UNIT-I

GENERAL PHARMACOLOGY

INTRODUCTION

Pharmacology is the science that deals with the study of drugs and their interaction with the living systems. The word pharmacology is derived from Greek- 'pharmacon' means drug and 'logos' means study.

DEFINATIONS (Terminology used)

Drug (As per WHO): A drug is any substance or product that is used or intended to be used to modify or explore **physiological** systems or pathological states for the benefit of recipient.

Pharmacokinetics is the branch of science which deals with the absorption, distribution, metabolism and excretion of drugs, i.e. what the body does to the drug.

Pharmacodynamics is the branch of science which deals with the mechanism of action and pharmacological action of drug, i.e. what the drug does to the body.

Therapeutics Index (TI) is the ratio of median lethal dose and effective dose.

$$\text{Therapeutic index} = \frac{LD_{50}}{ED_{50}}$$

Median lethal dose or LD_{50} is the dose which kills half the population of the animal tested.
Median effective dose or ED_{50} is the dose which produces the desire response in the half the animal population tested.
The therapeutics index provides an idea about the safety of the drug.

Pharmacotherapeutics: It is the application of pharmacological information together with knowledge of the disease for its prevention, mitigation or cure

Therapeutics is the branch of science deals with cure or treatment of disease.

Toxicology is the branch of science deals with the poisonous effects of drugs, its detection, diagnosis and treatment.

Chemotherapy deals with the use of chemical substances in the treatment of infectious disease.

SOURCES OF DRUGS

The sources of drugs could be natural or synthetic.

Natural sources

1. Plants: e.g. morphine, atropine, digoxin, quinine
2. Animals: e.g. Insulin, heparin, thyroid extract
3. Minerals: e.g. kaolin, iron, sulphur, radioactive isotopes
4. Marine: e.g. shark liver oil, cod liver oil
5. Microorganism: e.g. penicillins, streptomycin
6. Human: e.g. immunoglobulins, growth hormone, chorionic gonadotrophins

Synthetics Most drugs are now synthesized e.g. omeprazole, paracetamol, asprin. Many drugs are obtained by

Cell cultures e.g. urokinase. Some are now produced by

Recombinant DNA technology e.g. insulin

NATURE OF DRUGS

1. Alkaloidal : atropine quinine morphine
2. Glycocidal: Digoxin, sennoside
3. Resins: oleo-gum resins
4. Tannins: catechu, tannic acid
5. Fixed oils: castor oil, shark liver oil
6. Volatile oil: Clove oil, eucalyptus oil
7. Gums: agar, acacia, tragacanth

ROUTES OF DRUG ADMINISTRATION

The routes can be broadly divided into

1. Topical route
2. Oral route
3. Parenteral route
4. Transmucosal route
5. Novel drug delivery system

TOPICAL ROUTE

Drugs may be used for local applications in the form of dusting powder, lotion, paste, ointments, plasters etc.

Drugs are commonly applied on skin, eye, nose, ear, throat, rectum, vagina.

Merits/Advantages

- Easiest route of drug administration
- Prolonged effect of drug

Demirits/Disadvantages

- Watery soluble drug sometimes absorbed in blood which may lead to an undesirable toxic effect.
- Drugs for corneal application may penetrate and produce irritation, e.g. cocaine

ORAL ROUTE

Drugs are administered in the form of tablets, capsule, and liquid orals with the help of fluids i.e. water or milk.

Advantages

- Oldest and safest route
- Most convenient
- Most economical
- Self-medication is possible
- Withdrawal of drug is possible

Disadvantages

- Onset of action is slow
- Bio-avaibility is not 100%
- Required high dose
- Accuracy of dose is not possible
- Not suitable for uncooperative and unconscious patients
- Irritant and unpalatable drug cannot be administered
- Not suitable in emergency cases

PARANTERAL ROUTE

A. **INJECTIONS:** Drugs are administered by injection which takes the drug directly into the tissue fluid or blood without having to cross the intestinal mucosa.

   Advantages

   - Onset of action is very quick
   - Bioavaibility is 100%
   - Low dose are effective
   - Accuracy of dose is possible.
   - Suitable for uncooperative and unconscious patients
   - Irritant and unpalatable drugs can be given by this route.
   - Suitable for emergency case

Disadvantages

- Risky route
- Inconvenient
- Costly route
- Self-medication is not possible
- Withdrawal of drug is not possible
- Aseptic technique is to be followed to avoid possibility of infection

TYPES OF INJECTION

a) **Intradermal:** Drug is injected in the layer of skin. Only a small quantity can be administered by this route and are made for local effects.

