Pharmacology Chapter - 1

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- Bioavailability and the factors affecting bioavailability
- Drug distribution - definition, factors affecting drug distribution
- Biotransformation of drugs - Definition, types of biotransformation reactions, factors influencing drug metabolisms
- Excretion of drugs - Definition, routes of drug excretion

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Introduction Definition And Scope Of Pharmacology

- "Pharmacology" can be defined as the study of interactions between drug and biological system. It can be defined as the science of drugs or study of drug. The word "pharmacology " derived from Greek word.
- Pharmacon – Drug Logos – studied Which means pharmacology is the study of drug and their action of living body. It includes the knowledge of history source, biochemistry and physiological effects, mechanism of action and therapeutic uses of drug.

"Branch of pharmacology"

1. **Pharmacokinetics:–** What body does to the drug. In this the study of the action of drugs on target organ. It deals with the study of absorption, distribution, metabolism, excretion of drugs.
2. **Pharmacodynamics: –** What drugs dose the body. It deals with the mechanism of action and pharmacological effect of drug.

Scope of pharmacology Toxicology:-

- Toxicology is traditionally defined as "the science of poisons." It deals with effect of poisons methods for their detection, diagnosis and treatment.
- Chemotherapy:- It is the branch of pharmacology that deals with drugs, capable of destroying the causative organism without destroying host cells. The mechanism undertaken in chemotherapy.
- Pharmacopoeia :- It is an official code containing a list of selected established drugs and medical preparation with information about their physical property, taste for skin Identity purity and potency.

Ex- Indian pharmacopoeia, British pharmacopoeia, USP.

History of pharmacology:-

1. Francois Magendie (1783-1855):- A French physiologist loid down the dictres "Facts & Facts alone are the basis of science " Experimental procedures with animals are the testing grounds for determination of drug action.

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2. Claude Bernard (1813-1878):- Investigated the plant extract curare and proposal a site of action for this agent.

3. Rudolf Buchheim (1820- 1879):- In 1847 Buchheim established the first laboratory for experimental pharmacology in the basement of his home and named Cradle of experimental pharmacology.

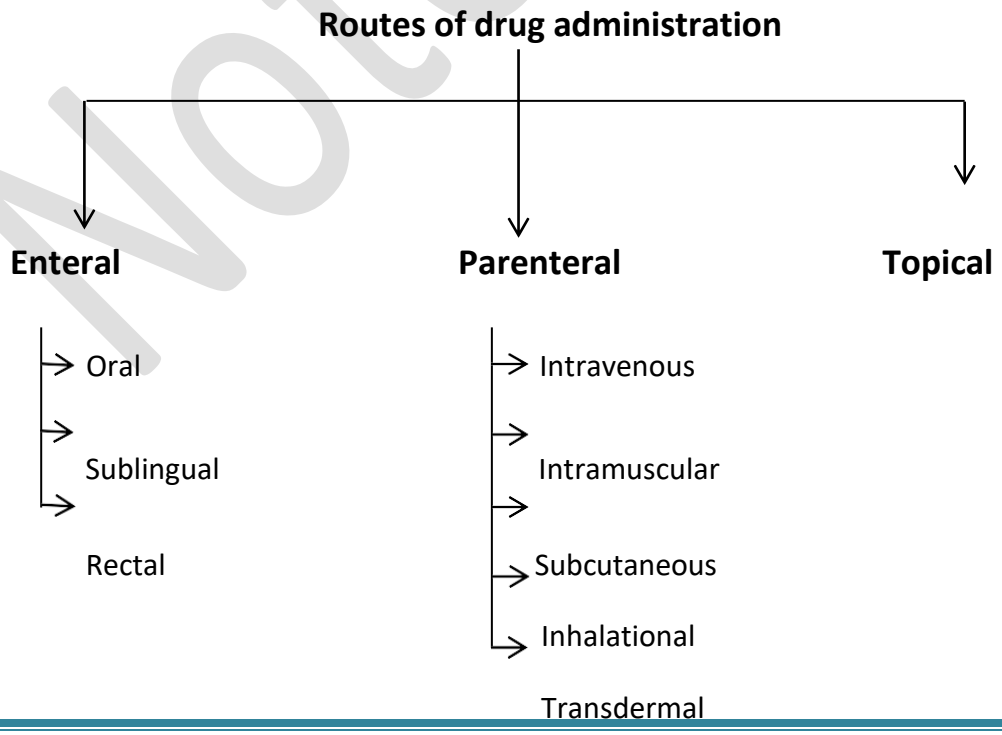
4. Oswald Schmiedeberg (1838-1921):- He is father of pharmacology and publish 1st journal of pharmacology. J.N. Longley (1852- 1925)- Herry dale (1875-1968):- Pioneered pharmacology in England taking physiological approach.

