PHARMACOKINETICS

Abstract

Pharmacokinetics includes absorption, distribution, metabolism and excretion. The rate at which a drug enters the systemic circulation from its site of administration is absorption. Drug distribution is the process of distribution of drug in various organs and tissues. Metabolism of a drug is changing the drug compound to a metabolite so that the drug can easily excrete out from the body. Excretion involves the elimination of drug from the blood circulation system into bile, urine, feces, sweat, and air. Bioavailability means the rate and extent to absorption of Active Pharmaceutical Ingredient from a drug product and its availability at the site of action

Keywords: Absorption, Distribution, Metabolism, Elimination, Bioavailability

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I. INTRODUCTION

Pharmacokinetics is defined as "what the body does to the drug" viz. ADME [absorption (A), distribution (D), metabolism (M), and excretion (E) of a drug. The rate and extent at which a drug reaches the blood circulation system from the site of administration is known as absorption. Drug distribution can be defined as the process that begins from the moment when drug enters the blood stream till the time, it gets eliminated from the body. Metabolism is defined as a biochemical processwhichchanges a drug compound chemically for easier elimination from the body. Excretion involves the elimination of drug in the form of urine, sweat, feces, bile and air from the blood stream.

Bioavailability means rate and extent of absorption of Active Pharmaceutical Ingredient from a formulation and its availability at the targeted site. Drug absorption plays a very vital role in determination of bioavailability (F) because the absorption process affects the time and extent to which drug remains in the body. Bioavailability can be measured by determining rate and/or extent through which API becomes available at targeted site for the formulations whose absorption is not necessarily intended.

Mathematically, Bioavailability of a drug from a formulation may be determined by the following equation:-

$$\boldsymbol{F = F_a \times F_g \times F_h}$$

where, F_a = fraction / proportion of absorbed drug from the formulation into the blood stream
F_g = fraction of drug that skipped GIT metabolism

F_h = fraction of drug that skipped hepatic first pass metabolism

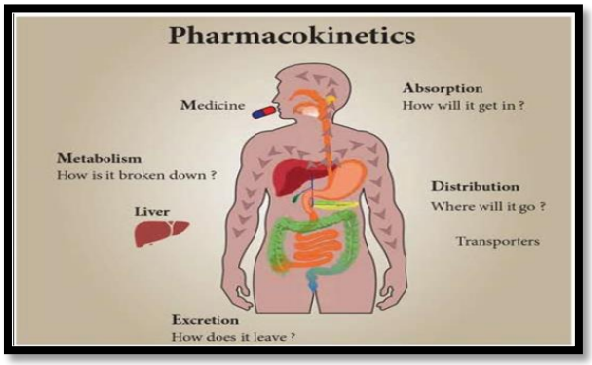

Figure 1: Processes of Pharmacokinetics

II. ABSORPTION

Small intestine is the principle site for absorption of drug which can occur through either para cellular transport, carrier-mediated transport, endocytosis or passive diffusion. Passive diffusion is favored mainly for lipophilic drugs. However, for hydrophilic drugs and other compounds, carrier-mediated transport is required. But for small molecules (hydrophilic), paracellular pathway is advantageous. Depending on the compound under consideration, the major absorption pathway may differ based on physiological conditions. Compound's

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absorption is governed by many processes. Drug absorption depends on two parameters viz. drug solubility and gastrointestinal permeability. Both these factors are proportional to oral absorption rate as well as extent. Solubility characteristics, intestinal absorption and stability in GIT (first pass metabolism) affects the drug's bioavailability. [1]

Absorption of a drug is affected by its route of administration, dosage formulation as well as its physicochemical properties. For a drug to be absorbed in systemic circulation, the foremost requirement is to be in solution form which is governed by its solubility in GI fluids. This is not only the major requirement, other factors such as crossing semipermeable membrane barrier (consists of bilipid layered matrix) are also considered for which lipophilic profile of a drug is studied to characterize membrane permeability requisites. Penetration of a drug molecule inside cellular membrane can occur through :-

1. Active transport
2. Passive diffusion
3. Pinocytosis
4. Facilitated passive diffusion (in some cases, globular proteins present in the body fluids may behave like receptors for persuading molecules to cross cellular membranes).

