A CONCEPTUAL DISCUSSION ON PHARMACOKINETICS

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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. Do not forget to check the question regarding this chapter and to understand your knowledge.

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Overview of Pharmacology

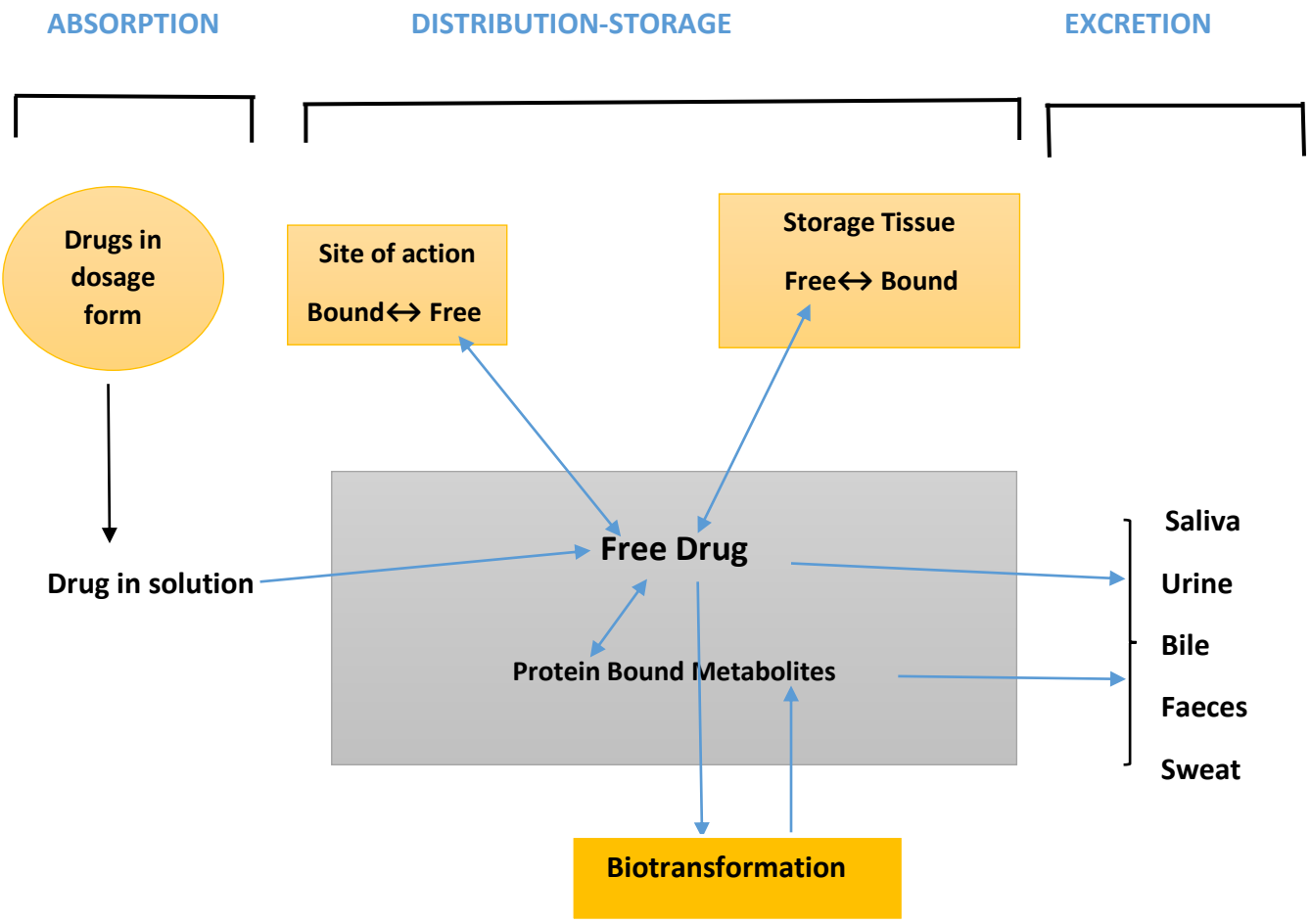
The term pharmacology was coming from two Greek word known as pharmacon-drugs and logos-discussion. In a broad sense, pharmacology deals an interaction between exogenously administered chemical molecules (drugs) and living system. It encompasses the discovery of drugs, their properties and their mechanism of action and effect on living system. For thousands of years, most drugs were crude natural products that have unknown composition and limited efficacy. Over the past 100 years or so, a vast variety of drugs with highly selective, purified and potent 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 with what the drugs does to the body and it includes the physiological and biochemical effects of drugs and their mechanism of action at molecular, cellular or organ system levels. Pharmacokinetics refers what the body does to the drugs.

