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INTRODUCTION TO PHARMACOLOGY

Learning Objectives

This chapter is designed to enable the learner to understand:

- Principles of pharmacodynamics, pharmacokinetics, classification and the principles of drug administration
- Effect of microsomal enzymes
- Type of drug formulations
- Drug related adverse reaction
- Drug schedules and laws
- Rational use of drugs

Chapter Outline

- Definitions
- Sources of Drugs
- Systems of Measurement
- Terminology Used
- Types of Dosage Forms
- Drugs Classification
- Pharmacodynamics (What the Drug does to the Body)
- Drug Potency and Efficacy
- Combined Effects of Drugs
- Factor Affecting Drug Action
- Adverse Drug Effects
- Pharmacokinetics (What the Body does to the Drug)
- Drug Interactions
- Plasma Half-Life
- Target Concentration
- Routes and Principles of Administration of Drugs
- Indian Pharmacopoeia
- Principle of Therapeutics

1 CASE SCENARIO

Parents came to hospital with a four-year-old child complaining of high-grade fever, cough and breathing difficulty. On examination, the child has tachycardia (HR >110/min), hyperventilation (RR >56/min), mild dehydration and hyperthermia with 104.3°F, on chest examination child had crepitation, wheezing and inspiratory chest indrawing. Acute pneumonia has been made as provisional diagnosis by pediatrician and decide to start an antimicrobial drug therapy. What would be the route of administration of the antimicrobial agent and why can't pediatrician wait for investigational reports?

Pharmacology is one of the basic medical sciences, which deals with the detailed study of various drugs, such as their chemical structure, mode of action, pharmacological effects on various systems, side effects and interactions when two or more drugs are given together.

This subject is the backbone of all the drug treatments that are being used in medical practice.

The first institute of pharmacology was founded in 1847 in Germany by Rudolf Buchheim. Oswald Schmiedeberg is regarded as the 'Father of Pharmacology' due to his extensive contribution in propounding the fundamental concepts in pharmacology.

DEFINITIONS

- **Pharmacology:** It is derived from the Greek word *Pharmacon,* which means *drugs;* and *Logos* which means *study or knowledge*. It deals with the detailed knowledge about drugs including their history, sources, physical, chemical properties and their effects on the various body systems, especially in relation to their effective and safe use for medicinal purposes.
- **Chemotherapy:** The therapeutic treatment of various local or systemic infections/malignancies, by using various drugs or chemicals (natural/synthetic/semisynthetic drugs) is called *chemotherapy*.
- **Drug:** Any substance, which is synthetic, semisynthetic, natural, or biotechnological used for diagnosis, prevention, treatment or cure of a disease or disorder is known as *Drug*. According to WHO's definition, "Drug is any substance or product that is used or is intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient". This term is derived from a French word, *Drogue* meaning a *dry herb.*
- **Pharmacodynamics:** *(What the drug does to the body)*: It is a branch of pharmacology, which deals with the effects of drugs on the different body systems and includes mechanism of action of drugs at the molecular, cellular and organ level.
- **Pharmacokinetics:** (*What the body does to the drug*): It is a branch of pharmacology, which deals with the journey or movements of drug *in, through and out* from the body. In other words, its deals with the scientific study of the administration, absorption, distribution, biotransformation (metabolism), and excretion (AADME) of drugs.
- **Pharmacy:** It is a branch of medical science, which deals with compounding and dispensing of drugs. It also includes preparing suitable dosage forms for administration of drugs to man or animals. It includes collection, identification, purification, isolation, synthesis, standardization and quality control of medicinal substances.
- **Pharmacotherapeutics:** It is a study of appropriate use of drugs in the treatment of various illnesses.
- **Pharmacogenetics/pharmacogenomics:** It is the study of variable effects of drugs on different individuals based upon their genetic constitution. The terms pharmacogenetics and pharmacogenomics can be used interchangeably.
- **Pharmacovigilance:** It deals with the detection, assessment, understanding and prevention of various drug-related problems.
- **Tachyphylaxis:** (*Tachy*: rapid; *Phylaxis*-Protection): when a drug is given repeatedly at shorter intervals, the effect of drug decreases due to development of tolerance. This is called tachyphylaxis.
  Example: Benzodiazepines, opioids analgesics.
- **Toxicology:** It is a study which deals with the toxic effects of various drugs. The drugs behave as poisons if used in higher dosage than prescribed.
- **Teratogenicity:** It is the ability of a drug to produce harmful effect of various drugs on fetus when given in pregnancy.

SOURCES OF DRUGS

The drugs are obtained from various sources. Let us discuss them one by one:

Natural Sources

- **Plants:** The drugs can be obtained from all part of a plant such as roots, stem, leaves and fruits.
- Examples: 1. Dhatura: a source of Atropine 2. Cinchona bark: a source of Quinine
- **Animals and human:** The drugs can be obtained from animals and human beings also.
- Examples: Heparin: liver, insulin from the pancreas of cows and pigs, serum from animal source (horse) and human gonadotropin hormone from pregnant women.
- **Microorganisms:** The bacteria and fungi are also the sources of various drugs, such as penicillin and streptomycin.
- **Heavy metals, minerals and mineral oils**: Aluminium, fluoride, iron, gold and liquids paraffin are also used to treat various conditions (Table 1.1).

Synthetic and Semi-Synthetic Sources

- The drugs synthesized from various chemical substances are called synthetic drugs.

Table 1.1: Medicinal uses of metals

Metals	Medicinal uses
Iron	Treatment of iron deficiency anemia
Calcium	Treatment of diseases due to calcium deficiencies. Such as rickets in children and osteoporosis in adults.
Aluminum and magnesium	As a part of various antacid combinations.
Fluorine	Prevention of dental cavities Prevention of osteoporosis
Radioisotopes	Radioactive Iodine for diagnosis and treatment of various thyroid disorders
Gold	Treatment of rheumatoid arthritis

Examples: paracetamol, aspirin, diclofenac sodium Sulphonamide, calcium channel blockers.

- The drugs obtained by changing the structure of naturally obtained substances are called semi-synthetic drugs.
  Examples: Penicillin, ampicillin, amoxicillin dicloxacillin, etc.

Engineered Sources

Some drugs are obtained by using modern technology methods, such as human insulin by recombinant DNA technology, monoclonal antibodies and various vaccines for rabies and hepatitis, etc.

SYSTEMS OF MEASUREMENT

There are three systems of measurement:

1. Apothecary system
2. Metric system
3. Household system

Apothecary System

- It is the oldest system of measurement.
- This system was based on arbitrary units and later on replaced by metric system.

Metric System

- Invented in France.
- It includes grams and liter as basic units.
- Arabic numerals, fractions and decimal were also included.

Household System

- This is household methods for measuring liquid items.
- The accuracy is not established for measuring medicine and other products but it is still in use.

Table 1.2 shows the systems of measurement:

Table 1.2: Systems of measurement

Metric system	Apothecary system	Household system
1 mL	15–16 minims	15–16 drops
4–5 mL	1 fluid dram	1 teaspoon or 60 drops
15–16 mL	4 fluid drams	1 tablespoon or 3–4 teaspoons
30–32 mL	8 fluid drams or 1 fluid ounce	2 tablespoons
240–250 mL	8 fluid ounces (½ pint)	1 glass or cup
500 mL	1 pint	2 glasses or 2 cups
1 L	32 fluid ounces or 1 quart	4 glasses or 4 cups or 1 quart
1 mg	1/60 grain	—
60–64 mg	1 grain	—
300–325 mg	5 grains	—
1 g	15–16 grains	—
1 kg		2.2 pounds

Contd...

TERMINOLOGY USED

- **Addiction:** The physical and psychological dependence caused by drugs is called addiction.
- **Anaphylaxis:** It is a hypersensitive reaction, which occurs due to ingestion of drugs or any foreign protein material.
- **Antagonist:** The drug which opposes the action of other drugs, when given together or in combination is called antagonist. The net response obtained by the combination of these drugs is always on the lesser side.
- **Antidote:** The drug or chemical which counteracts the harmful effects of another drug or chemical is called antidote.
- **Aqueous solution:** The solution obtained by dissolving one or more drugs in water is called aqueous solution.
- **Brand name:** It is the name given by the manufacturer or pharmaceutical companies to a particular drug and is the trademark or property of that particular company.
- **Capsule:** Solid form of drugs or liquids composed in gelatin cover.
- **Chemical name:** It is the name assigned by the manufacturer to a formula before getting an approved name. It is based on chemical formula of drugs. This is not used in prescriptions.
- **Contraindication:** Any condition or factor, which prevents or withholds the use of medicines/drugs.
- **Dose:** The amount of drug to be administered or given is called dose of that drug. It is usually calculated and written in milligrams. Example, like Azithromycin 500 mg once a day, or Amoxicillin with clavulanic acid (Augmentin) 625 mg thrice a day.
- **Emulsion:** It is the mixture of two immiscible liquids in which droplets of one liquid are dispersed throughout the body of second liquid. Example: Castor oil emulsion.
- **Enema:** This is a liquid preparation, which is administered rectally, for evacuation of the bowel.
  Example: Soap water enema.

- **Generic name:** It is the name by which the drug is known commonly. It is same throughout the world. It is based upon the salt name of a particular drug.
- **Half-life:** It is the time taken for the amount of drug in body to decrease to one half its peak level.
- **Iatrogenic:** The condition or disease, which is physician induced and is due to functional disturbances caused by the drug during treatment and persists even after the offending drug has been withdrawn. Example: Peptic ulcer by NSAIDs.
- **Idiosyncrasy:** It is genetically determined abnormal reactivity to a drug. Every drug has a potential to cause idiosyncratic reaction in the genetically susceptible individuals.
- **Inhalation:** Administering a drug in vapor or gaseous form, through the nose.
- **Loading dose:** Administering drug at a dose higher than the routinely used dose is called loading dose. It is given to achieve the required peak levels in blood.
- **Lotion:** This is usually aqueous solution or suspension intended for local administration. Example: Calamine lotion.
- **Oral administration:** Giving drugs by mouth.
- **Ointment:** This is a semi-solid preparation for external application. Example: Betadine ointment.
- **Parenteral administration:** Drugs, which are given by injection into veins or muscles in various parts in body.
- **Poisoning:** Overdose of a drug that causes damage to multiple body systems and has the potential for fatal reactions.
- **Powder:** It is a dosage form, when a solid drug is given in finely divided powdered state. A simple powder contains one ingredient and a compound powder contains more than one ingredient.
- **Receptor:** It is a macromolecule, which is present on the cell surface or inside the cell and is a site for the drugs to act.
- **Rectal administration:** Route of administering drug via colon or rectum.
- **Response:** It is the effect seen after administering drugs causing improvement of health or decrease in sign and symptoms.
- **Schedule:** It is timing or frequency of administering the drugs to the patients.
- **Side effects:** Any undesirable actions which occurs to the patient after administering the therapeutic dose levels.
- **Sublingual administration:** Route of administering the drug below the tongue.
- **Suspension:** According to **International Union of Pure and Applied Chemistry**, a suspension is dispersion of solid particles in a liquid.
- **Syrup:** This is a concentrated solution composed of sugar and various drugs to treat various conditions. Example: Cough syrup, B-complex syrup.
- **Tablet:** This is a solid disc-shaped form of medication prepared either by molding or compression in a special machine.
- **Therapeutic dose:** A dose of the drug which provide the biological effect for improvement of medical illness.
- **Tolerance:** The progressive decrease in the effectiveness of a drug, due to its repeated use.
- **Vitamin:** These are found in food and it is essential for growth and good health.

Must Know

Commonly used Abbreviations in Prescriptions

- **R_x:** The symbol R is an abbreviation for the Latin word RECIPE, which means take thou or you take. The line on the foot of R is set to designate an invocation to Jupiter, the God of knowledge, learning and healing.
- **Tab:** Tablet
- **Cap:** Capsule
- **Inj:** Injection
- **im:** Intramuscular
- **iv:** Intravenous
- **sc:** Subcutaneous
- **i/d:** Intradermal
- **od:** Once in a day
- **bd/bid:** (Bis in dic): Twice a day
- **tds** (ter in dte sumendum): To be taken thrice a day
- **tid** (ter in die): Three times a day
- **qid** (Quarter in die): Four times a day
- **hs** (hora somni): At bed time
- **stat** (staim): Immediately
- **Rept:** (Repitatur) repeat
- **non rept** (non reptatur): Non repeat
- **ac** (anti-cibum): Before meals
- **pc** (post cibum): After meals
- **npo** (nil per orally): Nothing to taken by mouth
- **bbf:** Before breakfast
- **ad:** After dinner
- **sos:** As and when required

TYPES OF DOSAGE FORMS

- It is the manner in which drug substance are presented in the market (e.g., solids, liquids or semi solids).

Advantage of converting drug to various dosage forms:

- Accurate dosing of drugs can be achieved.
- Optimal drug action.

