A CONCEPTUAL DISCUSSION ON PHARMACOKINETICS

Abstract

This chapter provide about the fundamental knowledge of pharmacology, pharmacokinetics and pharmacodynamics and discussed in detail about the knowledge of many aspects of pharmacokinetics or drugs utility that means after entry of drugs or any xenobiotic, how they absorbed, their metabolism, distribution and how they are excreted all are discussed here. Besides, what are the factors involved in drug utility, different routes of drugs entry and which routes is better for therapeutic action, their bioavailability, plasma protein binding, blood-brain barrier and how they influence drugs distribution, drugs and their metabolism and significance, finding organ, involving enzyme, process of excretion, renal clearance, elimination kinetics, order of kinetics etc. This is comparatively rigid chapter, do not easy to digest. So, study properly to enrich yourself and to boost your creative thinking.

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I. OVERVIEW OF PHARMACOLOGY

The term pharmacology was coming from two Greek words. One is known as pharmacon that means drugs and another is logos that mean discussion or knowledge. So, pharmacology means the scientific study of drugs. In detail, it refers the discovery of drugs, their properties and their mechanism of action and effect on living system. For thousands years ago the composition any many other properties are unknown to us but due to development of science, all the pharmacological properties with a vast variety, selective, purified and potent drugs have been discovered. So, pharmacology is one of the most important biomedical sciences in health sciences to characterize and understanding therapeutic drugs and drug treatment with safety measures. Pharmacology can be broadly divided into two branch named as pharmacodynamics and pharmacokinetics.

Pharmacodynamics deals the effect of drugs to the body with suitable mechanism at molecular, cellular or tissue levels whereas Pharmacokinetics refers how body handle the drugsthat means it indicate the absorption, distribution, metabolism and excretion of drugs by the body. Pharmacology also applied in other field like chemotherapy, toxicology, pharmacy etc. [1][2][3]

II. CONCEPT OF PHARMACOKINETICS

Pharmacokinetics is a branch of pharmacology. Pharmacokinetics (Greek: kinesis-movement) deals as the quantitative study of drugs movement in the body over a period of time and also alteration of drugs in the body. It deals absorption, distribution, binding/ localization, storage, biotransformation/ metabolism and excretion of the drugs by the body or, simply it is referred as ADME (A=absorption, D=distribution, M= metabolism, E= excretion). There are many routes of drugs entry in our body that may be ingestion, inhalation, penetration, injection though absorption rate are not same in all routes. The rate of absorption is high in case injection of drugs in comparison to all other route as injection of drugs direct contact to the circulation. After action drugs are excreted through various routes also like saliva, urine, bile, faeces, sweat etc. (see fig: 1). [1][2][3].

1. Pharmacokinetics

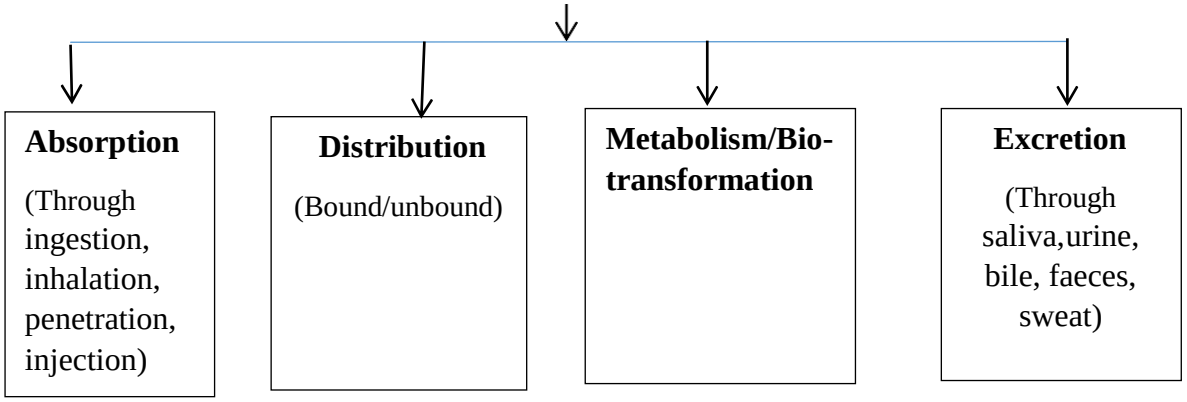

Figure 1: Schematic Diagram of Pharmacokinetic Processes

All the pharmacokinetics process involves transport of drugs across a biological membrane.