Various Routes of Drug Administration

Routes of administration

Introduction:- **Routes of drug administration** is the path by which the drug is introduced into the body for treatment of disease.

Drugs are available in various form like tablet, Capsule suspension, ointment, Cream, injection etc.



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1. External administration:- This route is best for drug administration unless any specific advantage is desired associated with other delivery route.

a) Oral :- In this route of administration the drug either liquid or solid preparation is placed in mouth cavity is swallowed along with drinks such as water, milk etc.

Advantage:-

- Most of medicinal preparations are consumed orally.
- Economical chance of acute drug reaction.
- Very convenient for children and aged people.

Disadvantage:-

- Sometime inefficient for the patients.
- Irritation to gastric mucosa.
- Can cause Nausea& vomiting.

b) Rectal: - Suppositories/ Enema are drug that are placed in rectal route.

Ex-Aspirin, Theophylline, Chlorpromazine.

Advantage:-

- Useful in the children/ adult.
- Use in the case of vomiting.
- Higher concentration of drug proparty achieved.

Disadvantage:-

- Irritation or inflammation of Rectal mucosa can occur.
- Absorption is slow of this route and Erratic.

Sublingual/ Buccal route

Sublingual:- This dosage form is placed under the tongue and allow to dissolve in the mouth cavity. The drug is absorbed by sublingual mucosa.

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Buccal route:- In buccal route drug kept within the mouth around the cheeks or buccal cavity, where it disintegrates and get absorbed.

Advantage:-

- Rapid absorption of the drug.
- Drugs do not undergo first- pass metabolism.
- Portal circulation is by passed.
- Maintained drug stability.
- No involvement of harsh GI environment.
- Less chance of infection.

Disadvantages:-

- Only small dose can take.
- Sometime complete drug is not absorbed.
- Not effective in emergencies.
- Drug couldn't be administered during emesis.
- Unpleasant teste of drugs.

2. Parenteral Administration:- The route of administration others than the enteral route comes under parenteral route. Parenteral Administration is injection or infusion by means of needle or catheter inserted in the body.

Intravenous (IV) Route

IV is the route of drug administration in which the drugs are administered into the veins. Injection are preferred for orally unabsorbed Drugs like Atracurium (neuromuscular blocker).IV route shows rapid effect the maintains level of drug in circulation.

Advantage:-

- 100% bioavailability.
- It this route shows rapid effect.
- This route is the best in the case of diarrhea and vomiting.

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- Take medicine in large quantities.

Disadvantage:-

- This route is less safe than oral route.
- Technical and trained person required.
- Costly.
- Inconvenient and painful causing irritation, cellulitis and thrombophlebitis.

. ***Intramuscular:-*** In this route the drug is administration into the muscles.

Advantage:-

- Rapid onset of action.
- No G.I.T. related factors.
- Mild irritants can be metabolism.
- The absorption is reasonably uniform.

Disadvantage:-

- Only 10ml of drug is given.
- Local pain cause, Abscess and infection.
- Can cause nervous damage.

Subcutaneous Route (SC)

This route of administration the drug gives under the skin.

Example:- Hormonal drug

(Insulin injection) Advantage:-

- Can be easily self-administering by the patient.
- Complete but slow adsorption.
- Low risk of systematic infection.

Disadvantage:-

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- Maximum 2ml of drug may be injected.
- Less painful then the IV /IM route.
- Irritatant drugs cause tissue damage.

Intara-arterial:-

This route of drug administration the drugs are given into the arteries. Vasodilator, anticancer drugs are given by skin route.

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Intara-arterial:-

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Advantage:-

- Bioavailability 100%.
- It is of great clinical value in administering anticancer drugs.

Disadvantage:-

- Only can used in cancer and vasodilator.
- Painful
- Risky

Inhalation :-

In case of inhalation route drugs are administered either as Aerosol system in the form of vapors

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Drug Absorption

Absorption is movement of the drug from its site of administration into the circulation. Not only the fraction of the administered dose that gets absorbed but also the rate of absorption is important.