- Modulate the drug release (Sustained and Controlled release medication).
- Improve patient compliance.
- Protection from gastric juice, e.g., coated tablets, capsules, etc.
- Masking taste and odor (to make palatable).
- Placement of drugs within body tissues.
- Insertion of drugs into body cavities (rectal, vaginal)
- Use of desired vehicle for insoluble drugs.

Classification

- Solid
- Semisolid
- Liquid
- Gaseous

Solid Dosage Forms

- **Powders**: It contains finely divided particles in micron size of drugs.
- **Tablets**: It contains medicaments with or without excipients.
- **Granules**: Aggregate of particles of drugs.
- **Capsules**: Drug enclosed with cylindrical gelatin containers, which alter the taste of drug.
- **Cachets**: Drugs enclosed with wafer sheet of rice.
- **Pills**: Small tablet containing excipients.
- **Lozenges**: It contains sugar and gum used to medicate mouth and throat, which dissolved and release the drugs without altering the taste.
- **Suppositories**: It contains medicament with suitable suppository base that inserted into the body cavities other than mouth, like rectum, nose, ear, and the drug is become liquify at body temperature for desirable effect.
- **Poultices**: Solid dosage form converted to paste-like preparation used externally in the skin to reduce inflammation

Semisolid Dosage Forms

- **Ointments**: Semisolid dosage forms for external use containing with or without medicaments with suitable ointment base.
- **Creams**: Semisolid dosage forms for external use containing with or without medicaments with suitable fatty base.
- **Paste**: Semisolid dosage forms for external use containing high proportion of finely-powdered medicaments with suitable fatty base.
- **Gels**: Transparent semisolid dosage forms for external use containing hydrophilic or hydrophobic base with gelling agents.
- **Poultices**: Semisolid dosage forms for external use containing medicaments applied to the skin to hold the dressing and protective.

Liquid Dosage Forms

- **Collodions**: Liquid preparations for external use having nitro cellulose used to protect the skin.
- **Droughts**: Liquid preparations for oral containing medicaments available in single dose or multiple doses.
- **Elixirs**: Liquid preparation for oral containing medicaments with suitable excipients.
- **Emulsions**: Biphasic liquid dosage form for oral containing medicaments in which fine oil globules dispersed in continuous phase.
- **Suspensions**: Biphasic liquid dosage form for oral containing medicaments in which fine solid particles suspended in continuous phase.
- **Enemas**: Liquid preparation for rectal containing medicaments.
- **Gargles**: Concentrated aqueous solutions for external use used to treat throat infections.
- **Gels**: Aqueous colloidal suspensions containing medicaments used as antacids.
- **Linctuses**: Viscous, liquid oral preparations used to relief cough.
- **Lotions**: Liquid preparations for external application usually applied without friction.
- **Liniments**: Liquid preparations for external application usually applied with friction.
- **Mixtures**: Liquid oral preparations containing one or more medicaments.
- **Mouth washes**: Concentrated aqueous solutions for external use used to treat mouth infections and oral hygienic.
- **Nasal drops**: Liquid preparations containing medicaments that are instilled into the nose with a dropper used to treat nose infections and blockage of nose.
- **Paints**: Liquid preparations for external application to the skin or mucous membrane with soft brush.
- **Solutions**: Clear liquid preparation containing with or without medicaments used to internal or external preparations.
- **Syrups**: Sweet, viscous, concentrated liquid preparations containing with or without sugar and medicaments.

Gaseous Dosage Forms

- **Aerosols**: Suspension of fine solid or liquid particles with gas used to apply drug to respiratory tract having atomizer with in device.
- **Inhalations**: Internal liquid preparations containing medicaments dissolved in suitable solvent or if insoluble suspended in the propellent.
- **Sprays**: Gaseous preparations of drugs containing alcohol applied to mucous membrane of nose or throat with atomizer or nebulizer.

DRUGS CLASSIFICATION

The drugs can be classified into the following categories:

- Prescription or legend drugs
- Nonprescription or over-the-counter (OTC) drugs
- Investigational drugs
- Illicit, or "street" drugs
- Orphan drugs
- Essential drugs

Prescription or Legend Drugs

The drugs, which can be sold to a patient in retail only against a prescription issued by a registered medical practitioner, are called 'prescription drugs. They have been placed in the ***schedule H*** of the Drugs and Cosmetic Rules (1945) in India.

Nonprescription or Over-the-Counter (OTC) Drugs

The drugs, which can be purchased by anybody from the medical store. Such drugs are considered to be relatively safe. Few drugs, like vitamins, paracetamol, aspirin, antacids, laxatives, etc. These drugs can be sold even by grocery stores.

Investigational Drugs

The drugs, which are still in the process of investigation regarding use in human subjects. These drugs are already proven to be effective on animals.

Illicit or Street Drugs

The drugs which cannot be sold legally in any country (e.g. heroin). Illicit drugs usually are used for non-medicinal purposes, generally to alter mood or feeling.

Orphan Drugs

The drugs or biological products, which are meant for diagnosis, treatment or prevention of a rare disease or condition. From the sale of these drugs, pharmaceutical companies may or may not be able to recover the cost of developing and marketing of these drugs.

Examples: Liothyronine (T3), liposomal amphotericin B, miltefosine, rifabutin, somatropin, etc.

Essential Drugs

According to the WHO, essential drugs are defined as "those drugs that satisfy the basic healthcare need of the majority of the population". These drugs should be available at the affordable price, in adequate amounts and at all the times.

In 2017, 20th list of Essential Drugs (1977) has been revised by WHO and 433 medicines have been added to this list and among them 25 drugs were is in fixed dose combination.

India prepared its first *National Essential Drugs List* in 1996 and it was amended in 2011 and 2015. The new list of *National List of Essential Medicines* are categorized and marketed into three level as primary, secondary and tertiary level of health care system with inclusion of 376 medicine and among this medicine 20 are FDC.

1 Case Scenario Explanation

As this child was diagnosed with acute pneumonia with indrawing of chest and increased respiratory rate, these are the red flag sign by Integrated Management of Neonatal and Childhood Illness (IMNC) and the treatment should be started as soon as possible with faster recovery which can be achieved by IV administration of antibiotics. Oral administration will have poor patient acceptance as the child is dull and irritated. Intravenous line also helps to nourish the patient to combat dehydration. Secondly, early start of antibiotics will help to reduce the bacterial load and improve the outcome. Waiting for Lab report to confirm the diagnosis will further deteriorate prognosis.

PHARMACODYNAMICS (WHAT THE DRUG DOES TO THE BODY)

2 CASE SCENARIO

A middle-aged man is brought to the casualty with severe breathlessness. On examination, patient is found afebrile, anxious, tachypnoeic, normotensive and tachycardic. Chest auscultation revealed bilateral wheezing. Provisional diagnosis of bronchial asthma has been made and intramuscular injection of epinephrine was given to relieve the symptoms immediately. After symptomatic improvement of patient, his medical history revealed of having mild hypertension for which propranolol 25 mg OD was given. Treating physician is advised to withdraw propranolol and start verapamil. Why did the treating physician change the medication and why is verapamil better for this condition?

Pharmacodynamics deals with the effects of drugs on the body and includes mechanism of action of drug at the molecular, cellular and organ level. It gives us a detailed view of the dose response relationship of various drugs and also helps us to understand how the action of drugs is modified, when two or more drugs are given together.

Under pharmacodynamics we study:

- Broad principles of drug action
- Therapeutic effects of drugs and their modifications

Broad Principles of Drug Action

The drugs, which are given to the patients, alter the basic physiological processes of the body. Broadly the drugs can control/alter the various body processes by the following principles.

- **Stimulation:** The drugs play a role in increasing the level of activity of specialized cells. Example: Salivary glands are stimulated by pilocarpine, adrenaline stimulates heart, and metoclopramide increases GI motility causing diarrhea.
- **Depression:** The drugs play a role in decreasing the level of activity of specialized cells. Example: Decreased gastric acid secretion by omeprazole, Codeine causes constipation due to depression in peristaltic movements.
- **Replacement:** Some diseases are caused by the deficiencies of certain hormones or some metabolites in the body, which are treated by replacing the deficient enzyme/hormones/metabolites. Example: Thyroid hormone in hypothyroidism, iron in iron deficiency anemia and insulin in diabetes mellitus.
- **Irritation:** Irritating effect of certain drugs are also helpful in therapeutics, such as irritant purgatives increase peristalsis. The various liniments act by irritation/counter irritation mechanisms, thus relieving pain. The decrease or loss of function can be achieved by strong irritation provided by certain drugs resulting in inflammation and morphological damage to the tissues. Example: Necrosis of hemorrhoids with the help of local injections of almond oil and alcohol.
- **Antimicrobial action:** Some drugs act by killing or inhibiting the growth of microorganisms by interfering with various metabolic activities of microbes without affecting the host cell. Example: Ampicillin, azithromycin, acyclovir, etc.
- **By altering the immune system:** The drugs may modulate the immune system by increasing or decreasing the immune status. Example: BCG vaccination, hepatitis vaccination and polio vaccination.

Mechanism of Action of Drugs

The mechanism of action of drugs can be divided into the following types:

Physical

The drug actions are based upon its physical properties.

- Laxative effect of agar, ispaghula, and psyllium seeds due to their mass effect
- Diuretic effect of mannitol due to its osmotic properties
- Soothing effect of pectin due to its demulcent property
- Antifoaming effect of dimethicone.

Chemical

The drug actions are based upon its chemical properties. Examples:

- Oxidizing effect of potassium permanganate
- Chelation by Dimercaprol
- Antacid having properties to decreases acid secretion in to the stomach, used in peptic ulcer disease

Cellular

The drugs act at the level of cell and its organelles, such as:

- Enzymes
- Ions channels
- Receptors
- Transporters
- Others

Enzymes

In the living system, almost all catalytic actions are carried out with the help of enzymes. The drugs may act by stimulation or inhibition of different enzymes depending upon the target cell (Table 1.3).

Table 1.3: Enzymatic receptors and their associated substance

Enzymatic receptor	Associated substance
Tyrosine kinase receptor	Insulin, endodermal growth factor, nerve growth factor, platelets derived growth factor, vascular endothelial growth factor, fibroblast growth factor
Tyrosine kinase associated receptor; tyrosine phosphatase receptor	Prolactin, interleukin-2, cytokines, T-cell, B-cell antigen receptor for depolarization of protein
Serine threonine kinase receptor	Phosphorylation of serine threonine residue
Guanyl cyclase receptor	Phosphorylation of atrial natriuretic peptide

Table 1.4: Differences between competitive and noncompetitive inhibition

Competitive inhibition	Noncompetitive inhibition
Antagonist binds with the same receptor	Binds to another site of receptor
Antagonist resembles chemically with the agonist	Does not resemble
The same maximal response can be attained by increasing dose of agonist (surmountable antagonism)	Maximal response is suppressed (unsurmountable antagonism)
Intensity of response depends on the concentration of both agonist and antagonist	Maximal response depends only on the concentration of antagonist
Examples: ACh—Atropine, Morphine—Naloxone	Diazepam—Bicuculline

Table 1.6: Receptors acting on cell membrane and intercellular receptors

Receptors acting on cell membrane	Intracellular receptors
• Serpentine/seven pass/G protein coupled receptor • Ions channels • Enzyme linked receptor	• Divided into intracytoplasmic and intranuclear • **Intracytoplasmic:** Glucocorticoids, mineralocorticoids, liothyronine (T3), thyroxin (T4), vitamin-D or cholecalciferol • **Intranuclear:** Retinoid, some nucleus of T3 and T4 • **Intracytoplasmic with intranuclear:** Progesterone, estrogen

Abbreviation: GABA, Gamma aminobutyric acid

The inhibition of enzymes may be competitive or noncompetitive in nature.

Differences between the competitive and non-competitive enzyme inhibition are given in Table 1.4.

Ions channels

There are various ions channel located on the cell membrane, which participate in transmembrane signaling process. Example: Sodium channels potassium channels calcium channels, etc. The drugs may act by stimulation or inhibition of different ions channels depending upon the target cell (Table 1.5).

Receptors

These are macromolecules, mostly protein in nature stimulation or inhibition of which causes biological/physiological effects. These are present on cell membrane or intracellularly (Table 1.6).

Table 1.5: Action of various drugs on ion channels

Drugs	Action	Ion channel
Nifedipine	Blocks	L-type voltage sensitive calcium channel
Sulfonylurea	Inhibits	Pancreatic ATP sensitive K^+ channels
Amioderone	Blocks	Myocardial sodium, potassium and calcium channels
Phenytoin	Modulates	Voltage sensitive Na^+ channel
Quinidine	Blocks	Myocardial sodium channel
Mimantine	Blocks	Potassium and magnesium channel post-synaptically

- The drugs may act by stimulation or inhibition of different receptors depending upon the target cell.
- The drug acts only, if it is having affinity for the receptor. As every lock has its own key to open it, similarly every drug acts through a particular receptor.
- Drug receptor combination is responsible for the activity through receptor.
  - **Agonist:** The drug having both affinity and intrinsic activity is called an agonist.
  - **Antagonist:** An agent which does not have any effect of its own, but prevents the action of an agonist on a receptor.
  - **Inverse agonist:** An agent which activates a receptor to produce opposite effect to that of an agonist.
  - **Partial agonist:** An agent which activates a receptor to produce submaximal effect.