Applications

- Diagnosis of shick test, tuberculosis test
- Introduction of vaccine like BCG
- Hypersensitivity test may be carried out by this route.

b) **Intramascular:** The drug is injected in the layer of muscle tissue. Muscle layer is more muscular and less sensitive so irritant drug is given by this route. IM is suitable for administration of solutions and suspensions

Applications

- Administration of sex hormones, steroids, penicillins etc

c) **Intravenous:** Drug is injected directly into the vein. Large volume parenteral are given by this route. E.g. Dextrose injection, saline injection

d) **Subcutaneous:** Drug is injected at subcutaneous region, lipid soluble drug are injected by this route. Only upto 2ml of drug can be injected by this route. Drugs like adrenaline, morphine, insulinare given through this route.

e) **Intra-arterial:** Drug is injected into an artery. Anticancer drugs are sometimes administered by this route

f) **Intra-thecal:** Drug is administered in the subarachnoid space. E.g. spinal anesthetics.

g) **Intra-peritoneal:** Drug is injected into the peritoneal cavity, by this route fluids like glucose and saline can be given to the children

h) **Intra-medullary:** The drug is directly injected into the bone marrow. This route is useful when veins are not available due to circulatory collapse or thrombosis. In adult sternum is chosen and in children tibia or femur is chosen for injection

B. **INHALATIONS:** Gases, volatile liquids, aerosols and vapors are giving through inhalation.

Advantages

- Rapid onset of action
- The systemic concentration of volatile liquid such as anesthetics can be effectively controlled.

Disadvantages

- Accuracy of dose is not possible
- Local irritation of the respiratory tract, may increase secretions.

TRANS MUCOSAL ROUTE

A. **SUBLINGUAL ROUTE:** Drug is kept below the tongue, allowed to dissolve. Drug mix with saliva and directly inters to the systemic circulation. E.g. Nitroglycerine for Angina pectoris.

   Advantages

   - Onset of action is very quick
   - Bioavailability is 100%

B. **TRANS-NASAL ROUTE:** Drug is used in the form of snuff or nasal spray. The drug is readily absorbed through the mucous membrane of nose.

C. **TRANS-RECTAL ROUTE:** Drugs can be absorbed through the rectum for producing systemic effects. E.g. Diazepam for status epileptics

   Advantages

   - Gastric irritation is avoided
   - Useful in old and terminally ill patients

NOVEL DRUG DELIVERY SYSTEM

A. **OCCUSERT:** Drugs are placed directly under the eyelid. It can release the drugs like pilocarpine for prolonged periods.

B. **PROGESTASERT:** It is an intrauterine contraceptive device. It produces controlled release of progesterone within the uterus for a year.

C. **JET INJECTION:** By using a gun like instrument, the drug solutions are projected as a high velocity jet (dermo jet). The drug solution passes through superficial layer of the skin and gets deposited in the subcutaneous layer.

D. **PRODRUG:** it is an inactive drug which after administration is metabolized into an active drug.

For example, L-dopa after metabolism converted into active Dopamine which is effective in Parkinsonism

L-Dopa ⟶ Dopamine

(Inactive) (Active)

PHARMACOKINETICS

Pharmacokinetics is the branch of science which deals with the absorption, distribution, metabolism and excretion of drug.

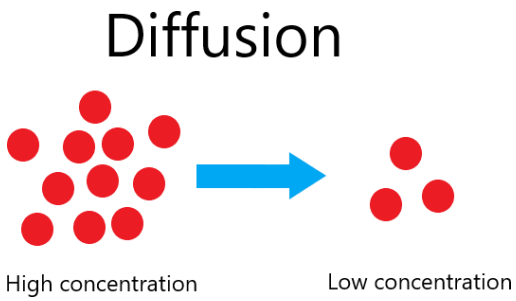
ABSORPTION

Absorption of a drug involves passage of drug across the cell membrane. Absorption involve three process.