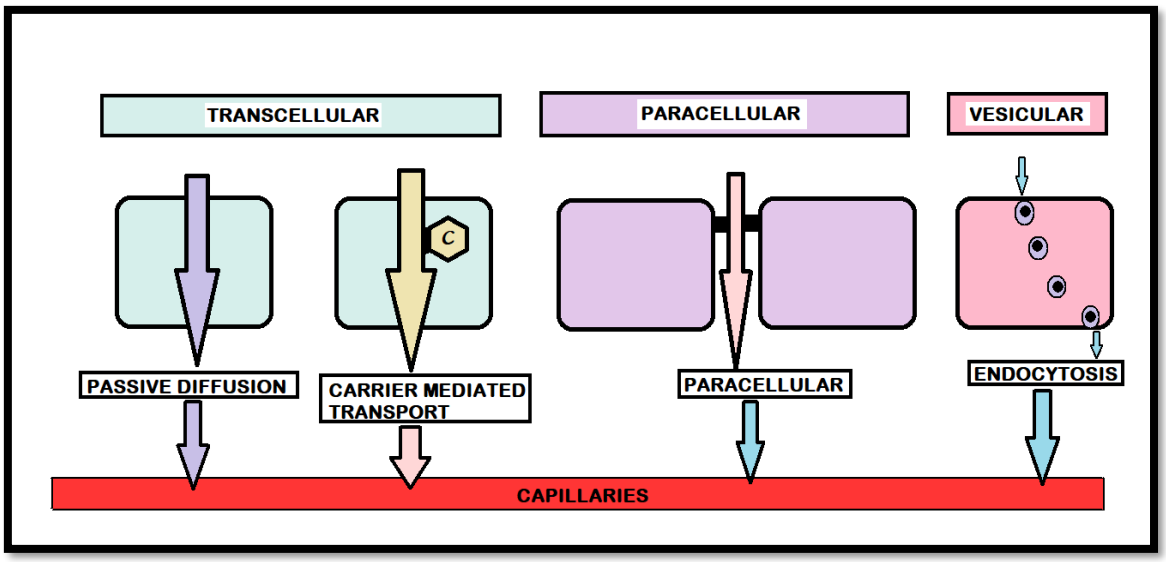

Figure 2: Methods of Absorption

1. **Passive diffusion:** Drugs diffusion occurs along the concentration gradient and diffusion rate is also proportional to it. Factors such as size of the molecule, extent of ionization, solubility profile and surface area available for absorption affects the rate of drug absorption to a great extent. Lipophilic drugs finds it very easy to permeate cellular membrane owing to its lipoidal nature. Smaller molecules penetrates across cell membrane faster than larger ones comparatively.

   Drugs gets either ionized or remains unionized in GI fluids based on the degree of ionization owing to their weak acidic or basic properties. Unionized molecules gets easily penetrated through cellular membrane as compared to ionized ones because electrical resistance is very high in case of latter one. Drug's pK_a and GI fluid's pH also

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affects the extent of ionization of drug molecules. pH and pK_a becomes equal when the 50% of the drug gets ionized and other 50% remains unionized. When $pH<pK_a$, drug (weak acidic in nature) remains mostly unionized but reverse for drug molecule of weak basic nature. A weak acidic drug's concentration in ionized form is 1000 times to that of its unionized form at pH 7.4 (blood plasma) while it is reverse at pH 1.4 of gastric HCl. Drug molecule of weak basic character (pK_a 4.4) remains ionized at gastric pH which imparts to its poor absorption through gastric mucosa for example, quinidine while this is just opposite for a drug molecule possessing weak acidic character administered orally for example, aspirin. Mostly absorption processes occur in the small intestine irrespective of drug's nature (acidic or basic) owing to its large absorptive surface area available and high membranous permeability.

2. **Facilitated passive diffusion:** This is a passive process running along the concentration gradient for shipping the molecules from membrane's outer surface towards inside by forming reversible bonding with them. It is capacity limited pathway and also for selective molecules possessing desired configuration. Glucose being poorly lipid soluble exhibits high membranous permeability owing to this process.

