretion.

Oral Antidiabetic Drugs

1. Sulfonylureas
   (a) First generation
   (b) Second genera

potency and least likely to

emia

e used in combination with
poglycaemia because of
ction. It may be useful in pa-
pairment or in the elderly

of action. Side effects are
d weight gain

For successfu
β cells are neces
absence of func
2. Sulfonylureas i
increasing the r
3. They reduce the

Pharmacokinetics. S
highly bound to plas
metabolized in liver a

Adverse Effects

3

Alimentary absorp
of glucose

ATP-sensitive potassium
insulin release. Repaglin
lized mainly in the liver
have rapid onset but sho
They are used only in ty

The main side effec
the episodes are less fr

DPP-4 (dipeptidyl pept

Vildagliptin

Sitagliptin inhibits DPI
covalently with the enz

Adverse Effects. Nausea, v
tation of heart failure in pa
and bladder cancer may occ
with rosiglitazone. Its use ha
Use. Pioglitazone is used al
in patients with type-2 diab

α-Glucosidase Inhibitors

These drugs should be given
Acarbose, Miglitol and Vog
drates by inhibiting the enzy
tine and reduce postprandial

Functions of Calcium

Controls
excitability of
nerves and muscles

Maintains integrity and
regulates permeability o
cell membrane

C

Clinical features of a
hypoparathyroidism

- Hypocalcaemia
- Tetany

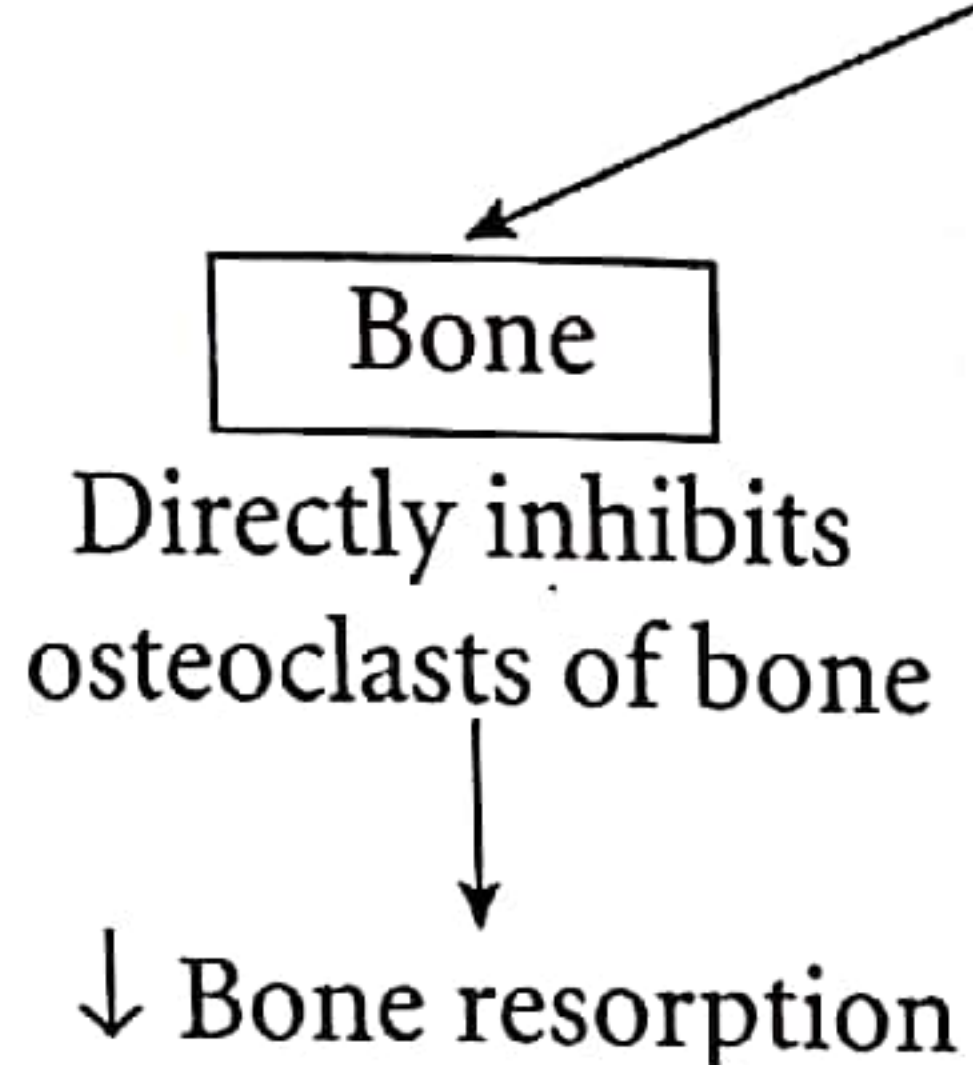
Hypoparathyroidism

Treatment

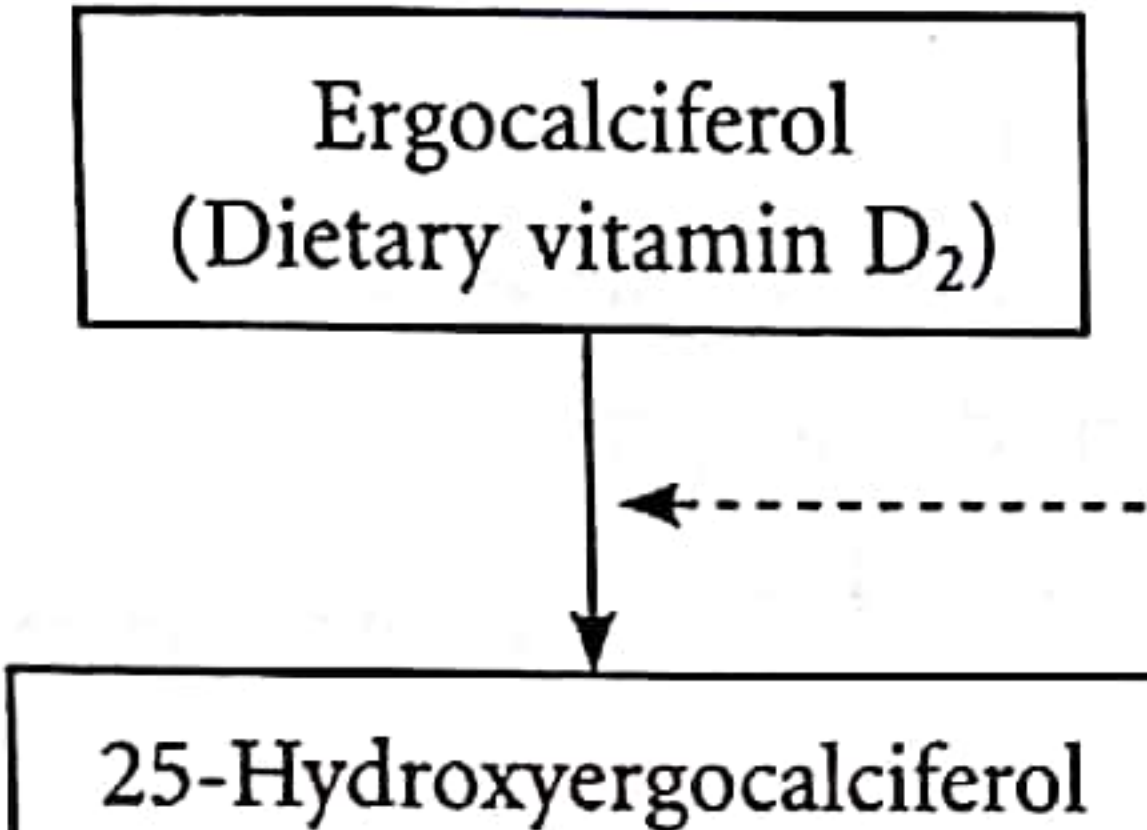
1. Emergency trea
   (a) 10% calci
   ceases.
   (b) Oral calciu
2. Treatment of c
   (a) The treatm
   (b) Oral calciu

Hyperparathyroidis

Actions of Calcitonin (Ger



Pathways of Vitamin D P



Vitamin D deficiency
Hypervitaminosis D may
min D. The signs and sym
and polyuria. If hypercalca
resulting in renal failure a
of vitamin D, low-calciu
glucocorticoids.