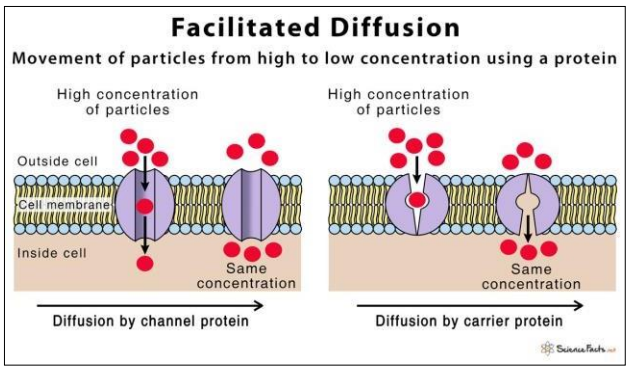
A) **PASSIVE TRANSPORT** The drug moves across the cell membrane without losing energy. They are of two types:

a) **Diffussion**

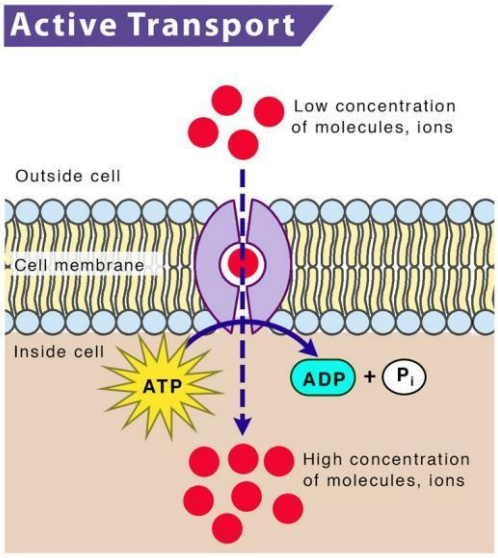
- Diffusion through lipid e.g. lipid soluble drug.
- Diffusion through aqueous channel e.g. water soluble drug.



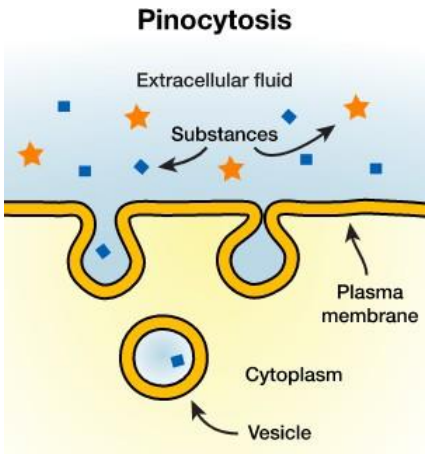
b) **Faciliated transport** Some high molecular drug unable to diffuse through semipermeable membrane like glucose, amino acids. Such substances are attracted by carrier proteins which binds with the drug to be transported. Carrier protein change its shape and deposit the substances to other side.



B) **ACTIVE TRANSPORT** The drug moves across the cell membrane by utilizing energy and sometimes it also required carrier proteins. Only drugs related to natural metabolites are transported by this process, e.g. iron, amino acids, levodopa.



C) **PINOCYTOSIS** The transport of the drugs by formation of vesicles. The protein and macromolecules are transported by this process



FACTORS MODIFYING DRUG ABSORPTION

A) **Physical state:** Drugs in the form of liquids are well absorbed than solids. Crystalloids are more readily absorbed than colloids.
B) **Particle size:** Smaller the particle size better is the absorption.
C) **Concentration:** Higher concentrated form of drugs are quickly absorbed than dilute solutions
D) **Solubility:** Lipid soluble drugs are easily absorbed in compared to water soluble drugs.
E) **Absorbing surface:** Drugs can be better absorbed from the small intestine than from the stomach because of large surface area.
F) **P_H of drug:** Acidic drugs are better absorbed from the stomach, e.g. salicylates. Basic drugs are better absorbed from the intestine, e.g. ephedrine
G) **Ionization:** Unionized drugs are lipid soluble and are well absorbed than ionized drugs
H) **Formulation:** Diluents used in the formulation of drugs may sometimes interfere with absorption, e.g. calcium and magnesium reduce the absorption of tetracycline when used as a diluents.
I) **Diseases:** Disease of guts like malabsorption, diarrhea reduced the absorption of drug.

J) **Presence of other agents:** Vitamin C enhance the absorption of iron, Liquid paraffin reduces the absorption of fat soluble vitamins A, D, E, K.

DISTRIBUTION

After a drug is absorbed, it is distributed to various body tissues and fluids. Drugs which easily pass through cell membrane achieve wide distribution while the drugs which do not easily pass through the cell membrane are limited in their distribution.

After a drug reaches to the systemic circulation, most drug bind to plasma proteins (albumin, alpha-acid glycoprotein) and prolong the duration of action. The free or unbound fraction of drug is only available for action, metabolism and excretion, while the protein bound form serves as a reservoir.