3. **Active transport:** This conveys molecules possessing similar structural features to that of endogenous substances viz. sugars, amino acids, vitamins, etc. against concentration gradient across membrane at specific sites only in small intestine and is energy-dependent-highly-selective process.

4. **Pinocytosis:** This is energy-driven-specific process for proteins mainly which involves inundation of drug molecules or fluid particles inside the cell via formation of membranous invaginations which later gets fused up again leading to vesicle formation and its further degradation inside cell.

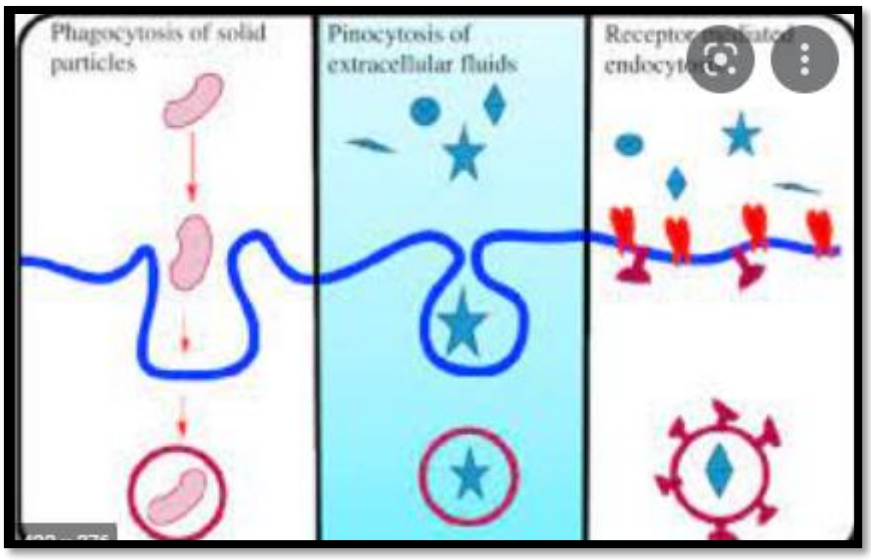

Figure 3: Mechanism of Pinocytosis

5. **Oral Administration:** The drug which is given orally have to survive in the low pH environment, GI secretions and various enzymes for its absorption in the body. Some

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drugs of peptide origin such as insulin are highly susceptible towards metabolic degradation or very low pH of gastric fluid, if administered orally. Membranous transport of drugs is very critical for absorption to occur. Certain other factors which affects absorption are described below

- Differences in luminal pH along with the GI tract
- Surface area
- Blood perfusion rate
- Presence of bile and mucus in body
- Nature of the epithelial cell membranes

Oral mucosa also shows good absorption owing to its thin epithelium and great vasculature. A drug given through buccal administration or sublingual administration is considered to retain for longer duration that increase the rate of absorption.

When a drug is given orally, the contact between the drug and GI fluids occur mostly in the stomach. The stomach has various properties that can affect drug formulation and behavior like thick mucus layer, large epithelial surface and short transit time limit drug absorption. Absorption is greatly affected by gastric emptying time as small intestine is the site for absorption. Gastric emptying, in turn, depends on the type of food present in the stomach for example, fats enhances the gastric emptying duration and further, retards absorption from intestine. This case is also true for drugs such as Parasympatholytics. This is the reason why some drugs are advised to be taken empty stomach. But in some cases, food enhances the absorption of drugs like griseofulvin which is a poorly water soluble drug by enhancing gastric retention time but this characteristic is not fruitful for drugs undergoing degradation at gastric pH for example, penicillin G.

Small intestine is the primary site for maximum drug absorption owing to its large surface area and great membranous permeability as compared to gastric mucosal membrane which can be considered as one of the most reason for even acidic drugs getting absorbed through it rather than stomach despite they remain unionized at gastric site. The pH increases from 4.5 (acidic) to 8 (slightly alkaline) on moving from duodenum to ileum.[2] Passive diffusion gets affected in shock conditions altering concentration gradient, poor blood supply to membrane, etc. which in turn limits absorption rate. Gut microflora may also contribute for the same. Absorption rate of many poorly soluble (B vitamins) and polar drugs (antibiotics) whose absorption is actively mediated is greatly affected by transit time of intestine.