Preparations of Vitamin D

- Ergocalciferol (vita
  rickets in children a
- Cholecalciferol (vit

- interfere with me
  quired for norma
  of action for alen

Pharmacokinetics. Bisp
through GI tract; a part
mains for long from m
urine. Zoledronate is les

Uses

1. Paget's disease o
   Paget's disease Th

Pharmacological Act

1. **Uterus:** Oxytoc
   Uterine sensitiv
   progestins. Oes
   - Non-pregna
   - In early pre
     oxytocin is
     oxytocin gra
     with a sharp

Oxytocin increases
contractions.

4. **Kidney:** Oxytocin (hig
put. Water intoxicatio
along with oxytocin.

Preparations and Route of

- Oxytocin is not effect
- Synthetic oxytocin is
sion or intramuscular
- Syntometrine (1 mL
grams), intramuscula

Uses

Carbetocin

It is an analogue of ox
prevention of uterine at

Ergot Derivatives

Ergometrine and Meth
a natural ergot alkalo
have similar pharmac
effect on uterus than e

Pharmacological Acti

Prostaglandins

PGE_1 (misoprostol) and P
the cervix, thus useful for

Prior use of prostaglan
oxytocin produces synergi
least 4–6 hours gap betwe

Misoprostol (PGE_1)
to prevent/treat postpa
sublingually.

UTERINE RELAXANT

Prostaglandin Synth

NSAIDs, like indom
synthesis. But they
closure of ductus ar
tension. These drug
labour. Both benefic
PG synthesis.

Magnesium Sulphat

Magnesium sulphate

C

GENERAL CONSIDERA

Chemotherapy

Classification of Antim

I According to thei

(a) Bactericidal a

- Penicillins
- Cephalosp
- Aminogly
- Fluoroqui
- Rifampicin
- Metronida

II According to thei

Resistance to Antimicr

It is said to occur when the
agent which would norma
natural or *acquired*. Natura
gram-negative bacilli are no

In acquired resistance, m
resistance to the same AMA
alteration in the sequence o
(e.g. resistance of staphyloc
that results in resistance, o
comes gradually less sensit
transfer of genes for drug re

5. *Absence of metaboli*
teria can utilize pr
bolic steps.

Cross-Resistance

Organisms that develop re
tance to other chemically
either be one-way or two-
amides is usually 'two-wa

- Tetracycline ⟷ I
- Sulphadiazine ⟷ S

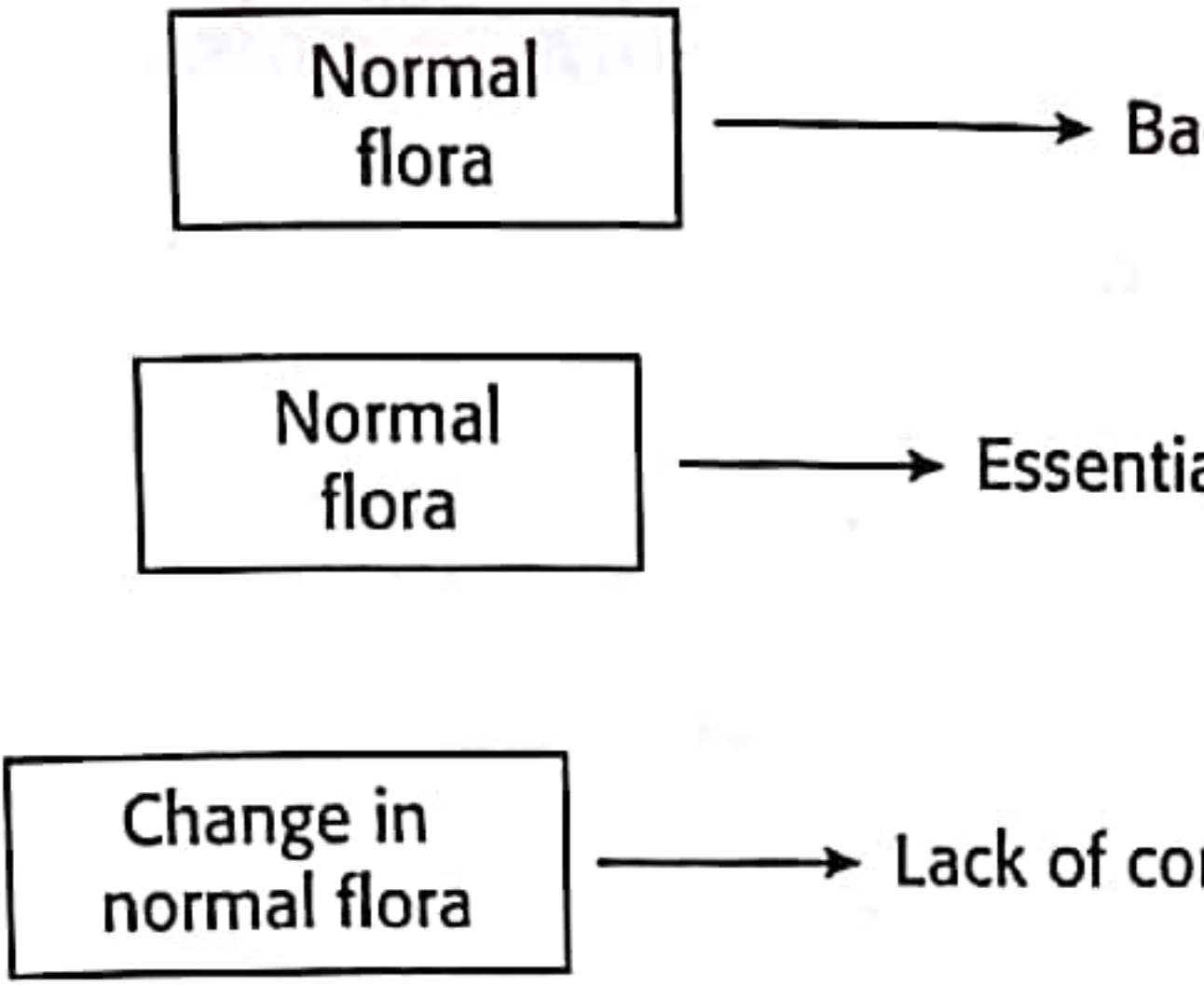


FIGURE 11.2 (a–c) Pathogenesis of superinfe
flora and pathogen).

Table 11.2 Che

Infection	
1. Meningococcal and *Haemophilus influen* meningitis	
2. Rheumatic fever	

Combination of Antimicrol

It is the simultaneous use of tw
of certain infectious diseases.

Indications/Advantages of An

1. *To broaden the spectrum of* pulmonary, hepatic, pelv and anaerobic organism therapy.
   - Metronidazole + ceft
2. *To broaden the spectrum o known*: Combination of

List of Microorganisms

1. Gram-positive co
   viridans, Streptoco
   Enterococcus.
2. Gram-negative coc
3. Gram-positive bacil
   tetani, Clostridium p
4. Gram-negative ba
   Salmonella, Shigell
   cholerae.
5. Acid-fast bacilli: M
   rium avium comple

2. **History of allergy:** In
fever, etc., there is an
should be avoided in
3. **Genetic abnormaliti**
phones, fluoroquino
G6PD deficiency.
4. **Pregnancy:** Most of
developing fetus. The
ter. For example, use
dentition and bone g
ity with tetracycline i
5. **Host defences:** In imp

- Concentration
  nolones, the a
  concentration
  effective than
- Ability to pene
  - Ability to
    against ana
    does not re
    abscess can
    rins or com
  - Levofloxaci
    urinary tra

being structurally similar to PA
and prevent the formation of
Sulphonamides are not effectiv
and thymidine. Mammalian ce
present in diet, hence are unaff