Transporters

These are specific carriers present on the cell membrane, which serve the purpose of transporting the substrate across cell membrane in concentration gradient or against the concentration gradient using metabolic energy (Table 1.7).

Others

- **Counterfeit/false incorporation mechanisms:** The artificial analogues of natural substrates, which have no effect on enzymes, ions, receptors or transporters, but are incorporated into specific macromolecules of the cell. It leads to alter the biological activity of cell causing destruction.
  Example: 5-flourouracil increases the mutation rate and chromosomal disturbances-(antineoplastic); Sulfa drugs—nonfunctional folic acid-(bacteriostatic).

Table 1.7: Transporters		
Metabolites	**Transporters**	**Drugs**
Serotonin	Serotonin transporter neuron	Selective serotonin reuptake inhibitor
Dopamine	Dopamine transporter neuron	Amphetamine
Acetylcholine	Choline uptake neuron	Hemicholinium
GABA	GABA transporter GTA1	Tigabine
Noradrenaline	Norepinephrine transporter neuron	Cocaine

- **Protoplasmic poisons:** These drugs act as poisons for the bacteria at their protoplasmic level. Examples: Germicides and antiseptics: phenol, formaldehyde
- **Formation of antibodies:**
  - **Active immunity:** Vaccines: induce antibody formation and stimulate defense mechanisms against the disease. Example: BCG, measles, DPT, hepatitis vaccination.
  - **Passive immunity:** Readymade antibodies (antisera) are injected into the patients for immediate action. Example: antisera against tetanus and diphtheria.
- **Placebo:** Placebo (Latin word) means *I Shall Please.*
  - It is inert and harmless substance, which physically resembles the actual medicine.
  - These are pseudo-drugs made by cellulose.
  - It works at psychological level and not at the pharmacodynamic level.
  - Patient may sometimes feel good on taking these placebo medicines.
  - These agents cause release of endorphins in brain and help to relieve subjective symptoms psychologically.
  - These are used in psychosomatic disorders and in clinical trials.

Therapeutic Effect of Drugs and their Modifications

Whenever drugs are administered to a patient, therapeutic effects are seen. A definite dose-response relationship is seen, which has two components:

1. **Dose: Plasma concentration relationship**
2. **Plasma concentration: Response relationship**

The response is different at different dosage of drugs.

Dose

- Plasma concentration relationship: Dose is the appropriate amount of a drug required to produce a certain degree of response in a given patient. Dose of a drug is governed by its concentration at which it should be present at its target site.

The recommended dose of a drug is based on population data and caters to an average patient. There are different types of dosages required to produce different level of plasma concentration, such as the dose which is same and appropriate for most of the patients is called **Standard dose**. The drugs given as standard dosages have a wide safety of margin. The effects of a drug differ with the different plasma concentrations.

It is the dose which differentiates a drug from a poison.

The plasma concentration of a drug may remain constant or keep on increasing as we go on increasing the dose. It depends upon the kinetics of elimination followed by a particular drug.

Plasma Concentration

Response relationship: Optimum therapeutic response in every disease is obtained by maintaining a particular plasma concentration of a drug for the treatment of a particular disease.

In other words, the therapeutic response changes with the change in plasma concentration of the drugs. The dose of a drug cannot be exceeded from the prescribed limits as it may lead to intolerable adverse effects. Sometimes a compromise has to be made between submaximal therapeutic effect and the tolerable side effects. Example: Anticancer drugs, corticosteroids.

DRUG POTENCY AND EFFICACY

Drug Potency

It refers to the amount of drug needed to produce a certain response. Relative potency is a more meaningful term in which we compare the dose of two similar drugs at which they produce the same response.

Example: 10 mg of morphine produces equal analgesic effect as produced by 100 mg of pethidine. It means that morphine is 10 times more potent than pethidine. Drug potency helps us to decide the dose of a drug.

Drug Efficacy

It refers to the maximum response, which can be elicited by a particular drug.

Example: Aspirin can never achieve the level of analgesic effect, which can be achieved by morphine. This means that morphine is more efficacious than aspirin.

Therapeutic Efficacy

It refers to the degree of relief provided by the drug in the recommended dose range. It is a comparable term between two drugs having similar action.

Example: In case of mixed dyslipidemia, combination of drugs, like statins with fenofibrate is much more beneficial than statins alone. Its means that the therapeutic efficacy is higher in combination therapy than monotherapy of statins.

Therapeutic Index (TI)

It is also called safety margin of a drug. It refers to the ratio of *the dose of drug that causes adverse effects* to that which causes *effective therapeutic effect*.

The therapeutic index is calculated as follows:

TI = LD50/ED50

where TI: Therapeutic Index

LD50: The amount of drug, which is lethal to 50 percent of general population.

ED50: The amount of drug, which is beneficial to 50 percent of general population.

For the drugs with narrow therapeutic index

- The slight deviation from the prescribed dosage can be harmful for the patients.
- The plasma levels monitoring is advocated.

For the drugs with wide therapeutic index

- The deviation from the prescribed dosage may not be harmful for the patients.
- The plasma levels monitoring is not advocated.

The examples of drugs having narrow and wide therapeutic index are given in Table 1.8.

Table 1.8: Therapeutic index of various drugs

Very narrow therapeutic index	Narrow therapeutic index	Wide therapeutic index
• Vancomycin • Amphotericin B • Polymyxin	• Warfarin • Levothyroxine • Carbamazepine • Lithium • Carbonate • Digoxin • Phenytoin • Theophylline • Morphine	• Almost all antibiotics • NSAIDS • Hypnotics/ Sedatives • Beta-blockers • Benzodiazepines

COMBINED EFFECTS OF DRUGS

Most of the times, patients are prescribed two or more drugs simultaneously. This may affect the action of one drug by either increasing or decreasing the effect of another drug. When two or more drugs are given together or one after another, they may exhibit either synergism or antagonism. This is due to interactions at pharmacokinetic or pharmacodynamic level.

Synergism

(Greek: Syn—together; ergon—work)

When the action of one drug is potentiated or increased by the other, they are said to be synergistic.

Synergism can be:

- ***Additive:*** The effect of the two drugs is in the same direction and simply adds up. **(1 + 1 = 2)**
  Effect of drugs X + Y = effect of drug X + effect of drug Y

Must Know

Additive Drug Combinations

- Aspirin + paracetamol as analgesic/antipyretic
- Amlodipine + atenolol as antihypertensive
- Glibenclamide + metformin as hypoglycemic
- Ephedrine + theophylline as bronchodilator

- **Supraadditive (potentiation):** The effect of combination is greater than the individual effects of the components. **(1 + 1 = 11)**
  Effect of drug X + Y > effect of drug X + effect of drug Y

Must Know

Supraadditive Drug Combinations

- Levodopa + carbidopa: Inhibition of peripheral metabolism
- Sulfamethoxazole + trimethoprim: Sequential blockade
- Telmisartan + hydrochlorothiazide: Tackling two contributory factors in the management of hypertension.

Antagonism

(Greek: *Anta—opposite*; *ergon—work*)

When one drug decreases or abolishes the action of another drug, they are said to be antagonistic.

Effect of drugs x + y < effect of drug x + effect of drug.

Depending on the mechanism involved, antagonism may be:

- **Physical antagonism:** Antagonism due to physical property of the drugs.
  Example: adsorption-charcoal adsorbs alkaloids, so used in alkaloidal poisonings.

- **Chemical antagonism:** Antagonism due to the chemical property of the drugs. The two drugs react chemically and the product formed is inactive.
  Examples: Such as titration of acid with base.
  - Chelating agents (BAL, Cal. Disodium edetate) complex toxic metals (arsenic and lead).
  - Potassium permanganate oxidizes alkaloids—used for gastric lavage in poisoning.
  - Nitrites form methemoglobin which reacts with cyanide radicals.
  - Two drugs should not be mixed in the same syringe or infusion bottle as they may react with each other. Example: Thiopentone sod. + Succinylcholine chloride, Heparin + penicillin.
- **Physiological/functional antagonism:** The two drugs may have pharmacological effects in opposite direction due to their overt effects on the same physiological function. The drugs act at different receptors and follow different mechanisms.
  - Glucagon and insulin on blood sugar level.
  - Histamine and adrenaline on bronchial muscles and BP.
- **Receptor antagonism:** Here, one drug (antagonist) blocks the receptor action of the other (agonist).
  Example: Acetylcholine-Atropine, calcium-iron

FACTOR AFFECTING DRUG ACTION

There are multiple factors which directly/indirectly corelated with action of drug.

These are:

- Body surface area/body size gender
- Age
- Gender
- Pregnancy
- Race and species
- Genetics
- Route of administration
- Environmental factors
- Psychological factor
- Pathological states
- Tolerance

Table 1.9 and Figure 1.1 show the factors affecting drug actions and response of drugs respectively.

Table 1.9: Factors affecting drug action

Sl.No.	Factors	Special points
1.	Body surface area/body size	• Body surface area/Body size provide better measurement for drug dose calculation. • Body size is used for dose calculation for obese, child and lean individuals. • The body surface area is more accurate the body size as it includes total body water, extra cellular fluid volume and metabolic activity.
2.	Age	• The dose calculation is different between infants, children and adults. As children's drug dose is calculated by Young's (child dose = age/age + 12 × adult dose) and Dilling's formulas (child dose= age/20 × adult dose). • Similarly, in elder individuals the dose is calculated based upon renal clearance; the renal GFR declines as the age progresses.
3.	Gender	• The administration of drugs among male and female is also different in certain condition; diuretics, methyldopa, β-blockers, clonidine are responsible for sexual dysfunction among males but not among females. Similarly, ketoconazole, spironolactone produces gynecomastia in males but not among females.
4.	Pregnancy	• Administration of drugs during pregnancy is very crucial as majority of drugs crosses placental barrier and cause direct effect to developing fetus. • The high/low concentration, duration of exposure, distribution of drugs may associate with teratogenic effect. • Example: Heparin as anticoagulant used in pregnancy as it does not cross placenta but warfarin also an anticoagulant, crosses placenta and produces teratogenic effect.
5.	Race and species	• The drug action is also dependent upon race and species. Example: As rabbit is resistance to atropine and mice and rats to digitalis. Similarly, in human, the requirement of dose of atropine in lowest among mangos as compare to black individuals.
6.	Genetics	• The genetical alternation (k/a polymorphism) can alter the response of administrated drugs. Example – Low dose of warfarin is required among Asian individuals due to VKORC-1 polymorphism.
7.	Route of administration	• The action of drugs also depends upon their site of action such as magnesium sulfate given through IV route, produces hypotension and sedation, if given by oral route, it produces purgative effect and if applied on the sprains, it reduces swelling.

Contd...

Sl.No.	Factors	Special points
8.	Environmental factors	• Exposure to environmental factors will directly impact with efficacy of given drugs. Example: Individuals with history of tobacco or narcotic intake needs high dose of anesthetics. Similarly, food also interferes with drugs absorption.
9.	Psychological factor	• To achieve desirable effect of drug; patient/individual psychological attitude is also required. Sometime a placebo drug which does not have any active pharmacological ingredient can show therapeutic effect (commonly practice in narcotics dependence).
10.	Pathological states	• Any pathological condition directly related to action of drug. As metabolism takes place mainly in liver and excretion in kidney; therefore, any pathology to kidney and liver will have hazardous outcome.
11.	Tolerance	• The progressive decrease in the effectiveness of a drug, due to its repeated use.