Some other important aspects of pharmacology are pharmacotherapeutics, clinical pharmacology, chemotherapy, pharmacy, toxicology etc. [1][2][3]

Concepts 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 by the body. It includes absorption, distribution, binding/ localization, storage, biotransformation/ metabolism and excretion of the drugs by the body. Intensity of response is depending on the concentration of the presence of drugs at the site of action which in turn depends on some pharmacokinetics properties such as routes of drugs administration, dose of drugs, latency of onset, frequency of drugs administration, rate of absorption, distribution and time of peak action etc. (see fig. 1:) *[1][2][3]*



[Fig. 1: Schematic depiction of pharmacokinetic processes]

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

Depending upon the chemical properties of drugs, drugs transport across the plasma membrane are of following type-

a) Passive diffusion
b) Filtration
c) Specialized transport

Passive transport: The lipid soluble drugs are easily diffuses across the membrane and it is depends on the concentration gradients. A greater difference in the concentration of drugs on the two side of plasma membrane result faster rate of diffusion. 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.

Filtration: Filtration is the passage of drugs through aqueous pores in the plasma membrane under hydrostatic pressure or osmotic pressure gradient. Lipid insoluble drugs also cross through the biological membrane by the filtration process. Majority of cells (e.g. intestinal mucosa, RBC etc.) have very small size of pores (4Aº) and drugs with MW> 100 or 200 are not able to penetrate.

However, capillaries (except in brain) have large pores (40Aº**)** and most drugs even albumin can filtrate through the capillaries and it depends on blood flow and PH of the medium.

Specialized transport: *The drugs with hydrophilic properties combines with carrier protein in the membrane and then translocate to the other side of the membrane. This is of two types***:**

a) Active transport: Movement of drugs across the membrane against concentration gradient with the help of energy and a specific carrier is termed as active transport. Drugs related to normal metabolites, e.g. levodopa and methyldopa are actively absorbed from the gut by aromatic amino acid transport process**.**

b) **Facilitated diffusion:** It helps to transport of drugs more rapidly than simple diffusion and translocate even nondiffusible substrate but along their concentration gradient, therefore, does not need energy.

Pinocytosis: It is the process of transport across the cell in particulate form by the formation of vesicles. This is applicable to proteins and other big molecules, and contributes little to transport of most drugs. [1]

ABSORPTION

Absorption is the movement of drugs from the site of administration into the circulation across the biological membrane. 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**: A poorly water-soluble drugs (aspirin, griseofulvin) have slower rate of absorption than fully water-soluble drugs (diclofenac sodium, dopamine hydrochloride).
2. **Concentration gradient**: Rate of drugs absorption is directly proportional to the concentration gradient in the both side of the membrane.
3. Area of absorbing surface: Larger it is, faster is the absorption.
4. **Vascularity of the absorbing surface**: Increase blood flow hastens drug absorption just as wind hastens drying of clothes.
5. **Route of administration**: Rate of drugs absorption is slower in case of orally administered drugs in comparison to the subcutaneous and intramuscular injection. [1]

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.