6. **Parenteral administration:** Drugs when administered intravenously enters directly into blood stream without facing any intervening biological membranous barrier but it is not the same case for drugs administered via i.m., s.c. route. Lymphatic system is the preferred route for high molecular weight proteins (>20,000 $gmol^{-1}$) when administered via i.m. or s.c. route as they face problem in traversing through fine blood capillary membranes owing to their large size which contribute to their little fraction available in blood stream. Moreover, the proteolytic enzymes present in lymphatic system causes their extensive first pass metabolism. For drugs of smaller size, absorption is greatly affected by capillary blood perfusion which becomes highly significant for patients with shock

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and hypotensive conditions. This is the reason site of injection is one of the factor that affect rate of absorption. [3]

7. **Controlled release dosage form:** These are fabricated for drug molecules possessing short half life, for controlling fluctuations in plasma drug concentration which provides uniformity in therapeutic efficacy and controlling ADRs. Through these novel approaches, absorption rate of drug molecules can be controlled by matrixing, combining with ion-exchange resin or clumping with hydrophobic materials such as wax. However, large intestine is responsible for most absorption of these types of dosage forms. Highly potent drugs possessing great skin penetration can be easily incorporated into transdermal controlled-drug delivery systems for achieving sustained drug action. Formulating antimicrobial drugs in salt form (relatively insoluble) and administering via i.m. route enhances duration of absorption which helps in prolonging drug action as in case of penicillin G benzathine. Non-aqueous vehicles can also be used for prolonging drug absorption from solutions and suspensions as done in insulin's crystalline suspension. [4]

Table 1: Routes of Administration, Bioavailability, their Advantages and Disadvantages

Route	Bioavailability	Advantages	Disadvantages
Parenteral			
INTRAVENOUS (IV)	Complete (100 %) systemic drug absorption	immediate or controlled effect of drug can be achieved large fluid volumes can be injected irritating drugs can be given	High ADRs rate Possible anaphylaxis -
INTRAMUSCULAR INJECTION (IM)	Rapid absorption from aqueous solution Slow absorption from non-aqueous (oily) solution	Easily injected compared to i.v. Administration of larger drug volumes than subcutaneous solution	Not suitable for Irritating drugs Variable rates of absorption depending upon muscle group injected and blood flow
SUBCUTANEOUS INJECTION (SC)	Rapid absorption from aqueous solution Slow absorption from depot formulations	Generally, for vaccines and drugs not absorbed orally e. g. insulin	Rate of absorption depends upon blood flow and injection volume -
Enteral Routes			
BUCCAL OR SUBLINGUAL (SC)	Rapid absorption of lipid-soluble drugs	No pre-systemic metabolism	Not suitable for swallowable and high dosage drugs
ORAL (PO)	Absorption may vary Generally slower absorption rate	Safest and easiest route of drug administration	Some drugs are unstable in GIT or undergo pre-systemic

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	compared to IV bolus or IM injection	Suitable for both immediate release and modified release drug products	metabolism or show erratic absorption
RECTAL (PR)	Absorption may vary from suppository More reliable absorption from enema (solution0	Useful when patient cannot swallow medication Used for local and systemic effects	Absorption may be erratic Suppository may migrate to different position Some patient discomfort
Other Routes			
TRANSDERMAL	Slow absorption, rate may vary Increased absorption with occlusive dressings	Transdermal delivery system (patch) is easy to use and withdraw Provides longer duration of action and can be made specific Suitable for smaller drug molecules possessing significant lipophilicity Low pre-systemic metabolism	Patch may produce irritation in some patients with sensitive skin Skin Permeability changes with conditions like age, anatomic site, gender Drug absorption affected by type of ointment/cream base used
INHALATION	Rapid absorption Total dose absorbed is variable	May be used for local or systemic effects	Particle size of drug determines anatomic placement in respiratory tract May stimulate cough reflex Some drug may be swallowed.

III. DRUG DISTRIBUTION

The entry of drug into the blood circulation system, either by intravenous routeor by getting absorbed from GIT cell membrane or from any extravascular site, the drug comes across the deposition process. The lowering of drug plasma concentrationtends to process is known as **DEPOSITION**. Drug deposition has two major processes:

1. **Distribution:** The reversible transfer of drug from one compartment to other or in between the compartments is known as distribution.
2. **Elimination:** The removal of drug from body is known as elimination. It has two important processes:
   - **Biotransformation:** when the drug's structure or properties gets permanently changed or irreversibly, it is termed as drug biotransformation or drug metabolism.