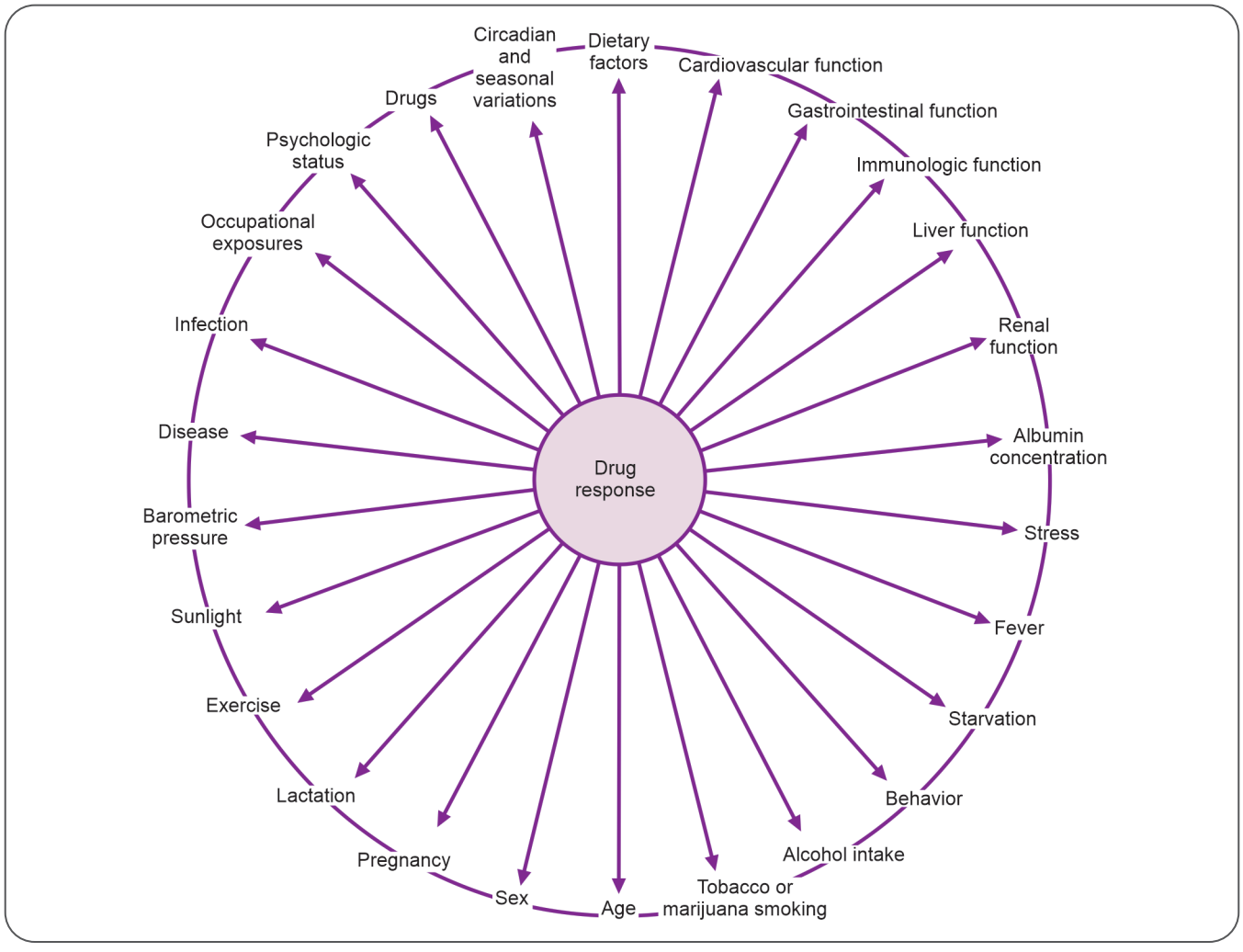

Fig. 1.1: Response of drugs

2 Case Scenario Explanation

Propranolol acts by blocking β-adrenoceptor (non-selective) and prescribed in patient with hypertension. It reduces the cardiac output and vascular resistance by acting on β2 adrenoceptor but also have broncho-constrictive effect on the pulmonary smooth muscle. On the other hand, verapamil, a calcium channel blocker, does not have broncho-constrictive action. β1 adrenoceptor antagonists are more preferred drug in this scenario, such as metoprolol.

ADVERSE DRUG EFFECTS

3 CASE SCENARIO

A 40-year mild obese man had routine health check-up and was found to have low HDL, high LDL and TG for which the treating physician prescribed rosuvastatin 10 mg OD and nicotinic acid 100 mg TDS with regular exercise. After 2 weeks of therapy, patient presented in clinic with complain of itching, red flash on the face and several part on the body with weakness and irritation. The treating physician stopped the nicotinic acid and added fenofibrate 150 mg OD. What could be the proper explanation of this condition and why the doctor changes the drug to fenofibrate?

Drugs are always given for the benefit of patients, but sometimes in addition to the desired effects, some undesirable events are seen in some patients, which may be trivial, serious or even fatal in nature. These undesirable events are called *adverse drug effects*.

Adverse effect is defined as *any undesirable or unintended consequence of drug administration in normally used dosages, and requires treatment or decrease in dose or indicates precaution in the future use of the same drug.*

Nature and severity of adverse drug effect differ with the route of administration employed.

Types

Adverse effects may be divided into:

- **Predictable (Type A or augmented) reactions:** These are also called mechanism-based adverse drug reactions. These are dose related, preventable and usually reversible. These include the side effects of particular drug.
- **Unpredictable (Type B or bizarre) reactions:** These are not based on known actions of drugs but depend upon the different behavior of the patient's body system (genetic basis) to a particular drug. They are not dose related, less common, and generally more serious and mostly require withdrawal of the drug. It includes allergy and idiosyncrasy.

Severity of adverse drug reactions *can be graded as:*

- **Minor:** No treatment, antidote or prolongation of hospitalization is required.
- **Moderate:** Change in drug treatment may be required. Specific treatment is needed for treatment of reaction and hospital stay may be prolonged.
- **Severe:** The reaction is life-threatening, may cause permanent damage and requires intensive medical treatment. Example: Stevens-Johnson syndrome
- **Lethal:** It contributes to death of the patient directly or indirectly. Example: Anaphylactic shock

Side Effects

- These are unavoidable and unwanted pharmacodynamic effects of drug, which occur at routinely prescribed therapeutic doses.
- Generally, these are not serious in nature.
- By reducing the dose, symptoms usually improve.
- These are based on the same action as the therapeutic effect.

Example

- Glyceryl trinitrate relieves angina pectoris by dilating peripheral vasculature and this dilatation is the cause for postural hypotension and throbbing headache, which is seen as a side effect of this drug.
- Atropine is used in preanesthetic medication for its antisecretory action. The same action produces dryness of mouth as a side effect.

Toxic Effects

- When some drug is used for prolonged period or in over dosage, excessive pharmacological action of the drug is seen. Which is termed as toxic effect of that drug.
- The symptoms are predictable and dose related.

Example

- Morphine (opioid analgesic) causes respiratory failure in overdosage.
- Streptomycin (aminoglycoside) causes vestibular damage on prolonged use.

Poisoning

Poison is *any substance which puts the life in danger by severely affecting one or more vital functions of the body*. The drugs, household and industrial chemicals, insecticides, etc. are frequently involved in poisonings. Every drug can behave as a poison, if administered in large dosages. Poisoning causes various harmful and deleterious effects on the human body, which can endanger life if not treated promptly. Example: Wild mushroom poisoning, organophosphorus poisoning.

Must Know

The common treatment guidelines for any poisoning are as follows:

- Resuscitation and maintenance of vital functions (*ABCD*) **A–Airway, B–Blood pressure, C–Cardiac care, D–Uses of drugs.**
- Termination of further exposure.
- To prevent the further absorption of poison.
- To promote elimination of drugs.
- Use of specific antidotes.

Idiosyncrasy

It is abnormal reactivity to a drug, which is genetically determined. This feature is not found in majority of patients and is a rare but important reaction. Every drug has a potential to cause idiosyncratic reaction in the genetically susceptible individuals.

Examples

- In some individual's barbiturates can cause excitement and mental confusion.
- In some individuals, quinine/quinidine can cause cramps, diarrhea, purpura, asthma and vascular collapse.
- Wheat (gluten) hypersensitivity.

Drug Allergy

- It is an abnormal individual immunologic response to a drug.
- It is not related to the pharmacodynamic behavior of the drug.
- It can occur even with very small doses of the drug.
- This is also called *drug hypersensitivity.*
- In drug allergy the skin, airways, gastrointestinal tract, blood and blood vessels are the major organs which are affected.
- Patients are advised to remember the drugs or food items to which they are allergic.
- These drugs or food items should be avoided in future.

Types of Allergic Reactions

Photosensitivity

It is a cutaneous reaction on sun exposure, resulting due to drug induced sensitization of the skin to UV radiation. Example: Sulphonamide, Thiazide, Chloroquine, Fluoroquinolone.

Types of allergic reactions are shown in Table 1.10.

Table 1.10: Types of allergic reactions

Humoral	Cell mediated
Immediate hypersensitivity reaction	Delayed hypersensitivity reaction
It includes: Hypersensitivity reaction-I IgE mediated E.g., wheal and flare reaction, anaphylaxis, atopic dermatitis, etc.	It includes: Hypersensitivity reaction-IV T cell mediated E.g., contact dermatitis, montoux test, multiple sclerosis, etc.

Drug Addiction

An individual likes to take the drug again and again to get the pleasurable effects of the drug. If not taken again, the person feels withdrawal symptoms which force him/her to take the drug again. Examples: alcohol, nicotine.

Physical Dependence

The drug seeking behavior develops in the individual, which is a strong impetus for continued drug use. Example: Amphetamines, cocaine, cannabis, LSD are drugs which produce addiction but little/no physical dependence.

There are specialized de-addiction centers which are helpful in de-addicting the patient.

Teratogenicity

The capacity of a drug to cause various abnormalities in fetus, when given during pregnancy, is called *teratogenicity.* The placenta behaves as an incomplete barrier, and any drug can cross it to a lesser or greater extent if given for a prolonged duration. The drug effects on the fetus are often irreversible and cause various malformations. Examples: The thalidomide disaster (1958–1961) resulting in thousands of babies born with phocomelia (seal-like limbs).

Drugs can affect the fetus at three crucial periods of pregnancy.

1. **Fertilization and implantation:** Conception to 17 days, it causes failure of pregnancy or abortions, which often goes unnoticed.
2. **Organogenesis:** 18–55 days of gestation; it is the most vulnerable period and various deformities occur in the fetus, if exposed to any teratogenic drugs.
3. **Growth and development:** 56 days onwards—Various developmental and functional abnormalities can occur, e.g., NSAIDs may induce premature closure of ductus arteriosus, lithium cause fetal goiter and angiotensin converting enzyme (ACE) inhibitors can cause hypoplasia of organs, especially of lungs and kidneys. Drugs that are safe and contraindicated in pregnancy and drugs contraindicated in lactation are given in Tables 1.11 and 1.12, respectively.

Table 1.11: Drugs that are safe and are contraindicated in pregnancy

Drugs safe in pregnancy (drugs which do not cross placenta)	Drugs contraindicated in pregnancy (drugs which cross placenta) or teratogenic drugs
Heparin	Lithium
Insulin	Ciprofloxacin

Contd...

Drugs safe in pregnancy (drugs which do not cross placenta)	Drugs contraindicated in pregnancy (drugs which cross placenta) or teratogenic drugs
Desmopressin	Tetracycline
Chloroquine	Aminoglycosides
Isoniazid, rifampicin, ethambutol	Angiotensin converting enzyme inhibitors
Methyldopa, hydralazine	Atropine
Acyclovir	Metronidazole
Penicillin	Theophylline
Macrolides, most Cephalosporins	Chloramphenicol
Quinine	Diazepam, corticosteroids
Warfarin (can be given in 2nd trimester)	Phenytoin, valproate
Propylthiouracil	Retinoid, tamoxifen, busulfan

Table 1.12: Drugs contraindicated during breastfeeding

Safe during breastfeeding	Contraindicated during breastfeeding
Propylthiouracil	Antithyroid drugs and radioiodine
Insulin	Lithium
Erythromycin, cephalosporin	Tetracycline
Warfarin	Phenindione
Digoxin	Ergotamine, gold salt
Antacids	Anticancer/cytotoxic drugs, e.g., methotrexate, cyclophosphamide

3 Case Scenario Explanation

This is the case of mixed dyslipidemia where the level of HDL is low and LDL, TG levels were high. In mixed dyslipidemia combination of dyslipidemic agent are generally prescribed. Nicotinic acid (niacin) is greatly improved patients HDL level but it also causes cutaneous vasodilation that can be responsible for these symptoms. These symptoms can be manageable by giving sustained release formulation of nicotinic acid or prescribing aspirin/laropiprant. Fenofibrate is another lipid lowering agent acting by inhibiting PPAR-α.

PHARMACOKINETICS (WHAT THE BODY DOES TO THE DRUG)

4 CASE SCENARIO

- An elderly woman with type-2 diabetes mellitus on second generation sulfonylurea (glibenclamide 5 mg BD). She experiences severe backache for which she took high dose aspirin, after few hours later she developed some sorts of weakness, sweating, palpitation and disorientation of time and place. Her children rushed to her and gave glucose-mixed water following which the symptoms were disappeared. What would be the possible explanation of above this condition? Is there any other drug available to replace aspirin?
- A newly-married female does not want a child for which she was taking OCP (ethinylestradiol 30 µg with levonorgestrel 0.15 mg). Later on, she felt weak, lost 1 kg of weight in past 4 weeks and had some lump in her left axilla for which FNAC was performed. The FNAC was suggestive of extra-pulmonary tuberculosis and she was started with rifampicin 600 mg, isoniazid 300 mg, ethambutol 1 g and pyrazinamide 1.5 g daily for two month followed by rifampicin 600 mg and isoniazid 600 mg thrice weekly. After 4 months of ATT, the menstrual cycle becomes irregular and her urinary pregnancy test becomes positive. What would be possible explanation of failure of contraception and how it can be managed?