Bioavailability:

In pharmacology the term bioavailability is very important. It refers to the rate and extent of a substance or a drug absorption into the blood from its entering dosage which is largely determined by its concentration-time curve in blood or by its excretion in urine (Fig. 2). Bioavailability of all drugs are not equal. The bioavailability of a drug injected i.v. is 100%, but is frequently lower after oral ingestion because:

(a) the drug may be not absorbed properly.

(b) the absorbed drug may undergoes firstly for metabolism in intestinal wall/liver or be excreted in bile.

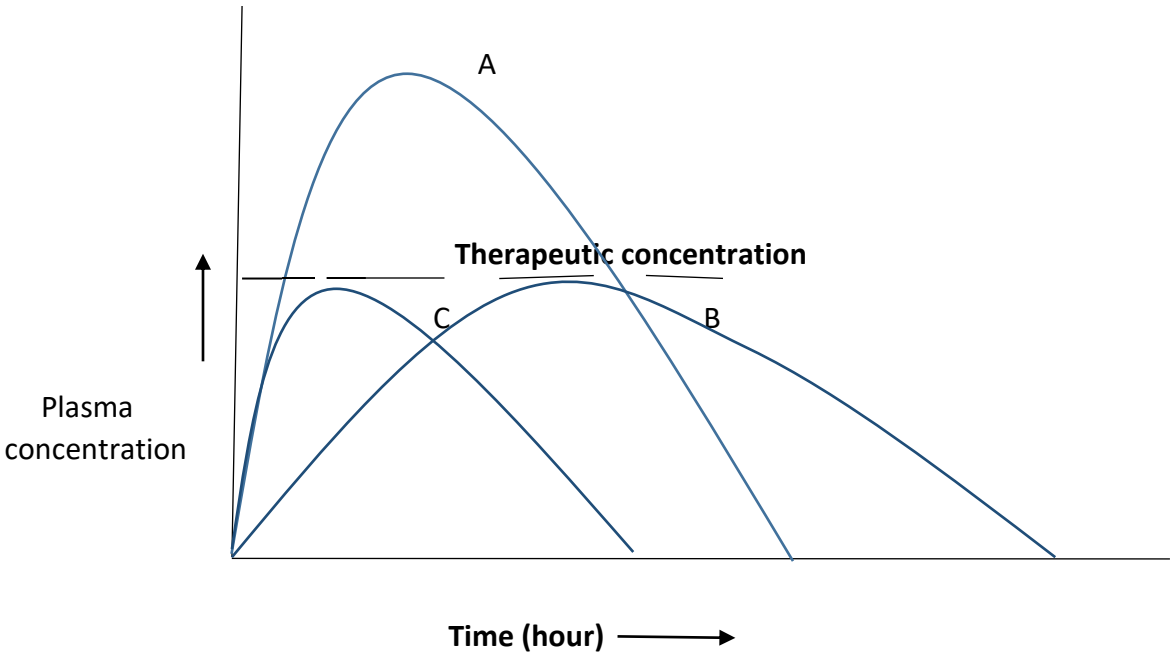


Fig. 2: Plasma concentration time curves show the differences in bioavailability between three preparations of a drug with same amount.

Note: Above graphical picture shown that the drug B is more slowly absorbed than A, and though ultimately both are absorbed to the same extent (area under the curve same), B may not produce therapeutic effect; C is absorbed to a lesser extent-lower bioavailability.

Differences in bioavailability are may be due to their poor solubility and slower rate of absorption. It also depends on particle size. If we reduce the particle size then the rate of absorption of any drug will be increased. [1][4]

DISTRIBUTION

Once a drug enters into the body then it gets circulated and distributed to another tissue. The extent of distribution of a drug depend on its solubility, ionization at physiological pH, extent of binding to plasma and tissue proteins and differences in regional blood flow. Movement of drugs proceeds until equilibrium is established between unbound drug in plasma and tissue fluids as well as there is a parallel decline in both due to elimination.