There are some areas in our body where only limited entries for most of the drugs, such areas are

A) **Entry into central nervous system:** Entry of the drug to CNS is limited by **Blood Brain barrier (BBB).** It exist between plasma and extracellular surface of the brain. The barrier is constituted by glial cells and tight junction of capillary endothelium in the brain. Only highly lipid soluble drugs readily pass through this barrier.

B) **Entry into fetal circulation:** Entry of drugs into fetal circulation is restricted by **Blood Placental barrier,**exist between maternal and fetal circulation. It permits only the entry of highly lipid soluble form of drugs.

STORAGE DEPOTS

Some drugs after distribution, get stored in different areas of the body such areas is known as storage depots. Tissue binding delays the excretion and thus prolongs the duration of action of the drug.

	TISSUE (STORAGE DEPOTS)	**BINDING DRUG**
1.	Adipose tissue	Thiopentone sodium, benzodiazepines
2.	Muscles	Emetine
3.	Bone	Tetracycline, heavy metals
4.	retina	Chloroquine
5.	Thyroid	Iodine

METABOLISM

Metabolism or biotransformation is the process of biochemical alteration of the drug in the body. These process convert the lipid soluble drug to water soluble compounds so that they are easily excreted trough the kidneys.

The most important organ of biotransformation is the liver. But drug are also metabolized by the kidney, lungs, blood, skin etc

RESULTS OF BIOTRANSFORMATION

Biotransformation generally inactivates the drugs, but some drugs may be converted to active or more active metabolites as follows:

A) **Active to inactive**

Most of the drugs are active and the metabolite is inactive form

E.g. Phenytoin ⟶ Sulphoxide formation

B) **Active metabolite from active drug**

E.g. Diazepam ⟶ Oxazepam

C) **Active metabolite from inactive drug (prodrug)**

E.g. Levo dopa ⟶ Dopamine

D) **Toxic metabolite from active drug**

E.g. Halothane ⟶ Trifluroacetic acid

METHODS OF BIOTRANSFORMATION

The pathways of drug metabolism can be divided into:

- phase I (Non synthetic reaction)
- phase II (synthetic reaction)

Phase I Includes Simple oxidative, reductive, and hydrolytic reactions.

a) **Oxidation** are the most important metabolizing reactions, occur mainly in liver, and mostly catalysed by mono amino oxygenase present in the liver.

Ethyl alcohol ⟶ Acetaldehyde ⟶ Acetyl CoA

b) **Reduction** is the less common process,drugs like chloramphenicol, halothane are metabolized by reduction.

c) **Hydrolysis** drugs like procaine, acetylcholine are metabolized by hydrolysis.

If the metabolite is not sufficiently water soluble to be excreted, it undergoes Phase II reaction.

Phase II reactions involve covalent attachment of small polar endogenous molecule such as glucuronic acid, sulfate, or glycine to form water-soluble compounds. This is also known as a ***conjugation reaction***.

FACTOR MODIFYING BIOTRANSFORMATION

A) **Inhibitors:** Drug metabolizing enzyme can be inhibited by certain other drugs like omeprazole, ciprofloxacin, leads to the increase in the duration of action.

B) **Stimulators:** Drug metabolizing enzymes can be more activated by certain drugs like phenobarbitone and rifampicin, leads to increase the metabolism of drugs like Phenytoin and warfarin.

C) **Age:** metabolism is poor in young children because of poor development of drug metabolizing enzymes.

D) **Genetic:** Primaquine produces hemolysis in genetic deficiency of enzyme glucose-6-phosphate dehydrogenase (G-6-PD)

E) **Body temperature:** Increase in body temperature increases drug metabolism, whereas decrease in body temperature has the opposite effect.

EXCRETION

Excretion is a process by which inactive metabolite are excreted from the body. The major organs of drug excretion are the Kidney, Skin, Lungs, Saliva, Milk etc

Kidney is the most important organ of drug excretion. E.g. morphine, paracetamol, salicylates, penicillin

Lungs: drugs like general anaesthetics, alcohol are excreted through lungs.

Skin: Heavy metals like arsenic, mercury are excreted through lungs.

Saliva: Drugs like iodides, metallic salts are excreted through saliva.

Milk: Drugs like pethidine are excreted through milk

PHARMACODYNAMICS

Pharmacodynamics deals with the study of actions of the drugs on the body and their mechanism of action. Drugs produce their effects by interacting with the physiological system of the organism and perform various actions such as,

Stimulation: Increases the activity of the specialized cells, e.g adrenaline stimulate heart.

Depression: Decrease the activity of specialized cells, e.g. barbiturates depress the CNS

Replacement: Drugs may be used for the replacement when there is a deficiency of natural substances, e.g. iron in anemia.