It is a branch of pharmacology, which deals with the journey or movement of the drug **in, through and out from the body'**. In other words, its deals with the scientific study of the **absorption, distribution, metabolism (biotransformation), and excretion** (ADME) of drugs (Fig. 1.2).

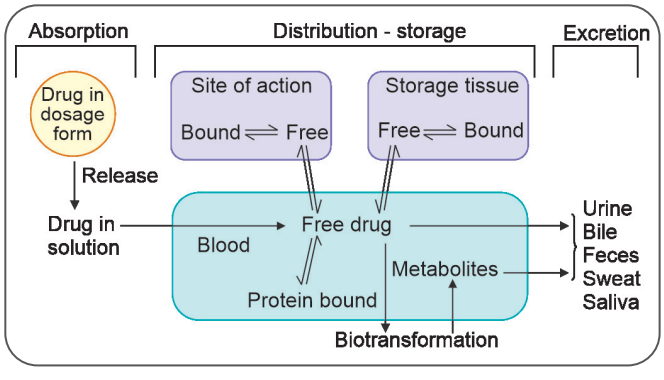

Fig. 1.2: Diagrammatic presentation of pharmacokinetics of a drug

- The transfer of drug from its sites of administration to the blood is called **absorption**.
- Its transfer from blood to tissues is called **distribution**. The drug attains its effective concentration at the site of action and produces its effects.
- Then the drug is metabolized, which is called **metabolism** or **biotransformation**.
- After the drug has done its work, it is to be thrown out of the body. This process is called **excretion**.

Absorption

Absorption is the process by which a drug passes from its site of administration into the blood stream or circulation of the body. From here, the drug moves to its site(s) of action. When given by oral route, absorption is the first step in the passage of a drug through the body. Whereas, it is introduced directly into the bloodstream when given by intravenous administration. Absorption of the drug is 100% when given by intravenous route and always less than 100% when given by intramuscular, subcutaneous or oral route.

Factors Affecting Absorption

- **Drug factors:** Aqueous solubility: The drugs are absorbed in liquid form only. So, the oral drug needs to be converted into liquid form before absorption. Drugs in liquid form are absorbed better. The dissolution and disintegration of a drug are the two important factors, which decide the rate and extent of absorption. Example: dispersible tablets are absorbed and act faster (Fig. 1.3).
- **Dose of drug:** The higher the dose, faster will be the absorption due to the concentration gradient and diffusion thereby.
- **Presence of food**: The presence of food may interfere with the dissolution and absorption of certain drugs, as well as delay the transit time of a drug from the stomach to the small intestine. Some food constituents may form absorbable complexes with the drugs which decrease absorption process. So, most of the drugs are absorbed better if taken empty stomach, **until or unless contraindicated**.
- **Body factors:** Area of absorbing surface: Absorption of the drug is faster, if area of the absorbing surface is more. Vascularity of the absorbing surface: increased blood flow at the site of absorption increases the rate of absorption, similarly as the wet clothes dry faster on exposure to the fast wind.

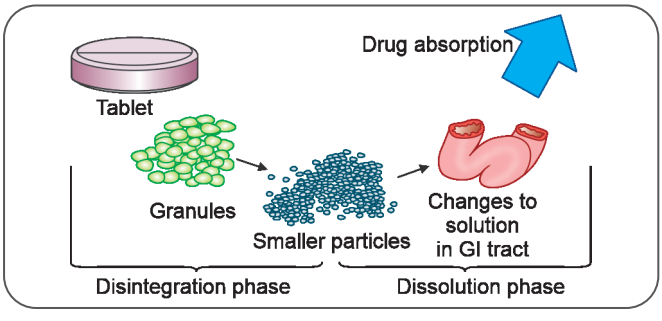

Fig. 1.3: Phases of solid drug absorption

Route of Administration

- **Oral:** The barrier in absorption from this route is the epithelial lining (biological membrane) of GIT. The drugs have to cross the biological membrane, which is a lipid bilayer and allows the more lipid soluble drugs to be absorbed faster.
- **Subcutaneous:** The drugs are deposited in the vicinity of capillaries and absorption occurs through the large paracellular spaces around the capillaries. The large molecules of drugs, which cannot be absorbed through capillaries, are absorbed via lymphatics. The absorption is slightly slower than the intramuscular route.
- **Intramuscular:** The absorption is faster than subcutaneous and more consistent. The muscular exercise and application of heat at the site increases the rate of absorption.
- **Intravenous:** Here the drug is directly put into the circulation and within no time the drug circulates throughout the body.

Bioavailability

- It is a measure or fraction of administered dose of a drug that reaches the systemic circulation in the unchanged or active form.
- Bioavailability of the drug injected intravenously is 100%.
- It is generally lower after oral ingestion because the drug may be incompletely absorbed or undergo first pass metabolism in the intestinal wall and liver.
- Bioavailability after subcutaneous or intramuscular injection is also less than 100% due to the local binding of drugs.
- Bioavailability variations have practical significance for drugs with low safety margin (digoxin) and also where dosage needs fine control (oral hypoglycemic, oral anticoagulants).
- It is also responsible for success or failure of an antimicrobial regimen.

Distribution

Drug distribution is the process by which a drug is carried from its site of absorption to its site of action. When a drug enters the bloodstream, it is carried most rapidly to the organs having rich blood supply, such as the heart, liver, kidneys, and brain. Areas with less blood supply receive the drug slowly, example: Muscle, skin, and adipose tissue.

- The drug remains in the body in bound and unbound (free) form.
- There is always equilibrium between bound and unbound form of the drug.
- The unbound form is the active form of the drug and while in the bound state, the drug is incapable of eliciting a pharmacological effect.
- When a plasma concentration of the unbound drug diminishes, the bound drug is released from its binding sites.
- The acidic drugs preferably bind to albumin and the basic drugs to alfa-acid glycoprotein.
- This protein-binding act as a temporary store house for drugs and also prolongs the drug action and acts like *sustained release technology*.

The distribution of drug depends upon the following factors:

- Lipid solubility and lipid water partition coefficient.
- Ionization at physiological pH
- Extent of binding to plasma and tissue proteins
- Differences in regional blood flow
- Diseases, like renal failure, liver failure, heart failure and cirrhosis of liver.

Some drugs have selective preference for the deposition in the various body tissues, which are important for the clinical as well as toxicological point of view and are given in Table 1.13.

Metabolism (Biotransformation)

It is also called the *biotransformation* of the drug. It is necessary for the elimination of a drug from the body through various excretory routes. To be eliminated from the body by way of the kidneys, a compound must be fairly soluble in water. Because many drugs are not very water soluble, they must first undergo drug metabolism or biotransformation to convert them to a more water-soluble form. In other words, it converts the drug in another form which is excretable.

- Metabolism permits the body to inactivate a potent drug before it accumulates and produces toxic effects.
- Metabolism permits the body to activate the prodrug into its active form.
- Most biotransformation reactions occur in the liver, but they also can occur in the gastrointestinal tract, lungs, kidneys, and skin.

Sites of Metabolism

The primary site is liver. The other sites are kidney, intestine, lungs and blood circulation.

Effects of Metabolism

Metabolism leads to:

- **Inactivation of the active drugs:** Drugs are made inactive or less active. Examples: paracetamol, ibuprofen, propranolol, etc.
- **Activation of the inactive drug:** Some drugs need conversion in the body to active form and are inactive as such. Such a drug is called *prodrug* (Table 1.14).
- **Active metabolites formation from an active drug:** Some drugs are active even after their conversion to their metabolites. These metabolites can also act as the original drug. These are called active metabolites. The effect on the patients is sum total of the effect of drug and its active metabolites.

Table 1.13: Drugs that get deposited in various body tissues

Tissue	Drugs
Bone and teeth	Tetracycline, heavy metals (bound to mucopolysaccharides of connective tissue)
Retina	Chloroquine (bound to nucleoproteins)
Liver	Chloroquine, tetracycline, emetine, digoxin
Thyroid	Iodine
Kidney	Digoxin, chloroquine, emetine
Skeletal muscle, heart	Digoxin, emetine (bound to muscle proteins)

Table 1.14: List of prodrugs

Prodrug	Active form
Acyclovir	Acyclovir triphosphate
Fluorouracil	Fluorouridine monophosphate
Bacampicillin	Ampicillin
Prednisone	Prednisolone
Sulindac	Sulfide metabolite
Enalapril	Enalaprilat
Alfa-methyldopa	α-methyl norepinephrine
Fosphenytoin	Phenytoin

Types of Metabolism Reactions

- **Nonsynthetic/phase I reactions:** A functional group is generated or exposed—metabolite may be active or inactive. The non-synthetic reactions involve oxidation, reduction, hydrolysis, cyclization and decyclization processes.
- **Synthetic/phase II reactions:** *Here the drug or its* phase I metabolites are conjugated with an endogenously derived substrate to form an easily excretable substance. This reaction requires energy. The synthetic reactions involve glucuronide conjugation, acetylation, methylation, sulfate/glycine/glutathione conjugation, etc.

Microsomal and Nonmicrosomal Enzymes

Microsomal Enzymes

- These are located on smooth endoplasmic reticulum.
- Present primarily in liver, kidney, intestinal mucosa and lungs.
- They catalyze the oxidation, reduction, hydrolysis and glucuronide conjugation.
- These are inducible by drugs, diet and other chemicals.
- Example: monooxygenases, cytochrome P450, etc.
- Microsomal enzyme induces and inhibitors are given in Table 1.15.

Table 1.15: Microsomal enzyme inducers and inhibitors

Microsomal enzyme inducer (GARIMAS)	Microsomal enzyme inhibitor
• G—Griseofulvin • A—Anti Epileptics (Phenobarbitone, Phenytoin and carbamazepine) • R—Rifampin • I—Isoniazid • M—Meat • A—Alcohol • S—Smoking • O—Other (Omeprazole, DDT, phenylbutazone,)	• Ketoconazole • Itraconazole • Metronidazole • Valproate • Verapamil • Protease Inhibitor (M/C Ritonavir) • Selective serotonin reuptake inhibitor • Ciprofloxacin • Clarithromycin • Oral contraceptive pills • Cimetidine • Chloramphenicol • Allopurinol • Amiodarone • Erythromycin

Nonmicrosomal Enzymes

- These are located in cytoplasm and mitochondria.
- Present primarily in liver and plasma.
- They catalyze some oxidation, reduction, many hydrolysis and all conjugations except glucuronide conjugation.
- These are not inducible by drugs, diet and other chemicals.
- Example: Esterase's, Amidases, Flavoprotein oxidases and Conjugates.

Some enzymes metabolize specific drugs such as alcohol by dehydrogenase, allopurinol by xanthine oxidase, succinylcholine and procaine by plasma cholinesterase, adrenaline by monoamine oxidase. Sometimes, the same enzyme can metabolize many drugs also.

Microsomal Enzymes Properties

- All antifungal drugs are microsomal enzyme inhibitors except Griseofulvin.
- All antiepileptic drugs are microsomal enzyme inhibitors except Valproate.
- Acute alcoholism is a microsomal enzyme inhibitor, while chronic alcoholism is microsomal enzyme inducer.

Hofmann Elimination

This is the inactivation of drug in the body, where no enzyme is involved in the inactivation of the drug, but spontaneous molecular rearrangement occurs. e.g., atracurium, cistracurium.

First Pass Metabolism

It is the metabolism of a drug at the site of absorption during its passage from the site of absorption into the systemic circulation. All orally administered drugs are exposed to drug metabolizing enzymes in the intestinal wall and liver. This is called *presystemic metabolism* as it occurs before the drug reaches the systemic circulation. It can be avoided by administering the drug through sublingual, transdermal or parenteral routes because the portal circulation is bypassed. The extent of first pass metabolism differs for different drugs and is an important determinant of oral bioavailability. The first pass metabolism is highest, when the drug is given by oral route. Due to this fact oral dose is always higher than sublingual or parenteral dose. Due to differences in the extent of first pass metabolism, the oral dose differs for individual patients. In patients with severe liver disease, the oral bioavailability is slightly increased.