Sulphonam

Drug Interactions. Sulp
ate, oral anticoagulants a
their metabolism and di
Therapeutic Uses. Sulp
tions. They are used in

1. Sulphadoxine an
   in the treatment
2. Sulphadiazine ar
   toxoplasmosis.
3. Nocardiosis: Sulp
4. Sulphamethoxaz

Cotrimoxazole (sulphameth
produces **sequential blocka**
in the same metabolic pathw
effect. Sulphamethoxazole i
hibits folate reductase enzym
match each other almost clo
lar half-life. Optimum syner
(sulphamethoxazole to trim
this combination are:

1. Individually, both are
2. Chances of developme

2. **Bacterial respi**
and chronic b
useful for acute
3. **Bacterial diarrh**
gella, E. coli and
4. **Typhoid fever**
levofloxacin, e
cefoperazone)
may also be eff
5. ***Pneumocystis ji***
treatment of in
It is useful for

uoroquinolones

	Drug interactions
e *onas* e ection e to	Inhibits metabolism of theophylline and warfarin

of fluoroquinolones—cont'd

	Drug interactions
t *iae*, egative ed hitis,	No interaction with theophylline and warfarin

Antibacterial Spectrum

Ciprofloxacin is the prototype c
bic gram-negative organisms—
Shigella, H. ducreyi, H. influenz
Campylobacter jejuni.

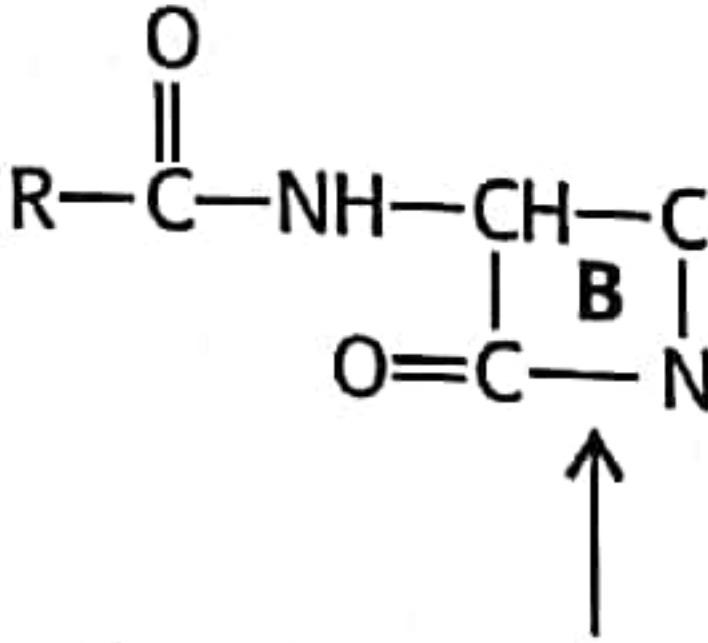
It has activity against—*S. a*
tuberculosis.

Most of the anaerobes—*Ba*
ciprofloxacin.

Newer fluoroquinolones like
greater activity against streptoco

Pharmacokinetics. Ciprofloxa
is well absorbed from the gut,

2. **Bacterial diarrh**
GI infections cau
diarrhoea (due to
zole. Norfloxacin
adequate.
3. **Typhoid fever:** C
ferred drug for
resolution of sy
They are also eff
typhi when thera
centration in bil
treated with ceft



Site of action of p

FIGURE

PENICILLINS

Penicillin was the first antibioti
accidentally by Alexander Flem
Penicillium chrysogenum.

β-Lactams, the structu
hibiting cross linking of
forms are produced whic
cidal effect when the bac

Penicillin-binding pro
and related proteins are
gram-positive bacteria is
which is 50–100 layers t
the peptidoglycan layer
lipopolysaccharide layer
penicillin than gram-po

Mechanism of Bacteria

(i) by producing β-lact

Table 11.5 Charac

	Penicillin	Ro do
1.	Penicillin G (benzyl penicillin, crystalline penicillin)	i.v. 20- mil (M
2.	Repository	

3. Sensitivity test sh
aspect of forearm
A negative skin te
4. Inj. adrenaline a
penicillin to treat

Other adverse effect

i.m. injection. Prolonge

Jarisch–Herxheimer react

It is an acute exacerbat
therapy due to release o
are fever, chills, myalgia

penicillin G is the ideal agent. It
month and continued for life in
treated with erythromycin or sulp

Limitations/Drawbacks of Peni

1. Acid labile—orally not ve
2. Short duration of action (
   developed).
3. Narrow spectrum of anti
   organisms).
4. Destroyed by penicillinas
5. Possibility of anaphylaxis

Table 11.6 C
o

Penicillins

(c) *Extended spectrum penicillins*

- Aminopenici
  lins

Table 11.7 Comparison

Ampicillin
Semisynthetic aminopenicillin
Acid stable; incompletely absorb from GI tract— alters intestinal fl hence diarrhoea is more commo (superinfection)
Food decreases the absorption o ampicillin
Effective against *Shigella* and *H. influenzae*

Ticarcillin is used in co
coside for the treatment o
Adverse Effects. They a
be precipitated due to sc
fere with platelet functio

β-Lactamase Inhibitors

They are clavulanic acid
β-lactam molecules. β-la
them. Co-administration
β-lactams by preventing
Clavulanic Acid. It is iso

sporins

ation	Fourth generation
O)	• Cefepime (i.v.)
ime proxetil (O)	• Cefpirome (i.m., i.v.)
ne (i.m., i.v.)	
e (i.m., i.v.)	
one (i.m., i.v.)	
ne (i.m., i.v.)	
ne (i.m., i.v.)	
))	
(O)	

'd

	Fourth generation
ss tration	Cross BBB
orins es ative	**Same as third generation.** They are reserve drugs

kidney either by glomerular filt
sporins are metabolized in th
deacetylated in the body before
through bile. Like penicillins, th
blocked by probenecid, resulting
action.

Adverse Effects

1. Hypersensitivity: The most
   They are skin rashes, urtic
   penicillin is seen in few pa
2. Gastrointestinal disturbanc
   also occur.
3. Pain at the site of i.m. in
   cephalosporins can cause t
4. Nephrotoxicity is also ass

Cilastatin, a dehydr
nem in urine. Hence, i

Imipenem–cilastatin
is used in mixed bacter
gynaecologic, skin, s
cross-reactivity with p
rashes are the commo

Other Carbapenems

Meropenem and Dori

- Injected intraven

3. They are mainly
the CSF.
4. They are not *me*
5. They are *excreted*
6. They have *bacte*
active at alkaline
7. They cause *ototo*
8. They exhibit pa
9. Transport of am
anaerobes are res

- is safer t
  aminog
  period c
- is conve

2. Multiple-da
   or three eq

Once-daily do
and patients wit

Uses. Streptomycin is
combination with othe
plague and brucellosis.

Gentamicin

It is the most commonl
bacillary infections due t
also effective against gra
cocci but not *M. tubercul*
Common properties, me

Paromomycin

An aminoglycoside w
amoebiasis, giardiasi
encephalopathy.

Netilmicin

It is resistant to amin
of the gentamicin-re

THERAPEUTIC USES

- **Tularaemia:** S
  quinolones an

5. Gentamicin, tobr
   topically for gram

BROAD-SPECTRUM

Tetracyclines and chlora
called because of their ef

- Gram-positive an
  gonorrhoeae

Table 11.10

Drugs
Chlortetracycline Oxytetracycline Tetracycline
Demeclocycline

is characterized by
with blood and m

6. **Effects on bones**
form tetracycline–
growing bone and
nancy can cause pe
to deposition of ch
such teeth. Tetracy
of hepatotoxicity
contraindicated du
It is also contrainc

7. They may cause ir

Tetracyclines ac
formation of free
11. **Malaria:** Doxycyc
agents for treatme
used alone for ma
12. **Amoebiasis:** See p
13. **Syndrome of ina**
ADH action; henc
14. **Leprosy:** It is one
Minocycline) regi

Advantages of Doxycycl

Pharmacokinetics. Chlo
idly absorbed from the gu
tion. It has a bitter taste; to
has been developed for pa
lipase. Chloramphenicol i
It also crosses placental ba
glucuronide conjugation a

Adverse Effects. Most o
bition of mammalian mi

4. **Rickettsial infectio**
   of rickettsial diseas
   infections in childr
5. **Eye and ear infecti**
   infections due to su
6. **Brucellosis:** Chlora
   dicated.