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- **Excretion:** Excretion defines the expulsion of drug from the body.

According to above all definitions, the Drug Distribution can be defined as the reversible intercomponent drug transfer inside the body. One of the compartments represent blood and plasma while the another represents extravascular fluids and tissues or cells.[5] Drug distribution is passive process which depends on the concentration gradient in between the blood and extravascular fluids it will occur until equilibrium is takes place between both the fluids. Drug distribution has an essential role in the onset of action and intensity. It also affects duration of drug action, its efficacy and toxicity. Due to the different structure of drugs, there is variation in distribution of drug among different type of tissues for example, muscles, fats and brain. However, tissues like brain and testes are less susceptible to distribution as they contain membrane barriers. Based on the solubility in water and lipids, drugs are classified as lipophilic or hydrophilic.

IV. LIPOPHILIC

1. They also known as fat soluble
2. They are non – polar compounds
3. They easily get diffuse across lipid bilayers of cell membranes
4. They show free diffusion across the blood brain barriers
5. They get metabolized in the liver
6. They mainly get excreted through the bile duct

V. HYDROPHILIC

1. They also known as water soluble
2. They are polar compounds
3. They undergoes facilitated transport of diffusion using ion channels or different membranous proteins for crossing hydrophobic bilayers of lipid present in cell membrane.
4. They are excreted from kidneys [6]

VI. STEPS IN DRUG DISTRIBUTION

The distribution of drugs from blood stream to extracellular fluid or intracellular fluid involves steps:

1. Drug permeates into ECF form blood present in capillaries in its free form.
2. The drug permeates from the ECF to the ICF by crossing the tissue cell membrane which is the critical rate determining step and controlled by two important factors on which it depends viz. :-
   - The rate of perfusion to the extracellular fluid.
   - The membrane permeability of the drug.

VII. ISSUES OF CONCERN

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The distribution of drug is not certain or uniform throughout the body because different tissues have different rate of perfusion and receives the drug at different rates and extent from blood plasma, we can say that different factors associated with drug (pH, binding affinity) and body (fat, age, gender, physiological barriers, perfusion rate, genetic diseases, water content) governs distribution of drugs.[3]

VIII. CLINICAL SIGNIFICANCE

The overall water content decrease with increase in the age but the water content present inside the cells remains constant from the first month of age to adulthood. In younger children, higher drug dose per kilogram weight is needed as they have more water.[3] lipophilic drugs get distributedmore to the areas with high lipid density.[4] Body fat is different in people of different gender, age and to certain extent, genetics too. Plasma proteins-drug binding increases the half-life of drug. The protein binding of drug affects the distribution of drug.

The binding of drugs with the blood components to form complex structure is known as plasma protein binding or the drug binding to the blood cells. The protein is mainly responsible for this complex formation. A drug is able to interact with various components of tissue. It is the major factor which affects both pharmacokinetics and Pharmacodynamics of the drug.

The drugprotein binding takes place in two areas:

1. **Blood**
   - **a -** Plasma protein
   - **b -** Blood cells

2. **Extra vascular tissue:** Protein, Fats, Bones etc.

Protein binding may be divided into:

- Intracellular Binding –In this binding shown with the enzymes which are present inside the cell.
- Extracellular Binding – In this binding shown with the enzymes which are present outside or on the cell. [7]

IX. PROTEIN DRUG BINDING PROCESS

The protein binding with drug mainly is a reversible process but sometimes it is shown as irreversible binding which is being the reason of carcinogenicity and tissue toxicity. Weak and transient bonds are involved in reversible binding, for example,

1. Hydrogen Bond
2. Hydrophobic Bond
3. Ionic Bond
4. Vander-waal force.

And there is sometimes irreversible binding occur though rare, arises due to the covalent bonding which is often a cause of toxicity.