Excretion

Excretion is the process of removing a drug or its metabolites from the body. Drugs and their metabolites may be eliminated from the body in several different ways. Such as in:

- Urine or renal excretion
- Feces
- Exhaled air
- Saliva, sweat and tears
- Breast milk

Urine or Renal Excretion

The substances which are made water soluble after biotransformation can be easily excreted through this route. The nephron is a basic renal unit. Three mechanisms of renal excretion operate simultaneously at the nephron level. These mechanisms are:

1. **Glomerular filtration:** The drug/metabolites/substances, which are smaller in size than the glomerular capillary pores are easily filtered through the glomerulus and reach the proximal tubules. The protein bound drug and bigger molecules cannot be filtered through the glomerulus. Hence, excretion depends upon glomerular filtration rate.
2. **Tubular reabsorption (selective):** The highly lipid soluble drugs are reabsorbed from the proximal tubules. The ionization of a drug also affects this process.
3. **Tubular secretion:** Certain drugs and natural metabolites are actively secreted in the tubule for the purpose of excretion.

We can say that:

Net renal excretion = (glomerular filtration + tubular secretion) -tubular reabsorption

Feces

Both the unabsorbed fraction of a drug and the drugs excreted through bile, are excreted in feces. Example: Erythromycin, OCPs, Ampicillin, etc.

Exhaled Air

The volatile liquids and gases are excreted through this route. Example: Alcohol and anesthetic gases.

Saliva, Sweat and Tears

Lithium and some heavy metals are excreted through this route.

Table 1.16: Kinetics of elimination

First-order kinetics	Zero-order kinetics
Rate of elimination of a drug is directly proportional to its plasma concentration.	Rate of elimination is constant irrespective of its plasma concentration.
Accumulation of drug does not occur	Accumulation of drug occurs
Level of drug remains constant, in spite of increase in dose	Toxicity can occur if dose of the drug is increased
Drug follows first-order kinetics till the saturation of various elimination mechanisms	Drug follows zero-order kinetics after the saturation of various elimination mechanisms
Example: most of the drugs	Example: Phenytoin, Warfarin, Theophylline, Tolbutamide

Breast Milk

More lipid soluble and less protein bound drug are excreted through this route. Example: Tetracycline, Methotrexate, indomethacin, etc.

Kinetics of Elimination is listed in Table 1.16.

4 Case Scenario Explanation

- Aspirin is an NSAID, commonly given for its analgesic, anti-inflammatory and antiplateletic effect. But when it is given with glibenclamide, aspirin removes the binding of glibenclamide with plasma protein as a result, high amount of active glibenclamide into the blood stream will lead to sudden reduction of blood glucose level, and precipitated these signs and symptoms, which are relieved by drinking/ eating glucose containing drinks of foods. Secondly, aspirin can be replaced by other NSAIDs such as Ibuprofen or paracetamol.
- Rifampicin is a potent microsomal enzyme inducer, i.e., it increases the metabolic activity of OCP when given concurrently, resulting early fall of steady-state concentration into the blood before inhibiting ovulation. The best method of contraception in ongoing ATT is use of condom and contraceptive devices. As the female is newly married, female/male condom should be preferred.

DRUG INTERACTIONS

When two drugs are given together, a drug interaction occurs. The pharmacological effects of one drug are potentiated or diminished by another drug. This is due to the interaction at pharmacokinetic or pharmacodynamic level.

If the administration of two or more drugs produces a pharmacological response that is greater than that which would be expected by the individual effects of each drug

together, the drugs are said to be acting synergistically. If one drug diminishes the action of another, it is said to act antagonistically.

- Drug interaction may be synergistic or antagonistic (explained earlier along with synergism/antagonism).
- Drug interactions may be beneficial or harmful:
  - **Beneficial:** For example, the use of a CNS stimulant such as caffeine with an antihistamine that may cause drowsiness as one of its side effects may be a useful drug interaction; the caffeine acts only to counteract the unwanted side effect (drowsiness) of the antihistamine without altering its intended pharmacological action.
  - **Harmful:** The use of an antacid with the antibiotic tetracycline would be likely to result in an undesirable drug interaction. Antacid forms a chemical complex with the tetracycline, thereby rendering it incapable of being absorbed into the bloodstream.
- Drug interactions may occur at any step in the passage of a drug through the body during its administration, absorption, distribution, metabolism, or excretion.
- Interactions may also take place at the receptor site of a drug.
- Drugs may interact with foods, laboratory test substances and environmental pollutants.

PLASMA HALF-LIFE

The plasma half-life (t½) of a drug is the time taken for its plasma concentration to be reduced to half of its original value.

- After 1st t½–50% drug is eliminated.
- After 2nd t½–75% (50 + 25) drug is eliminated.
- After 3rd t½ – 87.5% (50 + 25 + 12.5) drug is eliminated.
- After 4th t½–93.75% (50 + 25 + 12.5 + 6.25) drug is eliminated.

Thus, nearly complete drug elimination occurs in 4–5 half lives.

Half-life of some drugs is as follows:

- Aspirin 4 hours
- Digoxin 40 hours
- Azithromycin >50 hours
- Digitoxin 7 days
- Doxycycline 20 hours
- Phenobarbitone 90 hours

Clinical Implications of Plasma Half-life

Knowledge about the plasma half-life is an important factor which guides us to:

- Determine the frequency of drug administration
- Duration of drug action
- Time of excretion.

TARGET CONCENTRATION

It is the minimum level of plasma concentration of drug which is necessary to get the desired therapeutic effect.

To achieve this target concentration, we need to administer the drug in loading or maintenance dose at right interval of time depending upon the type of drugs and disease the patient is suffering from.

Loading Dose

To attain the target concentration rapidly, sometimes a large single dose or few quickly repeated doses need to be given in the beginning, this is called the *loading dose* of a drug. Example: Digoxin, Chloroquine, Doxycycline etc.

Maintenance Dose

To maintain the target concentration, the dose which is required to be given at specified intervals is called *maintenance dose*. This is always on the lower side than the loading dose. Example: Digoxin, Chloroquine, Doxycycline etc.

ROUTES AND PRINCIPLES OF ADMINISTRATION OF DRUGS

There are various routes available through which the drugs can be administered in the body, for their appropriate action. A detailed knowledge of exact route of drug administration is must for prescribing physician and nurses as well. The responsibility of administering various drugs lies on the shoulders of nurses, when the patient has been admitted indoor, day care centers or as an advisor to the outdoor patients.

The decision about the choice of route in a particular patient lies largely on the patient's requirement, condition as well as the drug preparation available.

The routes of drug administration can be divided into:

- Local routes
- Systemic routes

Local Routes

These routes are used where only the local action is desired keeping in view the patient's conditions, requirements,

convenience and tolerability to systemic drugs. The following are the commonly used local routes for drug administration:

- **Topical:** Here the drug is applied topically/externally on skin and mucous membranes to get the local effects only. The various preparations to be applied on skin and mucous membrane are: creams, gel, ointments, lotion, liniments, paints, jellies, paste, passeries, suppositories, drops, sprays, etc.
- **Local injections:** When we don't want to expose whole of the body to a particular medication. This is unnecessary when the patient is suffering from local disease only. We prefer local injection at a particular site as the drug remains confined to that particular diseased tissue. For example, intra-articular corticosteroid injection in arthritis, intramedullary anti-cancerous drugs in some bone cancers, intrafemoral or intrabrachial anticancerous drug infusion in some limb malignancies.

Systemic Routes

These routes are used, when the systemic action is desired keeping in view the patient's conditions, requirements, convenience and tolerability to systemic drugs**.** The drug administered by systemic routes reaches the blood circulation and it is distributed all over the body tissues including site of its action. The following are the commonly used systemic routes for drug administration.

Oral Route

- It is also called *enteral route*.
- It is the oldest, commonest and considered to be safest route of drug administration.
- Administering drug through this route does not need any assistance for adults. Pediatric and geriatric patients may need assistance.
- The oral formulations are usually cheaper than other formulations.
- The following forms of drugs can be given by oral route: tablets, capsules, spansules, caplets, powders, drops, syrup, gel, mixtures, suspensions, emulsions, elixirs, GITS (gastrointestinal therapeutic system), etc.
    - **Gastrointestinal therapeutic system:** There are some special preparations made for convenient dosing such as slow/sustained/extended/delayed/controlled/continuous release form of capsules or tablets. This is done to delay the absorption of the drug, so that frequency of dosing can be reduced. The enteric coated tablets protect the tablet from the acidic pH (HCl) of the stomach and the drug can safely pass into small intestine for better absorption.
    - Only scored tablets can be broken into the pieces. The unscored tablets should never be broken before administration.

This route is not suitable when:

- The patient is noncooperative, unconscious and vomiting constantly.
- The patient has been brought in emergency.
- The drugs are irritant and nonpalatable. Example: chloramphenicol
- The drugs are destroyed by gastric juice or enzyme. Example: trypsin, chymotrypsin
- The drugs are having high first pass metabolism in liver. Example, Nitroglycerine (GTN)
- The drugs cannot be absorbed, Example: Streptomycin

Sublingual (S/L) Route

- The tablet or pellet containing the drug is placed under the tongue or crushed in the mouth to be spread over the buccal mucosa for absorption.
- Absorption is relatively rapid action can be produced in minutes.
- The drug can be spit out once the desired effect has been obtained.
- Drugs given sublingually are: GTN, buprenorphine, desamino-oxytocin.
- This route is generally employed in emergencies. Example. GTN in myocardial infarction patients.

Rectal Route

- This route is used when the patient is having recurrent vomiting or is unconscious.
- The irritant and unpleasant drugs can be put into the rectum as suppositories or retention enemas for systemic effects.
- The absorption is slow and irregular by this route and the effect is unpredictable.
- Examples: Rectal diazepam for treating epilepsy in children; indomethacin, paracetamol, etc.

Cutaneous Route

- When slow and prolonged absorption of a drug is required for its systemic action, this route is preferred**.**
- The drug has to be highly lipid soluble.
- These drugs are presented in various forms like skin patches, etc.

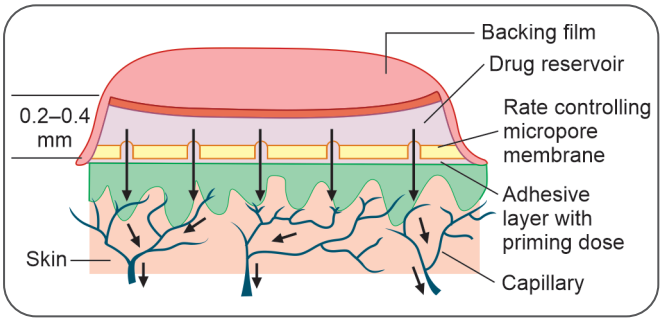

Fig. 1.4: Illustration of a transdermal drug delivery system

Must Know

Transdermal therapeutic systems (TTS): These are devices in the form of adhesive patches of various shapes and sizes (5–20 cm^2), which deliver the contained drug at a constant rate into systemic circulation via the stratum corneum layer of skin. The patch is to be peeled off just before application. The drug is delivered at the skin surface by diffusion for percutaneous absorption into the circulation. The usual sites for applying patches are chest, abdomen, upper arm, lower back, buttock and mastoid regions. Transdermal patches of GTN, fentanyl, nicotine, etoricoxib and estradiol are available in India. TTS (Fig. 1.4) have been designed to last for 1–3 days. Local irritation and erythema can occur in some patients, but is generally mild. This can be minimized by changing the site of application each time by rotation.

Inhalational Route

- Drugs given by this route are absorbed through respiratory tract.
- The drugs are either volatile liquids, aerosol form or gases used to produce general anesthesia.
- This route is also used for the treatment for some local lung diseases.
- Drugs are presented in the form of inhalers, rotahalers and nebulizers.

Parenteral (Par—beyond, Enteral—intestinal)

- It refers to administration of drug by injection.
- The action of the drug is faster and useful in emergency.
- This route is employed in unconscious, uncooperative or patients having vomiting.
- The preparation is costlier and has to be sterilized.
- The technique is painful as it is invasive.

The various parenteral routes are follows:

Intravenous (IV) Route

The drugs are directly injected into the superficial veins in the form of injection or infusion.

Advantages of this route are:

- The drug reaches directly into the blood stream.
- The onset of action is fastest.
- Effects are produced immediately.
- Very useful in emergency.
- The bioavailability is 100%.
- Response is accurately measurable.
- Highly irritant drugs can be injected by this route *as the intima of veins is insensitive to pain and the drug gets diluted with blood.*
- Titration of the dose with the response is possible.

Disadvantages are:

- The technique is invasive and painful.
- The formulations are usually costlier.
- Strict aseptic measures need to be followed.
- Self-administration is usually not possible.
- Once the drug is injected, it cannot be withdrawn.
- Sometimes, thrombophlebitis of the injected vein and necrosis of adjoining tissues can occur if extravasation of the drug occurs. This can be minimized by diluting the drug or injecting it into a running IV line.
- Chances of causing air embolism is another risk.
- The vital organs, like heart, brain, etc. get exposed to high concentrations of the drug, so it can prove to be a risky route also.

Precautions to be taken are:

- Drug sensitivity test should be performed before administration (where indicated).
- Make sure that needle is in the vein by withdrawal methods.
- Drug should be injected slowly.
- Oil-based preparations should not be injected by this route.