Depending upon the chemical properties of drugs, drugs transports across the plasmamembrane are of following type-

- Passive diffusion
- Filtration
- Specialized transport

2. **Passive Transport:** The lipid soluble drugs are easily diffuses across the membrane and it is depends on the concentration gradients. If the concentration gradient is between the two sides of the membrane then rate of diffusion is also high. Diffusion rate not only depends on lipid solubility and concentration gradient of drugs but also depends on degree of ionization, size of drugs and the surface area of absorptive membrane.

3. **Filtration:** Filtration is the second most important pathway of drugs passage that depends on the hydrostatic pressure and osmotic pressure gradient. For filtration of drugs, the size of the drugs mole must be less than pore diameter of membrane. It is found that the molecular weight (MW) greater than 100 diameter is unable to penetrate the membrane because the pore diameter is about $4A^0$ drugs diameter.

4. **Specialized Transport:** The drugs that are hydrophilic in nature are not able cross the membrane. They pass the membrane through special transport system: i. active transport (both energy and carrier dependent) or ii. Through facilitated diffusion (carrier mediated passive transport).

III. ABSORPTION

Absorption is process of drugs entry into the circulation. All drugs are not absorbed in the same rate due to difference their structure and chemical nature. Besides, some other factors that affect absorption are:

1. **Aqueous Solubility**: The drugs that are very less in water soluble like aspirin absorb slowly than the fully water soluble drugs (diclofenac sodium, dopamine hydrochloride).

2. **Concentration Gradient**: This is the most important factor of drugs absorption. The rate of absorption is directly proportional to the concentration gradient on the both side of the membrane.

3. **Area of Absorbing Surface:** Larger it is, faster is the absorption.

4. **Route of Drugs Administration**: Early mentioned the rate of drugs absorption is not same through all routes of drugs administration. It is slower in case of orally administered drugs in comparison to the subcutaneous and intramuscular injection.[1]

5. **Determinants of Absorption**: All drugs not absorbed into blood stream and not always absorbed in the same rate. It is determined as in terms of bioavailability.

IV. BIOAVAILABILITY

In pharmacology the term bioavailability is very important. It indicates the rate of drugs absorption to get the therapeutic concentration in a time dependent manner (see fig: 2).

The bioavailability is not same in all drugs for a same amount and that may be due tofollowing reasons:

- It may due to their poor solubility and slower rate of absorption.
- It may be due to first pass metabolism in the liver or excreted through bile.
- It also depends on particle size. If we reduce the particle size then the rate of absorptionof any drug will be increased. [1][4]