Type of Absorption:

1. **Oral :-**

- The effective barrier to orally administered drugs is the epithelial lining of the G.I.T.
- The oral absorption of certain drugs is low because a fraction of the absorbed drug is extruded back into the intestinal lumen by the efflux transporter P-gp located in the gut epithelium.

Example:

1. Non-ionized lipid soluble drug-

- Ethanol are readily absorbed from stomach.

2. Water partition coefficient acidic drugs-

- Solicylates, barbiturates etc.

2. **Subcutaneous and intramuscular:-**

- In these routes the drug is deposited directly in the vicinity of the capillaries.
- Lipid soluble drugs pass readily across the whole surface of the the capillary endothelium.
- Adsorption from subcutaneous site is slower than that from intramuscular site both are generally faster and more consistent predictable than oral absorption.

3. **Topical sites (Skin, cornea, mucous membrane)**

- Drugs are typically applied to the skin when the skin is the desired site of action. In these cases systemic absorption where the drug penetrates beyond the layers of the epidermis to reach the bloodstream is generally not desirable and can cause systemic safety concerns.

Factors affecting drug Absorption:

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1. Routes of administration: This affects drug absorption because each routes has its own peculiarities.

2. Area of absorbing surface:
Large is the surface area, factor is the absorption

3. Aqueous Solubility: Drugs given in solid from must dissolve in the aqueous biophase before they are absorbed.

4. Concentration: Passive diffusion depends on concentration gradient drug given as concentrated solution is absorbed faster than from dilute solution.

5. Vascularity of the absorbing surface:

- Blood circulation removes the drug from the site of absorption and maintains the concentration gradient across the absorption surface.
- Increased blood flow hastens drug absorption as wind hostens drying of clothes.

Bioavailability

- The rate and extent of absorption of a drug from a dosage from administered by any route as determined by its concentration time curve in blood or by its excretion.

- Bioavailability of drug injection I.V is 100% but is frequently lower after oral injection because..

a) The drug may be incompletely absorbed.
b) The absorbed drug may undergo first pass metabolism in the intestinal wall/liver or be excreted in bile.

Factors affecting Bioavailability:

There are various factors which affects the bioavailability of drug.

A. Pharmaceutical factors:

- It is expected that bioavailability of drug to be in this decreasing order.
  Solutions>Suspension>Capsule> Tablet> Coated Tablet.

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- Partical Size
- Salt form
- Crystal Forms
- Natural excipients
- Partition coefficient

B. Pharmacological factors

- Stomach pH
- GI blood flow
- Enzyme
- Endogenous and bacterial
- Drug - Drug interactions
- First pass metabolism

C. Routes of administration

- Parenteral, Oral, Topical, Rectal, Inhalation

Parenteral>Oral>Rectal> Topical

Drug Distribution

- A drug has gained access to the blood stream it gets distributed to other tissues that initially has no drug concentration gradient being in the direction of plasma to tissues.
- The extent of distribution of a drug and it's pattern of tissue distribution depends on its
- Lipid solubility
- Ionization at physiological pH.
- Extent of binding to plasma and tissue proteins.
- Presence of tissue specific transporters
- Differences in regional blood flow.

- Movement of drug proceds until on equilibrium between unbound drug in the plasma and the tissue fluids. Subsequently there is a parallel decline in both due to elimination.

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$$V = \frac{\text{Dose administered I.V.}}{\text{Plasma Concentration}}$$

Where -
V= Apparent volume of distribution.

- Presuming that the body behaves as a single homogeneous compartment with volume V into which the drug gets immediately and uniformly distributed.

Factors affecting drug Distribution:

1. Tissue Permeability of Drugs

a) Physicochemical Properties of drug like:

- Molecular size, pKa, o/w Partition Coefficient

b) Physiological barriers to diffusion of drugs

2. Organ/tissue size and perfusion rate

3. Binding of drugs to tissue components. a) Binding of drug to blood components b) binding of drug to extra cellular components

4. Miscellaneous

- **Age**
- **Pregnancy**
- **Obesity**
- **Diet**
- **Disease states**
- **Drug interactions**

Metabolism/Biotransformation of drugs:-

- Metabolism/Biotransformation means chemical atteration of the drug in the body.