MACROLIDES

To overcome the a
clarithromycin and a

Clarithromycin (Ta

Mechanism of actio
administered orally.
for the treatment of M
uses are mentioned i

Table 11.11

Azithromycin (Table 1

It can be administered ora
ther 1 hour before or 2 hou
active against *H. influenza*
has wide tissue distributio
tolerated and longer actin

Antibacterial Spectrum a

1. As a drug of choic

	Adverse effects
c,	Skin rashes Pseudomembranous colitis (superinfection)—diarrhoea with blood and mucus in the stools due

t'd

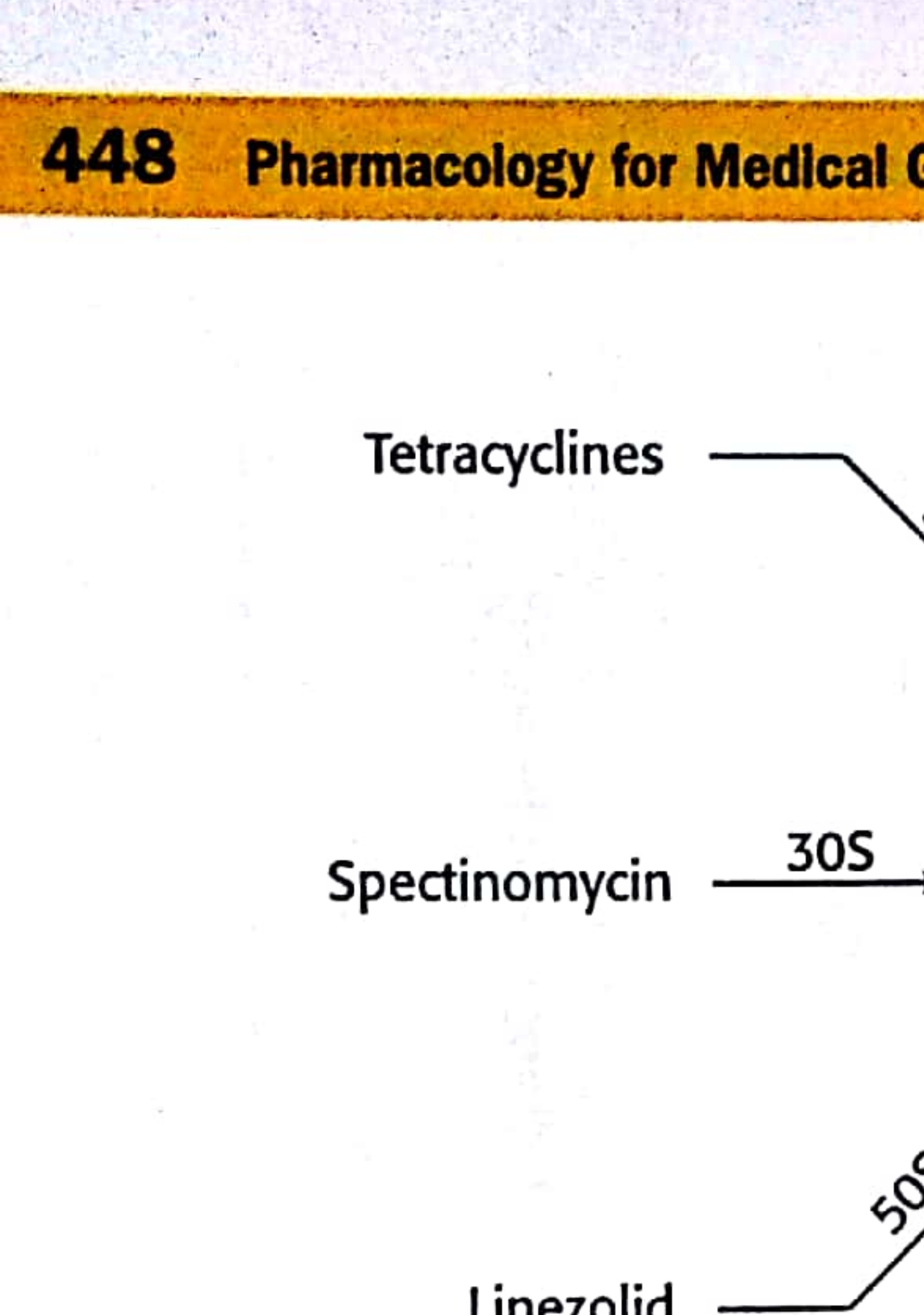
Adverse effects

Highly toxic, causes oto-
oxicity, nephrotoxicity
and hypersensitivity reac-
ions (skin rashes and
anaphylaxis). Rapid i.v.
nfusion may cause

c-
o
am

ns
g-
coc-
ent
ms

Skin rashes, fever and
pain at injection site


Tetracyclines
30S
Spectinomycin
50S
Linezolid

Nitrofurantoin

It is a bacteriostatic ag
prophylaxis of UTI due
effects are nausea, vom
fever, leukopaenia, ana
polyneuropathy.

Phenazopyridine

It is not an antimicrobi
It relieves pain, burnin

Table 11.13 Impo disea

Disease
Gonorrhoea
Syphilis

DRUGS USED IN AN

Nitroimidazoles: Metroni

β-Lactam Antibiotics

- Penicillins – Pipera
- Cephalosporins – C
- Carbapenems – Im

Fluoroquinolones: Moxifl

Broad-Spectrum Antibiot

Sulphonamides: Mafenid

Others: Vancomycin, clin

ANTITUBERCULAR

Tuberculosis is a chronic

Mycobacterial infectio
infection, it consists of ex
of the lesion is poor, h
decreased.

Classification

1. First-line antitube

Table 11.15

Drug (Route)
Isoniazid (H) – oral
Rifampicin (R) – oral
Pyrazinamide (Z) – or

Isoniazid inhibits the
etc. → increases plasma le

Rifampin (Rifampicin)

Rifampicin is a derivative
rapidly kills intracellular
ing in caseous lesion). It
subpopulations, hence rif
Mechanism of Action. Ri
merase and inhibits RNA

activity. Like INH, pyra
but by a different mech
is distributed widely th
liver and excreted in ur
dose-dependent hepato
peruricaemia and may
viduals. The other sid
rashes.

Ethambutol

It is a first-line antitube
volved in mycobacteria

nausea, vomiting and ab
the drug in divided doses
age, drug fever, skin rashe

Ethionamide

It is structurally similar t
colic acids. It is a bacteric
intracellular bacilli. It i
widely all over the body i
in urine. The common a

The choice of stan
mended by WHO—sh
of financial resources.

Short-Course Chemo

There are several sh
are convenient, highl
an intensive phase
4–6 months. An exan
is given below.

Table 11.16 WHO-

Treatment group	Type of pat
New patients (Category I)	• New sput smear pos tive • New sput smear neg

As per RNTCP 2012

Intensive phase (6

amide, Pyrazinamide,

(4 drugs for 18 mont

serine.

Pyridoxine should a

neurotoxicity due to et

All drugs are admini

To address the prob

plus. DOTS plus is des

is recommended in are

Indications for Chemopro

1. Newborn of a moth
2. Young children (<
3. Household contact
4. Patients with positi
   diabetes mellitus, m

Role of Glucocorticoids

Tuberculosis is a relative c
in certain situations, gluc

Borderline tuberculo
referred to as **pauciba**

Drugs Used for the Tre

Dapsone or diaminod
amide, ofloxacin, mox
used in leprosy.

Dapsone or Diaminod

Dapsone (Fig. 11.11),
agent for the treatment

Rifampicin

It is the most effective and
most of the lepra bacilli.