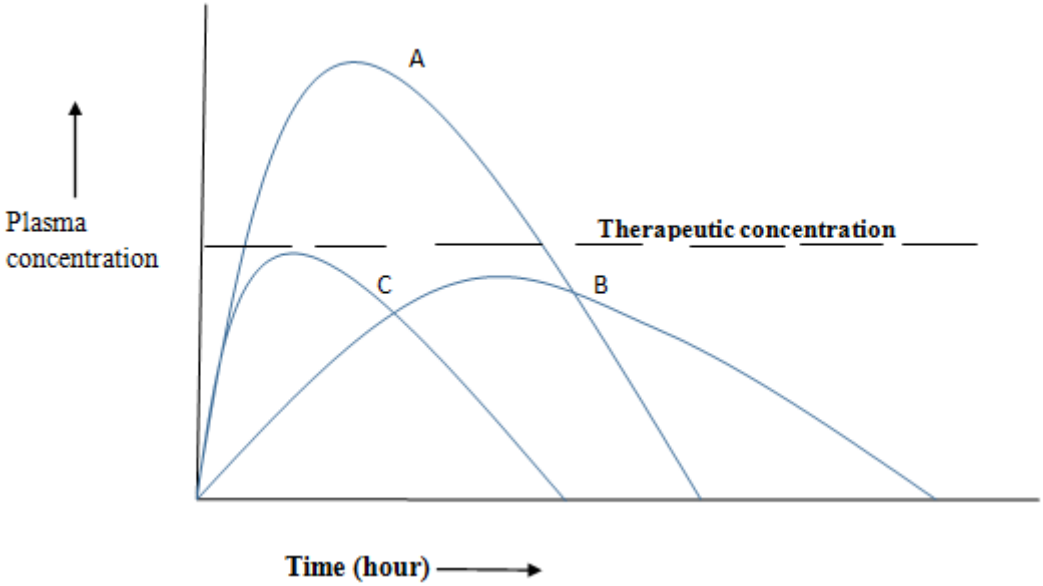

Figure 2: Bioavailability of three different drugs. [Here, drug A have greater bioavailability (that exceed the therapeutic concentration) than drug B and C. Drug B do not reaches to its therapeutic concentration due to its slower rate and greater extent of absorption.

V. DISTRIBUTION

Once a drug enters into the circulation get distributed to other tissue. The distribution of any drugs depends on its solubility to water, ionization properties, bound or unbound state etc. In different pathological condition like congestive heart failure, liver cirrhosis can alter the drugs distribution due to alteration of water distribution, plasma protein binding, permeability of membrane, accumulation of its metabolites.

1. **Drugs entry in Brain and CSF:** All drugs, toxin or pathogen do not enter in the brain due to presence of blood-brain barrier (BBB). The blood –brain barrier is a protective layer made up by specialized endothelial cells in the brain. Blood-CSF barrier also similar type barrier located in the choroid plexus having tight junctions. Mainly lipid soluble drugs easily penetrate through these junction and acts on CNS.

2. **Plasma Protein Binding:** Plasma protein plays an important role in drugs distribution specially albumin, α-acid- glycoprotein and beta-globulin. The drugs that are acidic in nature can bound to plasma protein albumin and basic drugs to globulin protein and binding efficacy depend on concentration of drugs.(see following table).

DRUGS BOUND TO PLASMA PROTEIN	
To Albumin	**To beta-globulin**
Barbiturates	β-blocker
Benzodiazepines	Quinidine
NSAID	Prazosin
Penicillin	Bupivacain
Sulfonamides	Lignocain
Tetracyclines	Methadone
Warfarin	Imipramine

Tissue Storage: As the drugs are accumulated in the organ or bound to tissue so, its high concentration leads to toxicity. There are some example of drugs and their storage site represented in the following table [1][2]

Tissues/	**Example of Storage**
1. Skeletal muscle, heart →	Digoxi
2. Liver and →	Chloroquine
3. Brain →	acetazolamide
Bone →	Tetracyclines,
Adipose tissue(lipid soluble drugs) →	Thiopentone,Phenoxybenzamine

VI. BIOTRANSFORMATION

(Metabolism)

Prodrug	Active form
Levodopa	Dopamine
Dipivefrine	Epinephrine
Bacampicillin	Ampicillin

Biotransformation or metabolism can be defined as the chemical alteration of drugs or xenobiotic (foreign) or endobiotic (endogenous) substances in the body. It is essential to transfer nonpolar (lipid soluble) compounds to polar (water soluble) so that they are nontoxic and easily pass through urine. When a drug is metabolized and its metabolite has a physiological effect then it is called active metabolite. But prior to metabolism it remains as inactive stage.Such a drug is called a prodrug.