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- It is needed to render non polar (liquid soluble) compound polar (liquid insoluble) so that they are not reabsorbed in the renal tubulars and are excreted.
- The absence of metabolism body will not be able to get rid of lipophilic substances and they will become very long acting.
- The primary site for drug metabolism is liver.

Other are - Kidney, Intestine, lungs, and plasma.

Type of Metabolism/Biotransformation :

1. Inactivation:- Most drugs and their active metabolites are rendered inactive or less active.
Eg. Ibuprofen, paracetamol, lidocaine etc.

2. Active metabolite from an active drugs :

- Many drugs have been found to be properly converted to one or more active metabolite.
- The effects observed are the sumtotal of that due to the parent drug and it's active metabolite.

3. Activation of inactive drugs:

- Few drugs are inactive as such and need conversion in the body to one or more active metabolites such a drug is called a prodrug.
- The prodrug may offer advantages over the active form in being more stable having better bioavailability.

Biotransformation reaction can classified into:

A. Nonsynthetic /Phase I /Functionalization reactions :

- A functional groups (-OH,-COOH,-CHO,-NH2,-SH) is generated or exposed - metabolite may be active on inactive.

B. Synthetic/Conjunction/Phase II reactions:

- An endogenous radical is conjugated to the drug - metabolite is mostly inactive. Except few drugs.

e.g. glucuronide conjugate of morphine and sulfate conjugate of minoxidil are active.

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FACTORS AFFECTING DRUG METABOLISM:-

1. Age differences

2-Species and strain differences

3- Sex differences

4- Enzyme induction

5- Enzyme inhibition

6-Stereochemical Aspects of Drug metabolism

Excretion

- Excretion is the passage out of systemically absorbed drug. Drugs and their metabolites are excreted in:

Routes of Excretion:

1. **Urine:** Drug excretion in urine occurs via the kidney. It is the most important channel of excretion for majority of drugs.
2. Faeces:
   - Apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile.
   - Liver actively transports into bile organic acids (especially drug glucuronides by OATP and MRP2), organic bases (by OCT), other lipophilic drugs (by P-gp) and steroids by distinct nonspecific active transport mechanisms.
   - Relatively larger molecules (MW > 300) are preferentially eliminated in the bile.
   - Most of the free drug in the gut, including that released by deconjugation of glucuronides by enteric bacteria is reabsorbed (enterohepatic cycling) and ultimate excretion occurs in urine.
   - Only the remaining is excreted in the faeces. Enterohepatic cycling contributes to longer stay of the drug in the body.
   - Drugs that attain high concentrations in bile include erythromycin,

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ampicillin, rifampin, tetracycline, oral contraceptives, vecuronium, phenolphthalein.Certain drugs are excreted directly in colon,
e.g. anthracene purgatives, heavy metals.

3. **Exhaled air:**

- Gases and volatile liquids (general anaesthetics, alcohol) are eliminated by lungs, irrespective of their lipid solubility.
- Alveolar transfer of the gas/vapour depends on its partial pressure in the blood.
- Lungs also serve to trap and extrude any particulate matter that enters circulation.

4. **Saliva and sweat:**

- These are of minor importance for drug excretion. Lithium, pot. iodide, rifampin and heavy metals are pres ent in these secretions in significant amounts.
- Most of the saliva along with the drug in it, is swallowed and meets the same fate as orally taken drug.

5. Milk:

- The excretion of drug in milk is not important for the mother, but the suckling infant inadvertently receives the drug. Most drugs enter breast milk by passive diffusion. As such, more lipid soluble and less protein bound drugs cross better.
- Milk has a lower pH (7.0)

General mechanisms of drug action and factors modifying drug action

General mechanisms of drug action:

- Pharmacodynamics is the study of drug ef fects.
- It starts with describing what the drugs do, and goes on to explain how they do it. Thus, it attempts to elucidate the complete action-effect sequence and the dose-effect relationship.

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- Modification of the action of one drug by another drug is also an aspect of pharmacodynamics.

1. Body size
2. Age – pediatric & geriatric
3. Sex
4. Species and race
5. Genetics –P'genomics and P'genetics
6. Routes of drug administration
7. Pregnancy & Lactation
8. Physiological states– GI diseases,congestive heart disease, thyroid disease, kidney & liver disease
9. Diet &Environmental factors
10. Psychological factors
11. Cumulation
12. Tolerance & resistance

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