Pathological states, e.g. congestive heart failure, uremia, liver cirrhosis etc. can alter the drugs distribution by altering the distribution of water, permeability of membranes, binding proteins or by accumulation of metabolites that displace the drug from binding sites.

Penetration into 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 junctions and acts on CNS and it limit the entry of non-lipid soluble drugs e.g. streptomycin, neostigmine, hexamethonium etc.

Plasma protein binding:

Plasma protein plays an important role in drugs distribution specially albumin, α-acid-glycoprotein and beta-globulin. Acidic drugs generally bind to plasma albumin and basic drugs binds to α-acid glycoprotein or beta-globulin (see following table).

DRUGS BOUND TO PLASMA PROTEIN

To Albumin	To α-acid glycoprotein/beta-globulin
Barbiturates	β-blocker
Benzodiazepines	Quinidine
NSAIDS	Prazosin
Penicillins	Bupivacaine
Sulfonamides	Lignocaine
Tetracyclines	Methadone
Warfarin	Imipramine

Binding to albumin is quantitatively more important and extent of binding is totally depends on concentration of drugs in plasma. High degree of protein binding generally makes the drugs long acting, because bound fraction is not available for metabolism or excretion, unless it is actively extracted by liver or kidney tubules. One drug can able to bind many sites on albumin molecule. Highly plasma protein bound drugs are largely restricted to the vascular compartment and so they tends to have lower volume of

distribution. In hypoalbuminemia, binding may be reduced and high concentration of free drugs may be attained.

Tissue storage: Drugs may also accumulate in specific organs or get bound to specific tissue constituents, e.g.

Drugs are differentially distributed in various tissue, tend to have large volume of distribution and long duration of action. Some may exert local toxicity due to high concentration, e.g. tetracyclines on bone and teeth, chloroquine on retina, emetine on heart and skeletal muscle. Drugs may also selectively bind to specific intracellular organelle, e.g. tetracycline to mitochondria, chloroquine to nuclei. [1][2]

Tissues/ Organs	Storage drugs
Skeletal muscle, heart	Digoxin, emetine
Liver digoxin.	Chloroquine, tetracyclines, emetine,
Kidney	Chloroquine, emetine, digoxin.
Thyroid	Iodine.
Brain	Chloropromazine, acetazolamide.
Retina	Chloroquine
Bone and teeth	Tetracyclines, heavy metals
Adipose tissue	Thiopentone, ether,DDT,
Phenoxybenzamine	

BIOTRANSFORMATION

(Metabolism)

Biotransformation or metabolism can be defined as the chemical alteration of drugs or xenobiotic (foreign) or endobiotic (endogenous) substances in the body. It is needed to render nonpolar (lipid soluble) compounds to polar (water soluble) so that they are nontoxic, not

Prodrug	Active form
Levodopa	**Dopamine**
Dipivefrine	**Epinephrine**
Bacampicillin	**Ampicillin**

reabsorbed in the renal tubules and are easily excreted through the 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 inactive metabolites affect all other aspect of pharmacokinetics.

Site: The primary site for drug metabolism is liver; others are-kidney, intestine, lungs and plasma.

Classification: Biotransformation reaction can be classified into:

a) Nonsynthetic / Phase I reactions-metabolite may be active or inactive.

b) Synthetic / Conjugation/ Phase II reactions-metabolite is mostly inactive.

Phase I reactions:

1. **Oxidation**: Oxidation is the most important drug metabolizing reaction. It involves addition of oxygen/ negatively charged radical or hydrogen removal/ positively charged radical. Various oxidation reactions are hydroxylation, oxygenation at C, N or S atoms, dealkylation at N or O atoms, oxidative deamination etc.
   R-H→R-OH (hydroxylation): Conversion of hydrogen to a hydroxyl group.
   R-C-OH→R-C=O (dehydrogenation): Conversion of hydroxyl group to a carbonyl group**.**
   R-C-NH2→R-C=O (deamination): Conversion of amino group to a carbonyl group.