Intramuscular (IM) Route

- The site of injection of drug is one of the large skeletal muscles like, gluteus maximus, deltoid, triceps, rectus femoris, etc.
- The drug is deposited in the muscles mass and from there it is absorbed gradually into the systemic circulation taking some time.

- The time taken for action of drug is slightly more than the time taken by the IV route.

Advantages of this route are:

- Muscles are more vascular and absorption of drugs is faster than oral.
- Even the mild irritant drugs can be injected as muscles are less richly supplied with sensory nerves.
- The vital organs, like heart, brain, etc. are not exposed to very high concentrations of the drug.
- Chances of causing air embolism are not there.

Disadvantages are:

- It can produce local hematoma in patients with blood coagulation disorders
- Self-injection impracticable
- Assistance is required in case of children
- Chances of local abscess formations are there, if strict aseptic measures are not followed.
- Inaccurate administration can lead to nerve injury sometimes (sciatic nerve injury).

Subcutaneous (SC) Route

- This route is used where, very prolonged action is required.
- The drug is deposited in the loose subcutaneous area.
- Self-injection is possible because deep penetration is not needed.

Disadvantages are:

- The absorption is slower than intramuscular route as the subcutaneous area is less vascular.
- Irritant drugs cannot be injected as it is richly supplied by nerves.
- Only small volume of the drug can be injected.
- It is not a preferred route in shock patients as the absorption is delayed due to vasoconstriction.
- Preparations are expensive.

Intradermal (ID) Route

- The drug is injected under the epidermis raising a bleb
- This route is employed for specific purposes only.
- Use for sensitivity testing of various drugs such as penicillin testing, Mantoux test.
- Use for BCG vaccination.

The comparative features of different routes of drug administration are discussed in Table 1.17.

Other Routes

- **Intraarterial:** Direct injection in arteries
- **Intracardiac:** Direct injection in chamber of heart
- **Intrathecal:** Direct injection in sub arachnoid space
- **Intraperitoneal:** Direct injection in peritoneal cavity
- **Epidural:** Direct injection in epidural space.

Special Drug Delivery System

Dermojet

In this method, no needle is used. A high velocity jet of drug solution is projected through a micro-fine orifice using a

Table 1.17: Comparative features of different routes of drug administration

Route	Absorption pattern	Special utility	Limitations and precautions
Intravenous	Absorption circumvented Potentially immediate effects Suitable for large volumes and for irritating substances, or complex mixtures, when diluted	Valuable for emergency use; Permits titration of dosage; Usually required for high-molecular-weight protein and peptide drugs	Increased risk of adverse effects; Must inject solutions *slowly* as a rule; Not suitable for oily solutions or poorly soluble substances
Subcutaneous	Prompt, from aqueous solution Slow and sustained, from repository preparations	Suitable for some poorly soluble suspensions and for instillation of slow-release implants	Not suitable for large volumes; Possible pain or necrosis from irritating substances
Intramuscular	Prompt, from aqueous solution Slow and sustained, from repository preparations	Suitable for moderate volumes, oily vehicles, and some irritating substances Appropriate for self-administration (e.g., insulin)	Precluded during anticoagulant therapy; May interfere with interpretation of certain diagnostic tests (e.g., creatine kinase)
Oral ingestion	Variable, depends on many factors	Most convenient and economical; usually safer	Requires patient compliance; Bioavailability potentially erratic and incomplete

gun-like device. The solution gets deposited in the subcutaneous tissue. It is painless method.

Pellet Implantation

The drug is presented in the form of solid pellet. It is introduced surgically with the help of trochar and cannula. The drug keeps on releasing for weeks and month. Example: DOCA, testosterone

Implants

Crystalline drug packed in tube and capsule made of suitable material are implanted under the skin. Uniform and slow a release of a drug occurs for months together.

Liposomes

These are minute vesicles made of phospholipids into which the drug is incorporated. These are used for targeted drug delivery. Example: Some anticancer drug and Amphotericin B.

Monoclonal Antibodies

These are antibodies which selectively react with specific antigen. These are produced using biotechnology and cell culture methods. Type is used for targeted drug delivery. Example: Rituximab. Cetuximab, etc.

INDIAN PHARMACOPOEIA

Pharmacopoeia (*Pharmacon—Drug, Poeia—is to make*) is the official publication, which contains all details about the established drugs, being in use in a particular country. It is one of the official drug information sources. All countries have their own Pharmacopoeias such as Indian Pharmacopoeia (IP), British Pharmacopoeia (BP), United States Pharmacopoeia (USP).

The Pharmacopoeia includes various informations such as:

- Description of chemical structure of drugs
- Physical and chemical characteristic of drugs
- Solubility, identification and assay methods
- Tests for their purity and potency
- Storage conditions
- Dosages, precautions and various indications for use.

First Indian Pharmacopoeia was published in 1868, but could not be followed for long under the British rule. After independence in 1947, a committee, which included experts from pharmaceutical industries, drug control laboratories and medical teaching institutions prepared a fresh Pharmacopoeia and released it in 1955. The pharmacopoeias are revised at regular intervals for adding the new research molecules (drugs) and deleting the harmful and un-useful drugs (proven by evidence-based medicine).

Drug schedules and their related laws are depicted in Tables 1.18 and 1.19.

Legal Issues

- The drug manufacturers have to strictly follow the Pharmacopoeia of a particular country, wherever the manufacturing plant is established. If a particular formula from some other Pharmacopoeia has been followed, they have to mention it on the strips.
- The regulatory authorities check the drug manufacturing units on the basis of Pharmacopoeia.
- The prescribing physicians hardly require Pharmacopoeia for their practical use but they can use it only for the reference purpose.

Table 1.18: Drug schedules and laws

Drug schedules	Definitions
A	• Gives the specimens of prescribed forms necessary for obtaining licenses, permits, certificates, intimations.
B	• This Schedule includes fees for test or analysis by the Central Drug Laboratory or the Government Analyst
C	• Includes biological and special products such as Sera, Vaccines, Antigens, Toxin, Antitoxin, Insulin, Bacteriophages, solution of serum proteins intended for injection, etc. • C_1: Includes Other Special products such as Digitalis Preparations, fish liver oil, ergot preparations, Liver extract, vitamins, hormones, etc.
D	• Provides extent and conditions of exemption regarding import of drugs.
E	• List of poisonous substances under the Ayurvedic (including Siddha) and Unani Systems of Medicine. Such as drugs of Vegetable origin (Bhang, Datura, Jaiphala), drugs of Animal origin (Snake Poison), drugs of Mineral origin [Hartala (arsenic), Parada (mercury)]

Contd...

Drug schedules	Definitions
F	• It includes requirements for the Functioning and operation of a blood bank and/or for preparation of blood components. • F_1: Give details of the standards of bacterial vaccines, antisera and diagnostic antigens. • F_2: Standards for Surgical Dressings that include bandage cloth, absorbent gauze, rolled bandage, etc. • F_3: Standards for Umbilical Tapes like umbilical polyester tape, cotton tape, etc.
G	• Medicines listed as schedule G medicines carry on the label a caution • It is dangerous to take this preparation except under medical supervision" • It is necessary to make proper bill of sale. • Records of purchase and sale of these medicines must be maintained for a period of 2 years. • Examples: Aminopterin, L-Asparaginase, Bleomycin, Busulphan, Chlorambucil, Chlorothiazide, Glibenclamide, Hydantoin, Hydroxyurea, Insulin, Metformin, etc.
H	• This Schedule includes PRESCRIPTION DRUGS, i.e., drugs and medicines which must be sold by retail only when a prescription by RMP is produced. • The time and date of prescription must be noted. • The drug label must display the texts "Rx" and "Schedule H drug. • If the drug is classified as narcotic or psychotropic then Rx should be relabeled to NRx. **Examples:** Abxicimab, Acyclovir, Diclofenac, Baclofen, Carbidopa, Terazosin, Gemifloxacin, Cefixime, Levofloxacin, Cefpodoxime, Clofazimine, Zolpidem, etc.
I	• Particulars as to proportion of poison in certain cases.
J	• Contains a list of various diseases and conditions which a drug may not purport to prevent or cure or make claims to prevent or cure.
K	• Drugs exempted from certain provisions relating to the manufacture and sale of drugs • Non-drug-licensed stores (e.g. nonpharmacists) can sell a few medicines classified as Household Remedies listed in Schedule K.
L	• Good Laboratory Practices and requirements of premises and equipment, chemicals and reagents, etc.
M	• This Schedule includes Good Manufacturing Practices and requirements of premises, plant and equipment for manufacture of pharmaceutical products. • Prescribes in detail requirements of factory premises for the manufacture of homeopathic drugs.
N	• List of minimum equipment for the efficient running of a pharmacy
O	• Deals with the provisions applicable to disinfectant fluids.
P	• It deals with life period of drug and the conditions of the storage of drugs. • P_1: Specifies the pack size of certain drugs, e.g., Aspirin (Low Dose) Tablets 14 Tabs per pack.
Q	• Gives the list of dyes, colors and pigments permitted to be used in cosmetics and soaps. • No drug should contain a colors other than specified by the Bureau of Indian Standards
R	• Standards for mechanical contraceptives, e.g. Cu-T, etc.
S	• Prescribes standard for cosmetics, e.g., skin powders, tooth powder, toothpaste, shaving creams, hair creams
T	• Lays down the good manufacturing practices for Ayurvedic, Siddha and Unani Medicines
U	• Gives the particulars to be shown in manufacturing records (raw materials, analytical records, etc.) and that should be retained for a period of 5 years for Drugs and 3 years for cosmetics from the date of manufacture.
V	• Give details of standards for patent and proprietary medicines.
W	• Gives the name of the drugs which shall be marketed under generic names only. • Inserted as per G.O.I. in 1981 and deleted in 2000.
X	• Contains list of narcotic drugs and psychotropic substance. • Have a warning mentioned on a label "Schedule X drug" Warning : to be sold on retail on prescription of a RMP only. • All the regulations of Schedule H apply. The drugs must be kept under lock and key.
Y	• This Schedule includes requirements and guidelines for permission to import and/or manufacture of new drugs for sale or to undertake clinical trials.

Table 1.19: Drug laws

Drug law	Passed (Yr.)	Definition
Opium Act	1878	This Act is associated with farming and cultivation of poppy and its manufacture, proprietorship, transport, import export, and sale of opium.
Poisons Act	1919	This Act deals with proprietorship, import export, and sale of poison.
Dangerous Drugs Act	1930	• This Act is associated with prohibition of opium farming and sales. • Only GOI has authority for the production, transport of opium.
Drugs and Cosmetics Act	1940	• This Act is associated with regulation of allopathic drugs in India. • Recently, it was amended and also includes Cosmetics, Ayurvedic, Siddha, Homeopathic, and Unani drug regulations.
Pharmacy Act	1948	This Act is used to regulate pharmacy profession in India except Jammu and Kashmir.
Drugs and Magic Remedies (Objectionable Advertisements) Act	1954	This Act is associated to prevent the false/misleading advertisements.
Medical and Toilet Preparations Act	1955	• This Act was used to prevent misuse of many medicinal drugs or substance such as alcohol. • This Act regulated by center and state government. • Government provides the license to the manufacturer for the preparation of spirit containing medicines to reduce the misuse.
Narcotic Drugs and Psychotropic Substances Act	1985	In this Act all narcotic and psychotropic drug manufacturing, farming, transport, import, export, sale, purchase, use is prohibited.
Drug (Price Control) Order	1995	Under this Act center government can control the pricing of any drug and/or drug formulations under Essential Commodities Act.

Rational Use of Drugs

As per the World Health Organization (WHO)—'rational use of medicines requires that the patients receive medication 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 to their community'.

Rational use of medicines requires to closely see every step in the supply-use chain of drugs, i.e., selection, procurement, storage, prescribing, dispensing, monitoring and feedback. For practical purpose the rational prescribing needs to be study in detail.

In simpler terms the rational prescribing is:

- Choosing an appropriate drug
- For an appropriate indication
- In appropriate dose, route and duration
- In an appropriate patient
- With correct dispensing
- Adequate monitoring.

The following irrationalities should be avoided:

- Use of drug when not needed; example antibiotics for viral fevers and nonspecific diarrheas
- Use of drugs, which are not related to the diagnosis, example chloroquine/ciprofloxacin for any fever, proton pump inhibitors for any abdominal symptom.
- Selection of the drug is wrong. Example. Tetracycline/ciprofloxacin for pharyngitis, β-blocker as antihypertensive for asthmatic patient.
- Unnecessary prescription of vitamins/tonics should not be there.
- Doubtful efficacy drugs should not be prescribed. Example. Memory enhancers, cough mixtures, etc.
- Incorrect route of administration; injection when the drug can be given orally.
- Under dosing or over dosing should be avoided.
- Unnecessary prolongation of treatment should be avoided, example prolonged postsurgical use of antibiotics or stoppage of antibiotics as soon as relief is obtained, such as in tuberculosis.
- Unnecessary and compulsive use of drug combinations, example ciprofloxacin + tinidazole for diarrhea; ampicillin + cloxacillin for staphylococcal infection; ibuprofen + paracetamol as analgesic.
- Economical drugs with good efficacy should be preferred as they are equally effective

- There should not be a craze for latest drugs, example routine uses of newer antibiotics.