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Drug enters into the blood stream after absorption and it will show protein binding and increase the half life of drug or it will bind to the receptor which is also protein and show the pharmacological action. For the therapeutic action of drug and for the sustain release doses, the protein binding is necessary.

X. DRUG BINDING TO BLOOD COMPONENTS

1. **Plasma protein drug binding**: The drug binds reversibly with plasma proteins. When the drug enters into the blood circulation system, the first of all, it interacts with components of blood such as like plasma protein, haemoglobin, erythrocytes. The large amount of interaction occurs with the proteins present in plasma because it occurs in ample amounts and in much variety. The extent or order of drug binding to various plasma protein is: Albumin > acid glycoprotein > lipoprotein > globules

XI. DRUG BINDING TO HUMAN SERUM ALBUMIN

The human serum albumin has highest binding capacity for a drug owing to its large molecular weight (~65000) and high abundancy (59%) in plasma (3.5-5.0 g%). The human serum albumin bind with variety of drug it can bind with acidic drug or with basic drug or with endogenous compounds like fatty acids tryptophan, bilirubin etc. There are four different sites on human serum albumin for binding of drug:

Site 1: This siteis known as Warfarin binding site and azapropazone binding site, at this region large numbers of drugs bound example NSAIDs, naproxen, indomethacin, sulphonamides, bilirubin, phenytoin, sodium valproate etc.

Site 2: This site is known as diazepam binding site example cloxacillin, probenecid, benzodiazepines, ibuprofen, ketoprofen, etc.

Site 3: This site is known as digitoxin binding site

Site 4: This site is known as tamoxifen binding site

1. **Most drugs binds to site 1 & 2:** A drug has the capacity to bind with multiple sites. The main binding site is known as primary site and the others is known as secondary site. Example for dicoumarol site 1 is the primary site and site 2 is the secondary site. There are drugs which have common binding sites, they compete with each otherfor binding but the drug which have binding property for site doesn't inhibit the other drug which have binding for another sites. However, the drugs can either increase or decrease drug binding to another binding site by energetic coupling mechanism.

XII. DRUG BINDING TO α-ACID GLYCOPROTEIN

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This binding is also called orosomucoid. The molecular weight of α-acid glycoprotein is 44,000 and a plasma concentration range of 0.04 – 0.1 g%. It shows binding mainly with the basic drugs example – quinidine, amitriptyline, propranolol, imipramine, disopyramide, lidocaine etc.

XIII. DRUG BINDING TO LIPOPROTEIN

Lipoproteins are amphiphilic (both hydrophilic and lipophilic) in nature. Lipids and apoproteins combine and form lipoproteins. The lipid (lipophilic part) consists of triglycerides and cholesterol esters and hydrophilc apoprotein portion consists of proteins and free cholesterol. The drug binding with human serum albumin & glycoprotein involves hydrophilic bonding whereas in case of lipophilic drug, they show hydrophobic bonding. They can also show binding because of their high lipid content, as the drug bind to lipoprotein, it dissolves in the lipid part of the protein which depends binding depend on its lipid content.

Since the chemical composition of lipoproteins vary, similarly, does their molecular weight (2-34 lakhs). They can be grouped under four different categories using density as the classifying parameter :-

1. Chylomicrons
2. VLDL (very low-density lipoproteins)
3. LDL (low density lipoprotein)
4. HDL (high density lipoprotein)

Triglycerides and cholesterol esters constitutes hydrophobic part and apoproteins constitutes the hydrophilic portion of lipoproteins. VLDL differs from HDL as the former has high content of triglycerides while the latter comprises apoproteins mainly.

There is no specific binding sites available and even this does not depend on concentration of drug so we can say that in this case the binding of drug to lipoprotein is non-competitive, the acidic as well as basic drugs get bound to the lipoproteins. Basic drugs show high affinity as compared to acidic drugs. Human serum albumin and glycoprotein has more plasma concentration as compared to lipoproteins. Lipids circulation to tissues via blood is the major role played by lipoproteins.

XIV. DRUG BINDING TO GLOBULINS

Globulins generally bind to endogenous substances that are present in the body. Globulins such as α_1, β_1, α_2, β_2 and Υ have been identified.