   Oxidative reactions are mostly carried by a group of mono oxygenase in the ER of liver e.g. cytochrome P-450 enzyme. More than 100 cytochrome P-450 isoenzymes have been identified for drugs metabolism or detoxification of xenobiotics and removal of free radical (ROS) etc.

   Barbiturates, paracetamol, steroids and many other drugs are oxidized by this enzyme. Some other drugs e.g. adrenalin, alcohol etc. are oxidized by mitochondrial and cytoplasmic enzyme.

2. **Reduction:** This is just opposite of oxidation reaction. The enzyme Cytochrome P-450 acts in opposite direction of oxidation. It involves addition of hydrogen or the removal of oxygen:
   R-OH→R-H (de-hydroxylation)
   R-C=O→R-C-OH (hydrogenation)
   R-NO2→R-NH2 (amination)
   An example of a reduction reaction is the inactivation of warfarin by the conversion of a ketone group to a hydroxyl group (hydrogenation) by reductase enzyme.
   Drugs primarily reduced are chloramphenicol, halothane.

3. **Hydrolysis:** It involves the cleavage of drugs molecule by taking up a molecule of water. This takes place in liver, intestine, plasma and other tissue. Examples:
   Ester + H2O $\xrightarrow{\text{Esterase}}$ Acid + Alcohol
   Similarly, amides and polypeptides are hydrolysed by amidase and peptidase. Choline esters, procaine, oxytocin etc. are biotransformed by hydrolysis process.

Phase II reactions: This is also known as conjugation or synthetic reaction. It is generally detoxifying step of drugs metabolism. The major enzymes involve in conjugation are UDP-glucuronosyltransferases, sulfotransferases, N-acetyltransferases, glutathione S-transferases and methyl transferases. The aims of conjugation are to transfer of a suitable endogenous moety such as glucoronic acid, sulphate, glycine etc. to a drug or metabolites of phase I reaction and form a polar highly ionized organic acid so that they are easily excreted through urine or bile. Conjugation reactions have high energy requirement.

1. **Glucuronide conjugation:** This is the most important synthetic reaction. Hydroxyl or carboxylic acid group containing compounds are easily conjugated with glucuronic acid (which is derived from glucose) with the help of UDP-glucuronosyl transferases (UGTs). This is the most important detoxification pathway for broad spectrum of drugs. Examples are- chloramphenicol, aspirin, morphine etc. Not only drugs but also some endogenous compounds like bilirubin, steroid hormone and thyroxine and dietary chemical, carcinogens etc. are utilize in this way.

2. **Methylation:** The amines and phenols can be methylated where methionine and cysteine acts as a methyl donor.
   Examples: Adrenaline, histamine and nicotinic acid.

3. **Acetylation**: Compounds having amino and hydrazine residues are conjugated with acetyl group by the enzyme acetyl coenzyme-A, e.g. sulfonamide, isoniazid, PAS and hydralazine. Multiple genes control the acetyl transferases and rate of acetylation.

4. **Sulfate conjugation**: The compounds that contain phenol group and steroids are sulfated by sulfokinases, e.g. chloramphenicol, adrenal and sex steroids.

5. **Glutathione conjugation**: The family of 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 are formed during metabolism of certain drugs (e.g. paracetamol) into inactive one. Generally,these enzymes catalyze a nucleophilic

attack of reduced glutathione on lipophilic compound that contain an electrophilic atom (C-, N- or S-).