Rational use by Nurses (Fig. 1.5)

The nurses can add a lot to the rational use of drug by keeping a vigil on the drug in use, such as:

- Generic or brand name as prescribed
- Drug manufacturer
- Date of manufacture
- Expiry date
- Indication
- Drug dose
- Route of administration
- Storage information
- Warning (if any written).

Advantages of Rational Prescribing

- Timely relief and cure of disease
- Minimum adverse drug effects
- Minimum hospitalization
- Decreased morbidity and mortality
- Helpful in preventing microbial resistance
- Minimizing financial loss to the patient/community
- Gain of patient's confidence in the health system
- Strengthening of health standards of patients/community.

PRINCIPLE OF THERAPEUTICS

The following principles should be followed for good therapeutic outcomes:

- Proper diagnosis should be made and therapeutic problem(s) should be identified. E.g., pain, infection, etc.
- We should define the goals to be achieved by treatment. E.g., symptom relief, cure, prevention of complications, etc.
- Selection of the drug capable of achieving each goal should be appropriate.
- It should be based on safety, efficacy and suitability of drug.
- The economical and best suitable drug should be chosen, keeping cost factor in mind, as the paying capacity differs from patient to patient.
- The route, dose and duration of treatment should be decided, keeping the patient's condition in mind.
- The patient should be informed and instructed about the medication properly.
- Adherence/compliance to the medication should be monitored properly.
- Monitor the extent to which therapeutic goal is achieved, example BP lowering, peptic ulcer healing, etc.

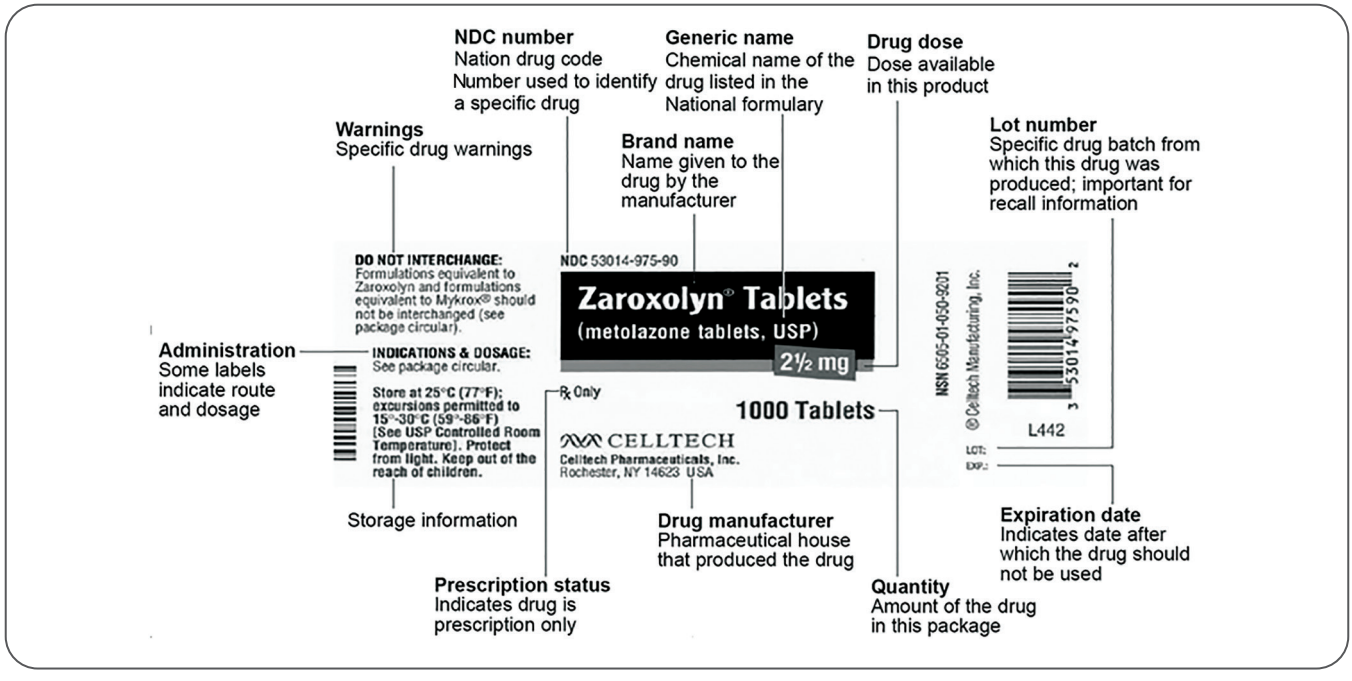

Fig. 1.5: Points to take care by a nurse during rational use of drugs

- The treatment should be reviewed promptly for any change required, keeping in view the latest clinical condition of the patients and therapy should be modified, if needed.
- Monitor adverse drug events, if any, regularly.
- We should try to treat the patient as a whole not the symptoms only.
- The palliative therapy/care should not be denied, if the disease is incurable.
- Morale of the patient should be boosted by regular counselling and psychotherapy.

Nursing Implications

- The different categories of drugs should be stored in different compartments. For example: tablets, liquids, powders, etc.
- The drugs for external use and that for internal use should be kept separately.
- The containers should be arranged alphabetically, so that it is easy to find the required drug.
- All poisonous drugs should be marked "poison" in red ink.
- Emergency drugs should be kept in a place from where they can be obtained readily for emergency use.
- The physician's orders should be read carefully regarding the patient's name, drugs to be given and the dose, route and frequency by which these are to be administered.
- Nurse should also be familiar with the trade names of the drugs and in case of any doubt; she should not hesitate to consult seniors, physicians or medical books.
- Nurse should know all the abbreviations and symbols, as these are frequently used in prescriptions.
- The medicines should be given before or after meals as per the prescription/orders.
- Nurse should stay with the patient until he/she has taken the medication.
- Any error, if occurs during the administration of drug, should be immediately brought in the notice of senior or physicians.
- Do not use the medicine with altered color, odor, consistency or taste and also guide the patients about same.
- Always observe the five rights:
  1. Right patients
  2. Right medicine
  3. Right dose
  4. Right time
  5. Right method of administration.
- Always give the drugs one-by-one.
- The notes about medicine should always be put soon after it has been administered and never before administering it.
- Nurse should be aware of his/her legal responsibilities.

ASSESS YOURSELF

Long Answer Questions

1. What is a drug? Describe the various sources of drugs.
2. Explain the various routes of drug administration.
3. Discuss the factors affecting drug absorption.
4. What are the different roles of nurses in drug administration?
5. What are the advantages and disadvantages of oral route of drug administration?
6. What are the advantages and disadvantages of parenteral route of drug administration?
7. Describe the factors affecting the drug action.

Short Answer Questions

1. Write short notes on:
   a. Pharmacokinetics
   b. Pharmacodynamics
   c. First pass metabolism
   d. Therapeutic index
   e. Competitive antagonism
   f. Synergism
   g. Idiosyncrasy
   h. Loading dose
   i. Prodrug
   j. Teratogenicity
2. What do you understand by the kinetics of elimination?
3. What is a placebo?
4. Enumerate the types of allergic reactions.

Multiple Choice Questions

1. **Alkalinization of urine is required for decreasing the poisoning due to:**
   a. Barbiturates
   b. Amphetamine
   c. Alcohol
   d. Morphine
2. **Which of the following is a prodrug?**
   a. Enalapril
   b. Clonidine
   c. Salmeterol
   d. Acetazolamide
3. **Which of the following drugs is commonly administered by intranasal route?**
   a. Adrenaline
   b. Desmopressin
   c. Ganirelix
   d. Insulin
4. **Which of the following does not induce microsomal enzymes?**
   a. Cimetidine
   b. Griseofulvin
   c. Rifampicin
   d. Phenobarbitone
5. **Loading dose depends on the following factors, except:**
   a. Drug concentration to be achieved
   b. Volume of distribution
   c. Clearance of drug
   d. Bioavailability of drug
6. **An old man enters the hospital with myocardial infarction and a severe ventricular arrhythmia. The antiarrhythmic drug chosen has a narrow therapeutic window. The minimum toxic plasma concentration is 1.5 times the minimum therapeutic plasma concentration. The half-life is 6 hours. It is essential to maintain the plasma concentration above the minimum therapeutic level to prevent a possibly lethal arrhythmia. Which of the following would be the most appropriate dosing regimen?**
   a. Once a day
   b. Twice a day
   c. Four times a day
   d. Constant intravenous infusion
7. **First order kinetics is characterized by:**
   a. Dose-dependent elimination
   b. Decreasing clearance as plasma concentration increases
   c. Increasing the rate of elimination as plasma concentration increases
   d. No relationship between the rate of elimination and plasma concentration
8. **The neurotransmitters; noradrenaline, adrenaline and dopamine act through which of the following receptors?**
   a. Single pass transmembrane receptors
   b. Four pass transmembrane receptors
   c. Seven pass transmembrane receptors
   d. Ligand gated receptors
9. **True statement regarding inverse agonist is:**
   a. Binds to the receptor and causes intended action
   b. Binds to the receptor and causes opposite action
   c. Binds to the receptor and causes no action
   d. Binds to the receptor and causes submaximal action
10. **Drugs that should be avoided in G6PD deficiency are:**
    a. Chloroquine
    b. Quinine
    c. Sulfamethoxazole
    d. Nitrofurantoin
    e. Primaquine
11. **'Drug efficacy' refers to:**
    a. Effectiveness of drugs in life-threatening conditions
    b. The maximal intensity of response that can be produced by the drug
    c. The dose of the drug needed to produce half maximal effect
    d. The minimum dose of the drug needed to produce toxic effect
12. **Therapeutic index is a measure of:**
    a. Safety
    b. Potency
    c. Efficacy
    d. Selectivity
13. **True about orphan drug is:**
    a. Developed for orphans
    b. Drugs used very rarely
    c. Drugs used for rare diseases
    d. Rare drug for common diseases
14. **Which of the following is true about 'placebo'?**
    a. Placebo is a dummy medication
    b. Placebo is the inert material added to drugs for making tablets
    c. Placebos do not produce any effect
    d. All patients respond to placebo
15. **All of the following drugs can cross the placenta; except:**
    a. Phenytoin
    b. Diazepam
    c. Morphine
    d. Heparin
16. **Drugs that can be safely given in pregnancy are:**
    a. Antifolate
    b. Quinine
    c. Chloroquine
    d. Primaquine
    e. Tetracycline
17. **Increase in cAMP is caused by:**
    a. Somatostatin
    b. β (Beta) receptor
    c. α (Alpha) receptor
    d. Acetylcholine

18. As per the Drugs and Cosmetics Act, prescription drugs are included in:
a. Schedule C
b. Schedule H
c. Schedule P
d. Schedule X

19. Usually, healthy human volunteers are taken in:
a. Phase I of clinical trial
b. Phase II of clinical trial
c. Phase III of clinical trial
d. Phase IV of clinical trial

20. A drug that competes for an active biWnding site is called:
a. Competitive inhibitor
b. Non-competitive inhibitor
c. Covalent inhibitor
d. Any of these

21. Bioavailability of a drug is nearly 100% when given by……. route:
a. Oral
b. IV
c. Transdermal
d. Inhalation

22. Tick the prodrug
a. Enalapril
b. Dopamine
c. Nitroglycerin
d. Aspirin

23. Major route of drug elimination is:
a. Biliary
b. Alveolar
c. Renal
d. Dermal

24. Solid drug preparation meant for rectal administration is:
a. Suppository
b. Emulsion
c. Pessary
d. Tablet

25. Maintenance dose is calculated by using value of:
a. Clearance
b. Volume of distribution
c. Oral bioavailability
d. Daily dosage

26. Which among the following is true about rectal route?
a. Used for irritant and unpleasant drugs
b. Cannot be used in unconscious patient
c. There is predictable absorption of drug
d. Diazepam cannot be given via rectal route of administration

27. Drug administered by intranasal route?
a. Adrenaline
b. Desmopressin
c. Ganirelix
d. Insulin

28. Major mechanism of transport of drugs across biological membranes is by
a. Passive diffusion
b. Facilitated diffusion
c. Active transport
d. Endocytosis

Answer Key

1. a.	2. a.	3. b.	4. a.	5. a.	6. d.	7. c.
8. c.	9. b.	10. a, b, c, d, e.	11. b.	12. a.	13. c.	14. a.
15. d.	16. b, c.	17. b	18. b.	19. a.	20. a.	21. b.
22. a.	23. c.	24. a.	25. a.	26. a.	27. b.	28. a