Sometime drugs also transformed into inactive metabolites. However, both active and inactivemetabolite affects all other aspect of pharmacokinetics.

Site: The major site of drug metabolism is referred as liver in comparison to kidney, intestine,lungs and plasma.

Classification: Drug bio-transformation occurs in two phases:

- Phase I reactions (non synthetic)
- Phase II reactions (synthetic or conjugation)

Phase I Reactions

1. **Oxidation:** Oxidation is the most important drug metabolizing reaction. Oxidation is the process of addition of oxygen or removal of hydrogen in any substances. Liver takes a crucial role in oxidation process. Cytochrome P-450 monooxygenase is an important enzyme for oxidation of many drugs and detoxification of xenobiotics. This enzyme is present in the ER of liver.

   Example: Barbiturates, paracetamol, steroids and many other drugs are oxidized by this enzyme.

2. **Reduction: It is just reverse** of oxidation reaction. The same enzyme like Cytochrome P-450 may involve in reduction process. Hence, they are also called reductase enzyme.

   Drugs primarily reduced are chloramphenicol, halothane.

3. **Hydrolysis:** Hydrolysis of drugs or any substances occurs with the help of water molecule. Liver, intestine is the major site of hydrolysis.

   Examples: Choline esters, procaine, oxytocin etc. are biotransformed by hydrolysis process.

Phase II Reactions

This is also known as conjugation or synthetic reaction. It is energy dependent process.It is generally detoxifying step of drugs metabolism. The major enzymes involves in conjugation are UDP-glucuronosyltransferases, sulfotransferases, N-acetyltransferases, glutathione S-transferases and methyl transferases. The aims of conjugation is to transfer of a suitable endogenous moiety such as glucoronic acid, sulphate, glycine etc. to a drug or

metabolites of phase I reaction and form a polar highly ionized organic acid and this conversion helps to release the metabolites through urine or pass through bile.

1. **Glucuronide Conjugation:** Maximum drugs are transferred by glucuronide conjugation. The drugs that contain -OH or -COOH groups are mainly conjugate to the glucuronic acid with the help of UDP-glucuronosyl transferases (UGTs). This is the most important detoxification pathway for broad spectrum of drugs. Examples: chloramphenicol. Besides, steroid hormone, dietary chemical, carcinogens etc. are utilize in this way.

2. **Sulfate Conjugation**: The compounds that contain phenol group are metabolized by sulfate conjugation.

   Example: Chloramphenicol.

3. **Glutathione Conjugation**: Glutathione tranferases plays a key role the detoxification different xenobiotics (e.g. drugs, environmental pollutants, endogenous metabolites etc.). It converts highly reactive quinone or epoxide intermediate which is formed during metabolism of certain drugs (e.g. paracetamol) into inactive one.

   Besides, there are many drugs that are also undergoes in phase II reaction by methylation (e.g. Epinephrine), acetylation, and conjugation (e.g. sulfonamide).

   It is very important to remember that, Drugs independently may follow phase I or phase II **but most of the drugs follow two phase consequently one after another** (see fig:3).**[1][2][4]**