Most drugs are metabolized by many pathways, simultaneously or subsequently (see fig: 3). Only few drugs are metabolized by enzymes of intermediary metabolism e.g. alcohol by dehydrogenase, succinylcholine and procaine by plasma cholinesterase. [1][2][4]

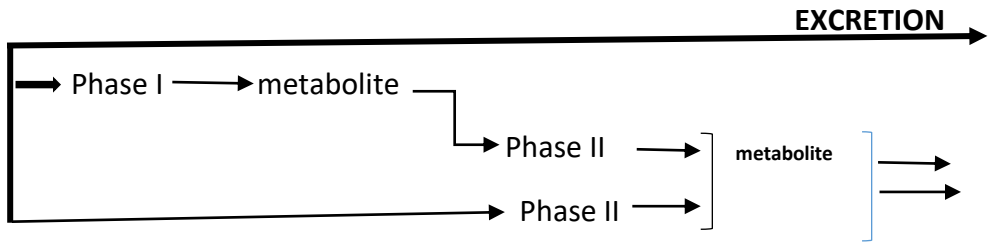


Fig: 3. Simultaneous and/or sequential metabolism of a drug by phase I and phase II reactions.

EXCRETION

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

1. **Urine:** Nephron in kidney plays a key role in urine formation and is the most important channel of excretion for most drugs especially all water-soluble drugs or substances. The total amount of drugs or its metabolites pass through urine is calculated by the summation glomerular filtration, tubular reabsorption and tubular secretion (see fig: 4)**.**

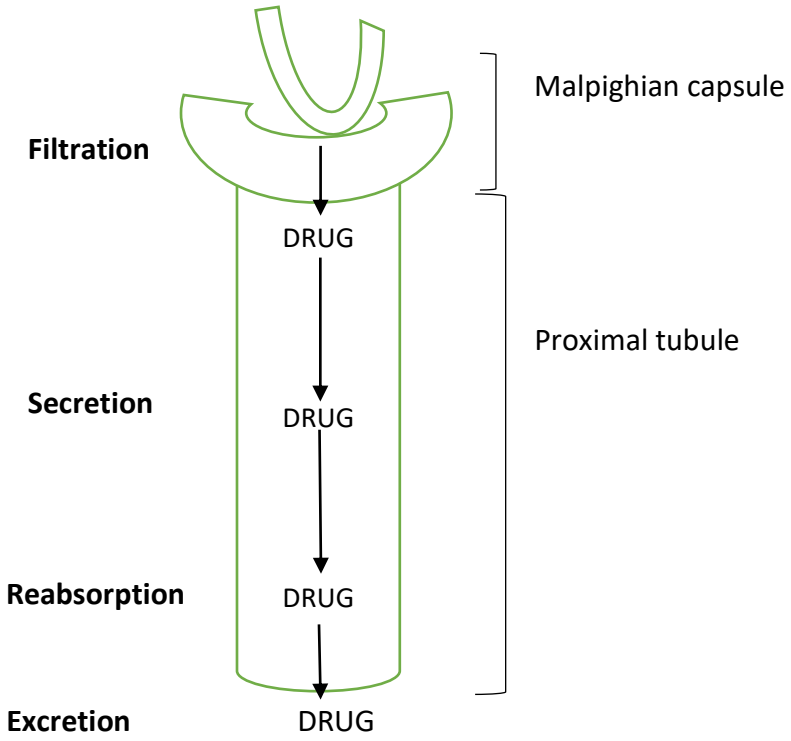


Fig 4: Renal excretion of drug

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 and the **rate of filtration** of drugs depends on its plasma protein binding and renal blood flow.

Tubular reabsorption is depends on lipid solubility and ionization of drugs at the existing urinary P^H. 90% glomerular filtrating lipid soluble drugs are reabsorbed through renal tubule but not lipid soluble and highly ionized drugs are unable to do so.