Anti-infective: Drugs may be act by destroying infective organisms, e.g. antibiotics

Cytotoxic: Drugs damage the cells, e.g. anticancer drugs

Modification of immune system: vaccine and sera act by improving immune system

SITES AND MECHANISM OF ACTIONS

Drugs may produce localized effects on certain cells, tissues, organs etc or systemic effects on most cells of the body. Drugs may act by one of the following mechanism:

Through receptors: Rantidine, Cimitidine block H_2 receptors and inhibit the gastric acid secretions.

Through pumps: Drugs like Omeprazole, Esinoprazole inhibit the proton pump which is the final step in gastric acid secretion.

Through enzymes: Drugs like Acetazolamide inhibit the enzyme carbonic anhydrase.

Through ion channels: Calcium channel blockers like Nifidipine, Amlodipine, Verpamil, Diltiazem are used in the management of cardio-vascular disorders.

Physical actions: Action of a drug could result from its physical properties.

- Adsorption - activated charcoal in poisoning
- Mass of the drug - laxatives like ispaghula

Chemical interaction: drug may act by chemical reaction.

- Antacids – neutralize gastric acids
- Chelating agents – Bind with heavy metals

Altering metabolic process: Sulphaonamides interfere with bacterial folic acid synthesis.

FACTORS MODIFYING THE ACTION OF DRUGS

The various factors which modify the response to a drug are as follows:

Age:

In newborn, the liver and kidneys are not fully developed, so the pharmacokinetics and Pharmacodynamics of many drugs may be changed resulting in altered response. Hence calculation of the appropriate dose, depending on the body weight is important to avoid toxicity.

Young's formula

(Young's formula)

$$\text{Child dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{adult dose}$$

In the elderly, the capacity of the liver and kidney to handle the drug is reduce, hence lower doses are recommended.

Body weight:

The normal dose is calculated for medium healthy built person, for the obese and underweight persons the dose has to be calculated individually.

Clark's Rule

$$\text{Child's dosage} = \frac{\text{Child's weight in pounds}}{150} \times \text{Adult dosage}$$

Sex:

Due to hormonal effects and smaller body configuration the drug response may influence in women and also special care must take while prescribing for pregnant and lactating women.

Route of administration:

Route of drug administration may modify the drug response, e.g. magnesium sulphate given orally is purgative. But when given I.V. it causes CNS depression and has anticonvulsant activity.

Time of administration:

Drugs which produce nausea, vomiting and irritation should be taken after meal. Sedative and hypnotic drugs are more active at night in compare to day time.

Diet: Food interfere with the absorption of many drugs e.g. tetracycline form with calcium present in food and are poorly absorbed.

Genetic factors: The effect of drugs may vary due to genetic factors, e.g. Primaquine produces hemolysis in individual with a deficiency of Glucose – 6 – Phosphate dehydrogenase.

Accumulation: Drugs like Digoxin are excreted slowly. So repeated administration leads to accumulation of a drug in the body resulting in toxicity. This phenomenon is called as accumulation.

Tolerance: It is the unusual resistance to the normal therapeutics dose of the drug. So large dose is required to produce same effect. Tolerance may be **natural** or **acquired.**

Tachyphylaxis: is the appearance of progressive decrease in response to a given dose after repetitive administration.

e.g. Ephedrine, Amphetamine.

Drug Interaction: When two or more drugs are given concurrently the effects may be additive, synergistic or antagonistic.

- **Additive effect:** the total pharmacological response produce by two drugs is equal to the sum of the individual effects. E.g. ephedrine with theophylline in asthma.
- **Synergism:** When the action of one drug is enhanced by another drug, the combination is synergistic. E.g. levodopa with carbidopa
- **Antagonism:** One drug opposing or inhibiting the action of another drug. Antagonism can be :-
  - **Chemical antagonism:** occurs as a result of chemical interaction between two drugs e.g. BAL in arsenic poisoning
  - **Competitive or reversible antagonism:** Occurs due to competition between two drugs for the same receptor. E.g. acetylcholine and atropine compete at muscranic receptor.
  - **Non-competitive or irreversible antagonism:** Occurs due to the inactivation of receptor by the antagonist. E.g. antagonism of acetylcholine by decamethonium.
  - **Physiological antagonism:** Two drugs act at a different sites to produce opposing effects. For example histamine act on H2 receptor to produce bronchospasm and hypotension while adrenaline reverses these effect by acting on adrenergic receptor