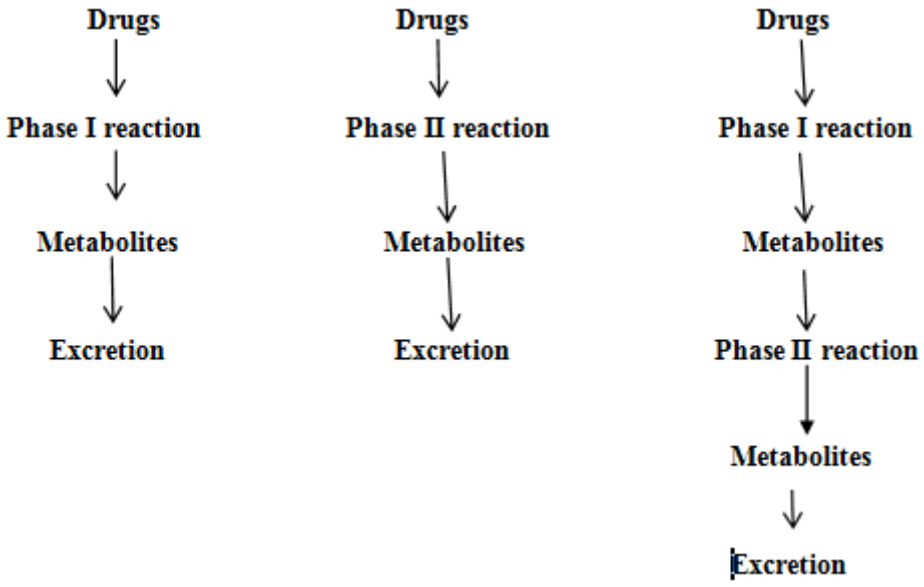

Figure 3: Drugs metabolism may occur only through phase I or phase II and or jointly follow both phase Iand phase II reaction sequentially.

VII. EXCRETION

This is a final process of pharmacokinetics. Excretion is the passage out of systemicallyabsorbed drugs and its metabolites from the body in different ways:

1. **Urine:** Nephron in kidney plays a key role in urine formation. Different portions of n e p h r o n are involved in drugs excretion (see fig: 4)**.**

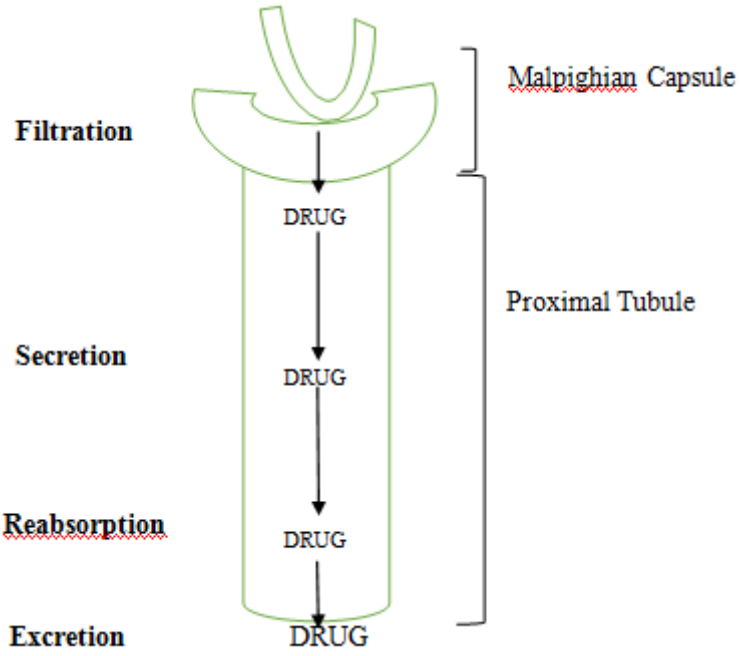

Figure 4: Renal Excretion of Drugs

Glomerular Capillaries of nephron have pores larger than usual; all non protein bound drugs that may be lipid soluble or insoluble are filtered through glomerulus.

About 90% glomerular filtrating lipid soluble drugs are reabsorbed through renal tubule but not lipid soluble and the drugs that are highly ionized unable to do so.

Tubular Secretion is depends on the renal clearance of a drug. Proximal tubules of nephrons are actively participating in tubular secretion for the elimination of many drugs and it is energy dependent. Tubular secretion involves two carrier system known as: a) basic carrier which transport basic drugs (e.g. dopamine, histamine etc.) and b) acidic carrier for transport of acidic drugs e.g. penicillin, furosemide etc.

2. **Faeces:** Orally administered drugs that are unable to absorb through gut, excreted in faeces coming from liver bile.

Example: Streptomycin, neomycin etc. drugs and some heavy metal that are excretedin the bile are arsenic, lead and mercury.