Tubular secretion is depends on the renal clearance of a drug. If the renal clearance of a drugs is greater than 120 mL/min (g.f.r.), additional tubular secretion can be assumed to be occurring. Proximal tubule of nephrons are actively participated in tubular secretion for the elimination of many drugs and it is energy dependent. Tubular secretion involves two carrier system knowns 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. Most of the unabsorbed drugs present in faeces is derived from bile. Liver actively transport into bile organic acids (especially drugs glucuronides), organic bases and steroid by separate nonspecific active transport mechanisms. Relatively larger molecules (MW>300) are preferentially eliminated in the bile. Example: Streptomycin, neomycin etc. drugs and some heavy metal that are excreted in the bile are arsenic, lead and mercury.

3. **Saliva and sweat:** These are minor important for drugs excretion. Lithium, thiocyanates, rifampin and heavy metals are excreted in these routes.

4. **Exhaled air:** Gases and volatile liquids (general anaesthetics, alcohol) are eliminated by lungs). Alveolar transfer of the gas/vapour depends on its partial pressure in the blood. Lungs also serve to trap and extrude any particulate matter injected **i.v.**

5. **Milk:** Most drugs enter in breast milk by passive diffusion. Most lipid soluble and less protein bound drugs cross better. Almost all drugs including alcohol, nicotine and caffeine taken by the mother are enter 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 includes anticancer drugs, lithium, iodine, amphetamines, statin, antiretroviral medication etc. Beside antidepressants and anticonvulsants drugs should be used by lactating mother in very low dose due to their adverse effect**. [1]**

KINETICS OF ELIMINSATION

Once a drug after entering into the body when start to eliminate by liver, bile, kidney, lungs etc. then this process reduce the plasma concentration of drugs per unit time. And the rate of drugs elimination is directly proportional to the concentration of the drugs that means the higher the drug concentration, the higher its elimination rate (**first order or exponential kinetics), CL** 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. Few drugs, however, saturate eliminating mechanism and are handled by –

Zero order (linear) kinetics where the rate of elimination remains constant irrespective of drug concentration, CL decreases with increase in concentration; or a constant amount of drug is eliminated in unit time (see fig: 6).

Clearance (CL): The clearance of a drug is the theoretical volume of plasma from which the drug is completely removed in unit time (analogy creatinine clearance). It can be calculated as:

CL= Rate of elimination/C where, C is the plasma concentration.

Plasma half-life: The plasma half-life of a drug is the time taken for its plasma concentration to be reduced to half of its original value. [1][2]

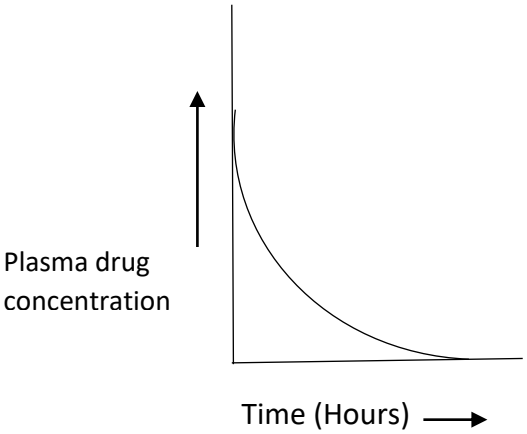


Fig 5: First- order elimination kinetics.

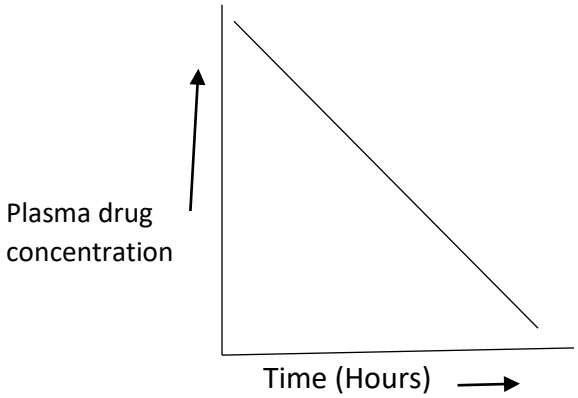


Fig 6: Zero-order elimination kinetics.

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