1. α1 – globulin (corticosteroid / transcortin binder) – various drugs like prednisolone (steroidal in nature), vitamins (cyanocobalamin) and hormones (thyroxine) usually binds with them.
2. α2-globulin (ceruloplasmin) – binds Cu^{2+} ions and fat soluble vitamins.
3. β1-globulin (transferrin) – binds Fe^{2+} ions
4. β2-globulin –binder of carotenoids.
5. Υ globulin –binds antigens.

XV. DRUG BINDING TO BLOOD CELLS

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In blood, erythrocytes are the major component (95%) among all formed elements present (45%) and they have large diameter compared to albumins (around 500 times). The RBC contains 3 different components which can bind to the drug:

Haemoglobin – The molecular weight of haemoglobin is 65,500 which is almost equal to that of HAS. Drugs like pentobarbital, phenytoin, phenothiazines bind to haemoglobins.

Carbonic anhydrase inhibitors – for example, chlorthalidone and acetazolamide etc.

Cell membrane – imipramine and chlorpromazine gets bound with cell membrane.
Lipophilic drugs can gain entry into erythrocytes easily as compared to hydrophilic drugs (ampicillin) and phenytoin.

XVI. DRUG BINDING TO THE EXTRACELLULAR TISSUES

The body tissue consists of40% of body weight which is 100 times the weight of human serum albumin. A drug gets bound to multiple components of a tissue. Apparent V_d gets enhanced when the drug binds to the extracellular tissue which may get hampered by binding with proteins present in plasma. However, the plasma protein binding decrease it. The drug binding to the tissues result in drug's localization at various sites of body which can enhance the half-life of the drug and the numbers of drug tissue binding irreversibly, example carbon tetrachloride, oxidation product of paracetamol, bromobenzene and phenacetin they bind covalently to the hepatic tissues.

A tissue is considered as the storage site for many drugs

There are some factors on which drug localization in tissue depends like structural features of the drug, rate of perfusion, pH difference and lipophilicity, [3]

Drugs binds with extra vascular tissues in the following order :-

LIVER > KIDNEY > LUNGS > MUSCLES

There are various examples of extravascular tissue drug binding: liver, muscles, kidney, skin, eye, hairs, lungs, bones, fat, nucleic acid etc.

XVII. DETERMINATION OF PROTEIN DRUG BINDING

1. **Indirect techniques:** dynamics dialysis, equilibrium dialysis, gel filtration, ultra-filtration, ultracentrifugation.
2. **Direct techniques:** UV spectroscopy, fluorimetry, HPLC.
   - **Factors affecting protein drug binding:** Factors affecting extent of protein-drug binding have been broadly classified as below
   - **DRUG related factors:** Physicochemical characters of the drug
     - Concentration of drug in the body
     - Affinity of drug for a particular bindingcomponent
     - Drug Interaction
     - Protein/Tissue Related Factors

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- Patient Related Factors

The half-life and affinity of drug vary with the protein binding phenomenon and these factors alter the protein binding property of drug, which alter the bioavailability of the drug into the body. [4]

XVIII. METABOLISM

The primary site for metabolism of different drugs is usually liver though it can take place in different tissues which have specific metabolic enzymes. The main objective of metabolism is to render drug molecules and their metabolites inactive and their easier passage for excretion. However, in some cases, the metabolites, so generated, are pharmacologically more active than the parent drug which are often referred to as prodrugs
The processes which are most commonly involved in drug metabolism include oxidation, condensation, conjugation, isomerization, reduction, hydration and hydrolysis. Metabolic rate varies from patient to patient which depends upon certain factors associated with individual's genetic inheritance, disorders already existing in body (chronic liver diseases) and to certain extent involving drug interactions. Some have such a high metabolic rate that the drug gets inactive before achieving targeted pharmacologically and therapeutically active blood and tissue concentrations while in others, it can be so slow leading to drug toxicity and adverse drug reactions.[8]

Generally, there are two phases involved in metabolism (biotransformation) for most of the drugs viz.