Clofazimine

It is a phenazine dye and ha
matory effect, hence is also
mine binds to mycobacteri
against dapsone-resistant o
tion. It accumulates in tissu
of the skin on exposed part

2. For paucibacillary
   - Rifampin 600
   - Dapsone 100 m

   The duration o
   followed up fo
3. Alternative regime
   - Clofazimine +
     mycin, etc.) da
     minocycline da
   - For single-lesio
     Rifampicin 60

5. **Allylamine:** Terbina
6. **Antimetabolite:** Flu
7. **Other topical antif**
   thiosulphate, seleniu

Table 11.17

Superficial myc

1. Dermatophyt

(a) Epidermo

Adverse Effects. Amp
toxic reactions are feve
phlebitis at the site of i
Anaemia and electro
lipid formulations.
Nephrotoxicity with
therapy.
Hepatotoxicity can o
Headache and convu
Formulations of Amphe
intravenous preparatio

Echinocandins

Caspofungin Acetate

Caspofungin acetate is a se
Aspergillus. It is an antifunga
in fungal cell wall. It is n
metabolized in liver and m
treatment of invasive asperg
or intolerant to other antifu
flushing, fever and phlebiti

Micafungin

Table 11.18

Amphotericin B
Active drug
Has broad spectrum
Antifungal antibiotic
Fungicidal
Not absorbed throug
Highly bound to plas

	Caspofungin Acetate	
Terbinafine		
Griseofulvin	Candidiasis	
		o-

Mechanism of Action. A
demethylase enzyme (Fig

FIGURE 1

Miconazole and Clotrima

4. KTZ × Warfarin
5. KTZ × Terfenadine

Uses

1. **Dermatophytosis:**
   T. versicolor.
2. **Candidiasis:** Ketoc
   replaced by triazol
3. Other uses include

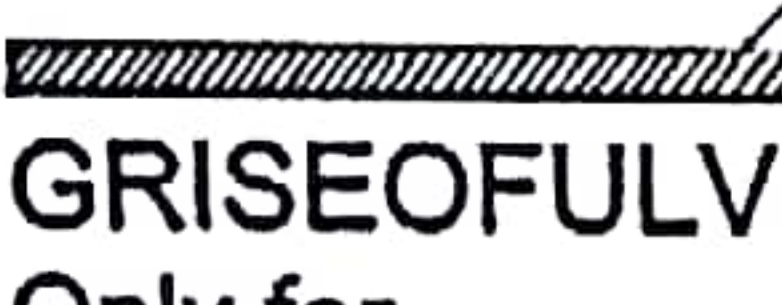
3. Dermatophytos
4. In onychomyco
5. It is also effecti

Voriconazole

It is a triazole. It is use
Candida infections. V
effects include visual
skin rashes. It inhibits

Posaconazole

Av



GRISEOFULV

Only for

dermatophytes

Antiherpes Agents

Acyclovir

It is a synthetic, purin
is more effective agai
infections.

Mechanism of Action

A

Adverse Effects. Acyclovi
and headache are the othe
tremor, confusion, disorie
irritation and burning.

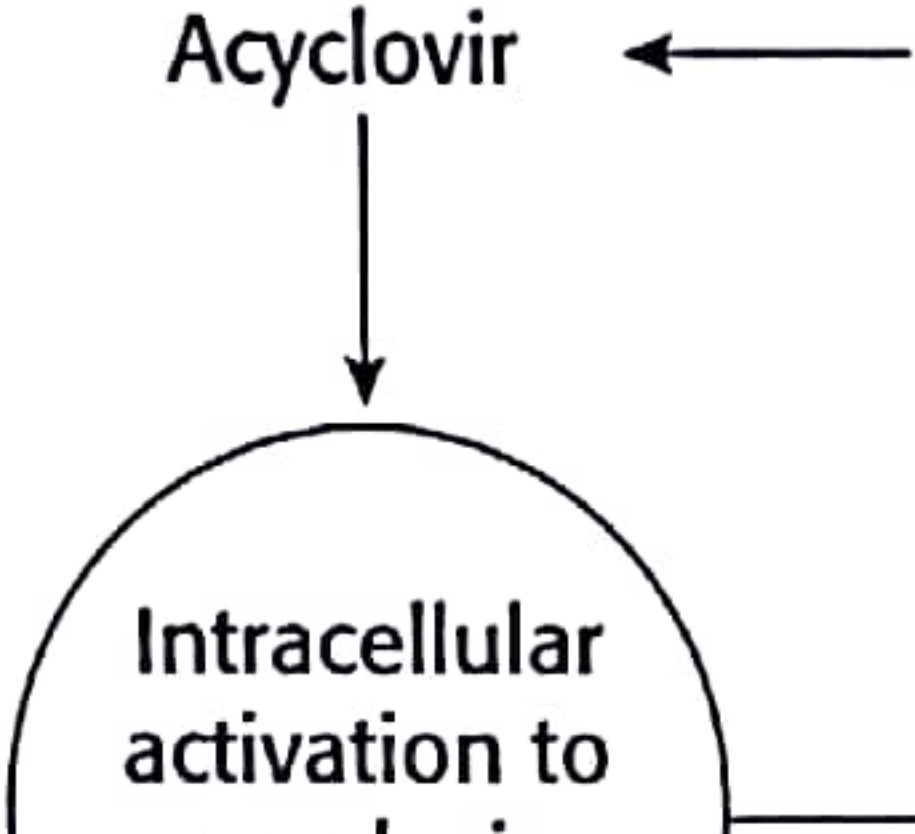


Table 11.20 Impo

	Valacyclovi
Adverse Effects	Nausea, vomiting, skin rashes, CNS symp-toms (in hig doses)

ANTIRETROVIRAL DR

Classification of antiretro
transcriptase inhibitors, pr
against both HIV-1 and H
and entry inhibitors are ac

Nucleoside Reverse Trans

These drugs, after entering
phate forms by cellular ki
tase. They get incorporated

from GI tract, metaboliz
urine. It crosses placenta
Adverse Effects and Dru
neutropaenia are the cor
fort, headache and insc
therapy. Long-term thera
lactic acidosis.

1. **Zidovudine × pa**
tion. Paracetamol
zidovudine. This
and its toxicity.

rashes, fever, nausea, pru
insomnia, bad dreams, ar

- Nevirapine
- Delavirdine
- Efavirenz

→ Bi

Nevirapine

It is a highly lipid-solubl
tract. It freely crosses the

Entry or Fusion Inhibitors

Enfuvirtide and Maraviroc

Enfuvirtide prevents fusion
→ blocks viral entry into th
reactions like pain and eryth
add-on drug in patients wh
hibit cross-resistance with r

Maraviroc is a CCR5 ch
CCR5– tropic strains of HIV
ated. Adverse effects like co

- Efavirenz (EFV): 600
- Nevirapine (NVP): 20

Regimens: For HIV-positive p
ARV naïve adults and adoles

- TDF + 3TC/FTC + EF
- TDF + 3TC/FTC + NV
- AZT + 3TC + EFV or
- AZT + 3TC + NVP
- If NNRTI cannot be u