3. Beside these two major sources of drugs elimination, there are few drugs and heavy metal that also pass through saliva (e.g. thiocyanates), sweat (e.g. lithium), and gases (mainly alcohol and anesthetics). Different researcher shown that milk is also another important route of drugs elimination. Almost all drugs including alcohol, nicotine and caffeine taken by the mother are entering into breast milk and to infants. So, every mother needs special caution about the adverse effect of drugs. Drugs that are contraindicated during breast feeding include anticancer drugs, lithium, iodine, amphetamines, statin, antiretroviral medication etc. Beside antidepressants and anticonvulsant drugs should be used by lactating mother in very low dose due to their adverse effect**. [1]**

VIII. KINETICS OF ELIMINSATION

Once a drug enters into the body and starts to eliminate by liver, bile, kidney, lungs etc. then this process reduces the plasma concentration of drugs per unit time. Eliminationof drugs is directly proportional to its metabolism and plasma concentration (**first order or exponential kinetics), CL (clearance)** remain constant. Here specific ratio (not amount) of the drug is eliminated per unit time (see fig: 5). It is also called flow dependent elimination. CL can be expressed as:

CL is equal to the ratio of a drug elimination rate from plasma (mg/min) devided by its concentration in plasma (mg/ml).

Rate of drug elimination (mg/min)

CL (ml/min) =
Plasma drug concentration (mg/ml)

If the drugs are eliminated at constant rate per unit time and it is independent on its plasma concentration then it is referred as zero order or linear kinetics. The plasma half life (Time taken to reduce 50% of total plasma concentration of any substances) and plasma clearence (CL) value is not same in both first-order and zero-order elimination kinetics (see fig: 5). [1][2].

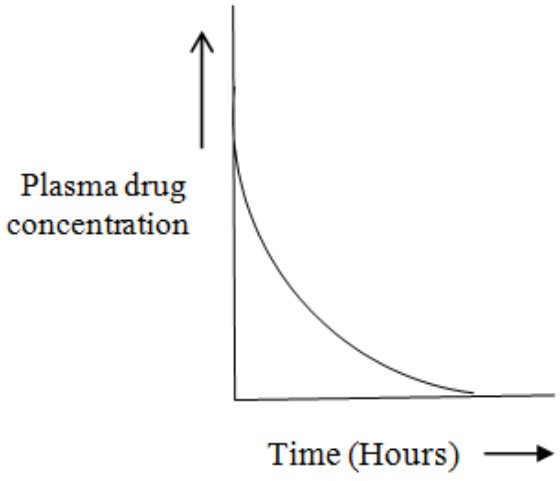

Figure 5: First- Order Elimination Kinetics.

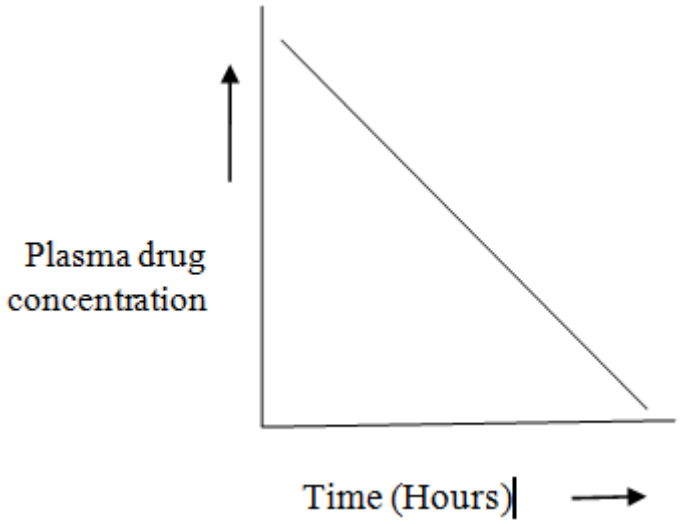

Figure 6: Zero-Order Elimination Kinetics.

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