Adverse Effects. These
bone marrow suppressio

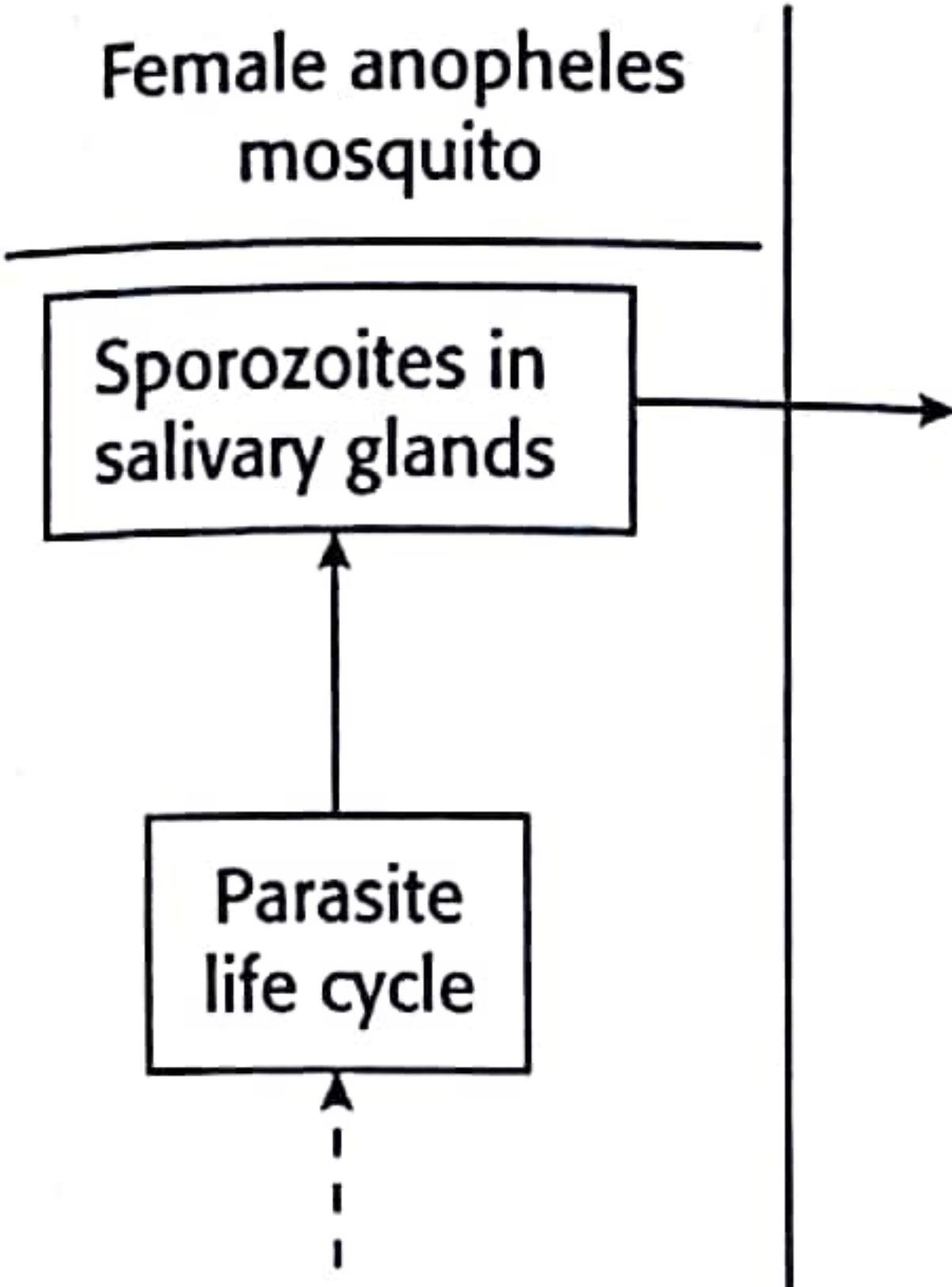
Ribavirin

It is a synthetic purine nu
Ribavirin monophospha
for the synthesis of guan
phosphate also competi
by oral, aerosol or i.v. ro

Ribavirin is effective a
treat influenza, parainflu
fections. Oral ribavirin is

Table 11.21 Antima cycle

	Hepa
Stages of malarial parasite	Primary tissue forms
Drugs	Sulphadoxine Pyrimethamin


Female anopheles mosquito
Sporozoites in salivary glands
Parasite life cycle

(v) Drugs used
mosquito
effect again

4-Aminoquinolines

Chloroquine

Chloroquine is a 4-amino
schizontocide against *P. viv*
P. falciparum and *P. knowles*
and hypnozoites).

Table 11.22 R

1. **Treatment of uncor**

   (a) **For acute attac**
   sensitive *P. falc*
   Oral chloroquine
   Chloroquine 600
   later–First day
   300 mg base–
   300 mg base–

   (b) **For radical cure**
   Chloroquine (as

Table 11.22 Re

2. **For severe or comp**

Parenteral antimalari
started.

Then complete the t
able to take orally.

Artesunate

Dose: 2.4 mg/kg at
Then, once a day till
If patient is able to t

Infectious mononuc
Autoimmune disord

Note: Uses of chloroquine:
Tablet chloroquine pho
Tablet chloroquine pho

Amodiaquine

It is a congener of chloroq
quine. It is an erythrocytic s
the treatment of chloroqui
phylaxis of malaria owing

Alkaloids

Quinine and Quinidine

Cinchona bark contains
important.

Mechanism of Action. S

Pharmacological Effects

1. Antimalarial actio
against all the four
P. vivax. It has no a
tissue forms)

Quinoline Methanol

Mefloquine

It is a synthetic quinoline
schizontocide and has no
hypnozoites of *P. vivax*. It
Mechanism of Action. Si
Pharmacokinetics. Mefloq
use because of its local irri
bound to plasma proteins,
cling. It is slowly excreted in
Uses. Mefloquine is used

along with artesunate is us
malaria. Pyrimethamine–s
toxoplasmosis in immuno
Preparations. Pyrimethan
Pyrimethamine 25 mg +

Pyrimethamine is com
plasma proteins, accumul
plasma half-life (80–90 h)
rashes, urticaria, megalobl

Proguanil (Chloroguanide

Tafenoquine

It is an 8-aminoquinolin
ites) of *P. vivax*; also has
action ($t^{1}/_{2}$ is 15–19 days

Artemisinin and Its Deri

Artemisinin is derived fr
tives of artemisinin are
compound, arteether, wa

They are highly effec
are highly potent, rap

Uses of Artemisinins

Artemisinins are used in t
falciparum malaria and sev

Artemisinins have a sh
They should not be used as
tance. They are used in com
combination therapy (AC
vides faster clinical cure, ra
velopment of resistance. Ar
slowly eliminated antimala
diaquine, etc. for the trea

in pregnancy and young c
such cases.

ANTIAMOEBIC DRUG

Amoebiasis is a protozoal i
mitted through faeco-oral

Classification (According

1. **Luminal amoebicid**
   hence attain high co
   the gut lumen and k

Adverse Effects. Adverse
tion of the drug.

1. **Gastrointestinal:** A
distress, abdominal
2. **Allergic reactions:** T
3. **CNS:** Dizziness, ve
sions and ataxia m
therapy.
4. Disulfiram-like reac
flushing, etc.) may
warned to avoid alc

Adverse Effects. Adverse
tion of the drug.

1. **Gastrointestinal:**
distress, abdomina
2. **Allergic reactions:**
3. CNS: Dizziness, v
sions and ataxia
therapy.
4. Disulfiram-like rea
flushing, etc.) may

3. **Giardiasis:** Metronidazo
for 7 days).
4. **Anaerobic infections:**
the anaerobic infectio
intra-abdominal infect
other anaerobic organi
(a) In anaerobic brain
tion with a third-ge
(b) In antibiotic-associa
effective. It is cheap
(c) Vincent's angina: M
for treatment of V

Table 11.25 Other nitr features–

Drug	Route of administration
Ornidazole	Oral and i.v. infusion
Satranidazole	Oral

Amides

Diloxanide Furoate

Diloxanide furoate is a s
which form cysts are kille
effective against tissue trop
in the gut is split into dilo
absorbed, the unabsorbed
drug of choice for asympto
amoebiasis, diloxanide fu
eradication of the organis
is administered in a dose
and rarely causes side effe

Table 11.26 Treatm

Disease and causative organism	Clinical
Giardiasis: *Giardia lamblia*	Diarrho flatulen
Trichomoniasis: *Trichomonas vaginalis*	Itching discharg vagina

ANTHELMINTICS

Anthelmintics are drugs used
intestinal tract or tissues of th
are called *vermicides* and thos

Roundworm
(Nematodes

Table 11.27 Drug

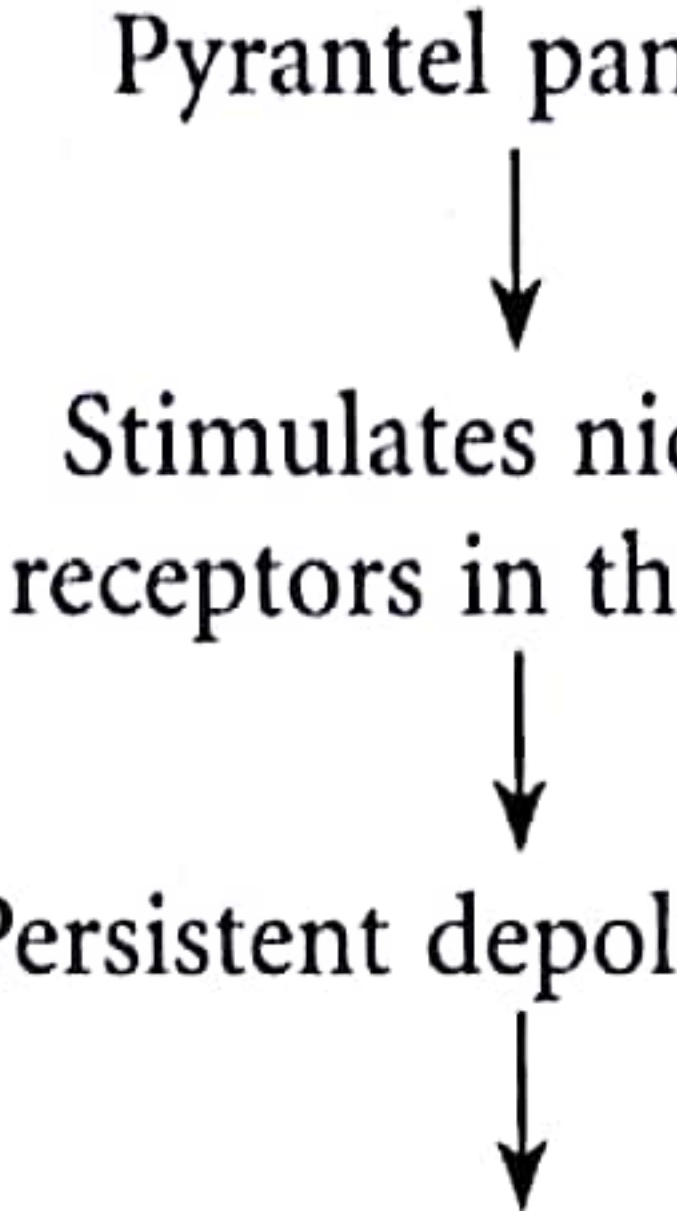
Infestation and parasite

1. **Nematodes**
   (a) Roundworm (*Asca*
   (b) Hookworm (*Ancylo*
   Necator americanu
   (c) Pinworm (*Enterob*
   (d) Whipworm (*Trichu*

Uses

1. **Nematodes:** Albendazol
roundworm, hookworm
mixed worm infestations
2. **Neurocysticercosis:** Bo
in neurocysticercosis. B
of the following reason
   (a) It is cheaper.
   (b) Duration of treatm
   (c) It reaches high con
   (d) It is less toxic and l

Mechanism of Action



times daily taken a
dazole 400 mg to D
Diethylcarbamazin
transmission of fila

2. **Tropical eosinophi**
histaminics and glu

Ivermectin

It is the drug of choice in
microfilaria of *W. bancrof*

Mechanism of Action

Pharmacokinetics. Praziq
undergoes extensive first-p
teins, crosses the BBB and
Adverse Effects. The mos
are nausea, vomiting, abdo
itching, muscle and joint p

Uses

1. **Schistosomiasis:** Pra
tosomes. Praziquant
cure rate. It is well to

2. **Synthetic phase (S**
3. **G_2 phase (premito**
   (proteins and RNA
4. **Mitotic phase (M**
5. **G_0 phase (resting**

Cell cycle

Antimetaboli
Antibiotic: Bl
Taxane: Paclit
Epipodophyll

3. **Vinca alkaloids:** Vi
4. **Taxanes:** Paclitaxel,
5. **Epipodophyllotoxi**
6. **Camptothecins:** To
7. **Antibiotics:** Actino
   norubicin.
8. **Enzyme:** L-Asparagi
9. **Miscellaneous age**
10. **Hormones and ant**
    (a) Oestrogens: Eth
    (b) Selective oestro

ulcers are due
mucosa.

(d) **Skin and hair:**
follicles. Alopec
titis and skin ra

(e) **Gonads:** Cytoto
mia and infertili

(f) **Fetus:** Adminis
causes abortion

(g) **Hyperuricaemi**
excessive cell

- Cross linkage (inhib
- Abnormal base pair
  than cytosine and re
- Break in the DNA st

↓

Cell death

Alkylating agents can al

Nitrogen Mustards

Cyclophosphamide

Mechlorethamine

It is one of the componer
and procarbazine) regime
care should be taken to av

Chlorambucil

It is a slow-acting nitroger
produces marked lympho
ment for chronic lymphoc

Melphalan

Cisplatin is highly effectiv
and bladder cancer. It is also
Adverse Effects. Cisplatin is
iting can be controlled by 5-H
Nephrotoxicity: It can be
Ototoxicity with hearing l
Electrolyte disturbances:
mia are common. Neuropath
shock may rarely occur. Cis
properties.

Carboplatin

depletes the intracellular TH
purines and thymidylate wh

Methotrexate is well abs
i.v. or intrathecally. It is be
most of the drug is excrete

Methotrexate is the drug
leukaemias, Burkitt's lympl

Low-dose methotrexate
tis. It prevents joint erosio
effects. It is also used in pso
plantation.

Adverse Effects. See gene

Pyrimidine Antagonists

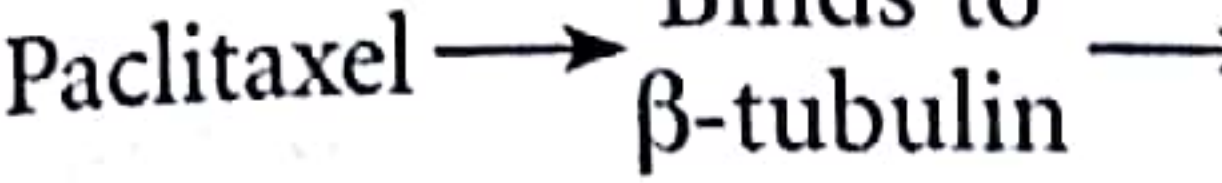
Fluorouracil (5-FU)

5-Fluorouracil is activated
(Fig. 11.18). This interfere
thymidylate synthetase enzy

It is used in colorectal, u

Fluoroura

Mechanism of Action



Paclitaxel is administere
ian, lung, oesophageal and
suppression, peripheral ne

Camptothecins

Topotecan and irinotecan
Mechanism of Action Ca

Bleomycin

It can be administered thro
of testicular and ovarian tu
Its main side effects are hy
There is very little bone ma

Doxorubicin and Daunorub

Daunorubicin is effective i
tumours. The side effects a
diomyopathy with CCF, hy

Other anticancer drugs a

Monoclonal antibodies

rituximab is used in chro

infusion.

Table 11.29 Misce

Drug
Tyrosine kinase inhibitor
Imatinib
Angiogenesis inhibitor
Bevacizumab (vascular

7. **Aromatase inhibitors**
in postmenopausal w
8. **GnRH agonists:** The
goserelin, leuprolide,
(FSH) and luteinizing
ever, suppresses the p
ceptors. These agents
breast cancers.

CHELATING AGENTS

Table 12.1 Summa

Drug	ROA*
British Anti-Lewisite; **BAL** (Dimercaprol)	i.m.
Disodium edetate	i.v.
Calcium disodium edetate	i.v. infu

Desferrioxamine (Defero
tive orally as it is poorly
(i.m./i.v.). It chelates iro
iron in haemoglobin or
poisoning (thalassaemia)
acute iron poisoning. It
dialysis.

Adverse Effects. It inclu
ing, flushing and anaph
dysuria, hypotension and
insufficiency. It can cause

Adverse effects

Nephrotoxicity, hepatotoxicity, hypertrophy of gums, hypertension, hyperglycaemia, hyperlipidaemia, hirsutism, increased susceptibility to infections,

Alopecia, cystitis

Diarrhoea, vomiting,
infections (CMV), etc.

	Adverse effects
g	Opportunistic infections

Immunostimulants

They are drugs that enhan
lants and their uses are giv

Table 12.3 **Immun**

Drugs	Uses
Levamisole	As an
Thalidomide	Rheum

Classification

1. Phenols and relate
   nol, cresol, resorcin
   xylenol.
2. Alcohols: Ethyl alcol
   pyl alcohol.
3. Aldehydes: Forma
   glutaraldehyde.
4. Oxidizing agents: H
   ide and potassium p
5. Halogens and hal

- It has keratolytic an
  worm and seborrho

6. **Hexachlorophene**
   - Chlorinated phenol
   - Greater than 2% so
   - Used as an antisep
     rhoeic dermatitis.

Chlorhexidine

- Used as a mouthwash
- Chlorhexidine mouthw
  procedures. It is used a
- Taste alteration and

Oxidizing Agents

They act by releasing nascen

1. **Hydrogen peroxide**
   - Colourless liquid.
   - Effervescence is se
     enzyme catalase, w
   - Used for cleaning wo
   - Can also be used t
     cal prostheses.
2. **Potassium permanga**
   - Dark purple crystal

(b) Mandl's paint
(i) It contains
(ii) Used topic
(c) Lugol's iodine
(i) Contains 5
(ii) Used in th
(d) Iodophores
(i) Act by rele
(ii) Non-irrita
(iii) Used in bu
ments and
(iv) 1% soluti

Dyes

They are used topically as a

- Gentian violet and b
  sores, chronic ulcers,
- Methylene blue is use

Surface Active Agents (Su

They act by lowering the s
surfactants:

1. Anionic surfactants:

(Signs toms)	Uses
ndness of con- and cornea alacia and almia—dry	• Prophylaxis: 4000 IU/day PO • Treatment: 50,000–100,000 IU PO for 3 days

nd

	Uses
s	• Required for patients on regular haemodialysis • Patients with severe vomiting
s, s	• Chronic alcoholics

mia, nd	• Megaloblastic anaemia due to B_{12} deficiency • Pernicious anaemia along with B_1 and B_6 for neuropathies
mia	• Megaloblastic anaemia • Prophylaxis in pregnancy

MINERALS

Minerals are inorganic co
potassium, calcium, magn
hence are *major minerals*.
minute quantities, hence

Sodium

It is widely distributed in

As an antacid and
osmotic purgative (o

Reduces intracranial te
(rectally)

Phosphorus

The important sources of p
The daily requirement of p
tion of bone and teeth al
acid–base balance. *Hypop*
phosphorus, chronic use o
ate), hyperparathyroidism
alcoholism, etc. Clinical f
and bones. It can be treate
tration of phosphorus sal

Mixed Vaccine

Vaccine containing more t
and tetanus toxoid (DPT),

Active Immunization

It can be achieved by ad
production.

Passive Immunization

Measles–Mumps–Rubella

It is a mixed vaccine. It provi
is given intramuscularly. It r

Antisnake Venom Serum F

Snake Bite

1. Hospitalization.
2. Symptomatic treatm
   Paracetamol can be u
   nus toxoid. Immobil

supplied by the sar
pain), capsaicin, tur

6. **Keratolytics**: They a
of the skin, e.g. salic
warts and chronic d
7. **Antipruritics**: These
glucocorticoids, cala

Some of the topical dr
Tables 12.8–12.10.

Table 12.10 Some

Drug	Pr
Ciprofloxacin	0.2
Clotrimazole	1%
Gentamicin	0.3
Betamethasone	0.1
Sodium bicarbonate	5%

Table 12.11 Drugs pedic

Drug	Formulatic
Crotamiton	10% lotion 10% cream

sorption of drugs and
c., i.m. or intra-articularly
rption of extravasated fluid
ematoma or post-operative

e diffusion of local anaesthetic
gy

Table 12.13 Drug

	Emergency condition
1.	Anaphylactic shock
2.	Hypoglycaemia

Table 12.14 Drugs

Topical therapy	
Topical steroids Hydrocortisone, clobetasol, triamcinolone, betamethasone	• Ant imn anti • Low (e.g for • Pot met

Table 12.14 Drugs

Systemic therapy	
Acitretin (oral) Systemic retinoid	• An de • Se ps
Methotrexate (oral)	• De of • Us

A

Abacavir, 472
Abciximab, 323
Abortion, 260
Absorption of drugs, 11, 306
Acarbose, 389
Acebutolol, 103, 108t
Acenocoumarol, 313

Anticonvulsants, 206 *See* Antiepileptic drugs
Antidepressants, 240–241
  atypical, 241
Antidiarrhoeal drugs, 293–295
Antidiuretics, 172–175
Antidiuretic hormone (ADH), 397
Antiemetics, 286–293
Antiepileptic drugs, 206–207
Antifibrinolytics, 321
Antifungal drugs, 495–496t
Antihaemophilic factor, 312

Calcitriol, 395
Calcium, 534
carbonate, 247–248, 534
channel blockers (CCBs), 111
channels, 257
edetate (calcium EDTA), 518
gluconate, 47, 390
lactate, 390, 533
Candidiasis, 469
Capreomycin, 452, 456, 459
Captopril test, 113
Carbachol, 57, 60–61t
Carbamazepine, 201, 208f, 210–211
Carbapenems, 431–432
Carbaryl, 57f

Cross tolerance, 39
Crotamiton, 540t
Cumulation, 36
Curare, also, 68, *see* Tubocurarine
Cutaneous larva migrans, 501, 503
Cyanide poisoning, 129–130
Cyanocobalamin, also, 330, *see* Vit. B_{12}
Cyclic AMP (cAMP), 278f, 279
Cyclic GMP (cGMP), 279
Cyclizine, 165
Cyclooxygenase (COX)

Drug *(Continued)*
efficacy, 360f, 361f
essential, 1
excretion, 20–21
factors modifying action of, 35–39
interactions, 39–40
nomenclature, 2–3
orphan, 2
potency, 33
resistance, 437
routes of administration, 3–9
selectivity, 132
Duloxetine, 241, 224
Dutasteride, 350

Fosphenytoin, 210
Framycetin, 435
Frovatriptan, 256
Frusemide. 167, *See* Furosemide
FSH (Follicle stimulating hormone), 336–337
Fulvestrant, 354
Furazolidone, 498t
Furosemide, 166–167
Fusidic acid, 444
Fusion inhibitor, 476f

Imatinib, 515
Imidazole, 463
Imidazoline, 101
Imipenem, 431
Imipramine, also, 240t,
see Tricyclic
hepatitis B, 477
tetanus, 82
Immunosuppressant drugs,
371–374
in inflammatory bowel
disease, 295–297
in organ transplantation, 519
in rheumatoid arthritis, 273
Implants, 362
Inamrinone. *See* Amrinone

M

MAC (*Mycobacterium avium* complex): drugs for, 410
Mafenide, 412f
Magnesium, 155
  hydroxide, 306
  sulphate, 402
Maintenance dose of drug, 23
Malaria, 481
  drugs for, 481–493
  prophylaxis of, 327
  radical cure of, 490
Malathion, also, 70, *see*

Nitrofurantoin, 449
Nitrofurazone, 524
Nitrogen mustards, 508–509
Nitroglycerine. 126, 128, *See* Glyceryl trinitrate
Nitroprusside sod., 121–122
Nitrous oxide (N_2O), 242
Non-nucleoside reverse transcriptase inhibitors (NNRTIs), 477–478
Nonsteroidal antiinflammatory drugs (NSAIDs), 255
Nootropics, 233
Noradrenaline, 94
Noradrenergic and specific

Phenolphthalein, 298
Phenoxybenzamine, 99f
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