1. Phase I Reactions
2. Phase II Reactions

Phase I reactions (functionalization or non-synthetic reactions) involves generation of either a new functional group or modifying the existing ones by cleavage reactions including oxidation, reduction and hydrolysis. The main purpose of these reaction is to make drug metabolites more hydrophilic or polar so as to enable their easy excretion through kidneys from the body. However,

Phase II reactions(synthetic or conjugation reactions)are slightly different as they involves conjugation of drug metabolite with an endogenous substrate such as glucuronic acid, glycine, sulfate, etc. through reactions such as glucuronidation, acetylation, glutathione conjugation, etc. which renders them even more polar and hydrophilic for easier excretion. It is not necessary for every drug moiety to undergo through both phase I & II reactions. There are some drugs which preferably undergoes only phase I reactions. Phase number depicts only functional classification rather than sequential.

XIX. PHASE I REACTIONS

1. Oxidative reactions

- Oxidation of aromatic carbon atoms
- Oxidation of olefins (c=c bond)
- Oxidation of benzylic, allylic carbon atom and carbon atom alpha to carbonyl and imines

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- Oxidation of aliphatic carbon atoms
- Oxidation of alicyclic atoms
- Oxidation of carbon-heteroatom system
  - Carbon-nitrogen system (aliphatic and aromatic amines):
    - ✓ N-dealkylation
    - ✓ Oxidative deamination
    - ✓ N-oxide formation
    - ✓ N-hydroxylation
  - Carbon-sulphur system:
    - ✓ S-dealkylation
    - ✓ Desulphuration
    - ✓ S-oxidation
  - Carbon-oxygen system (O-dealkylation)
- Oxidation of alcohol, carbonyl and acid function
- Miscellaneous oxidative reactions

2. Reductive reactions

- Reduction of carbonyl function (aldehyde/ketone)
- Reduction of alcohol and c=c bonds
- Reduction of N-compounds (nitro, azo and N-oxide)
- Miscellaneous reductive reaction

3. Hydrolytic reactions

- Hydrolysis of esters and ethers
- Hydrolysis of amides
- Hydrolytic cleavage of non-aromatic heterocycles
- Miscellaneous hydrolytic reactions

XX. PHASE II REACTIONS

1. Conjugation with glucuronic acid
2. Conjugation with sulphate moieties
3. Conjugation with alpha amino acids
4. Conjugation with glutathione and mercapturic acid formation
5. Acetylation reactions
6. Methylation reactions
7. Miscellaneous conjugation reactions [3]

Drug's metabolism, excretion and its hepatic disposition is mainly affected by drug transporters which are wide spread in hepatic parenchymal cells. These hepatic transporters are basically of two types: **influx transporters** which governs entry of drug molecule into liver and **efflux transporters** which are responsible for exit of drug molecules either in blood or bile. The expression as well as function of these transporters is greatly affected by genetic polymorphism which can bring about significant change in patient's response to ADRs and sometimes, may even lead to hepatic injury caused by drug moiety. For example, statins used

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in treatment of hypercholesterolemia may induce myopathy in patients having certain genotype which leads to increase in plasma statin concentration.

1. **Rate:** Every metabolic pathway involving enzymes, transporters, etc. exhibits capacity limitation which depends on number of active binding sites available on enzymes for substrate molecules. At initial stage, the binding sites are not fully occupies, so, increase in substrate concentration at this level leads to simultaneous increase in metabolic rate (first order elimination kinetics) which eventually determines drug's half life.

2. **Cytochrome P-450:** This enzyme, indeed a superfamily of isoenzymes, is responsible for oxidation of drugs which is a very important part of **phase – I** metabolic reactions. NADPH-CYP450 reductase (flavoprotein) supplies electrons form NADPH towards it. Drug interactions cause either its induction or inhibition. Elderly people and infants have difficulty in metabolizing drugs through CYP450 because in the former case, there is reduced hepatic volume and blood flow which accounts for reduction in enzyme activity by $\geq$ 30% while in the latter case, hepatic microsomal enzyme system has not been developed substantially. It subsequently leads to prolonged half lives of drugs in either case.

3. **Conjugation:** It mainly involves conjugation of drug metabolites with endogenous substrates such as glucuronides (through glucuronidation), glutamine, glycine, glutathione (through glutathione conjugation), acetyl group (acetylation), etc. Out of these, glucuronidation is the most common conjugation reaction in **phase – II** which occurs in hepatic microsomal enzyme system. This is not affects by ageing, however, in infants, this reaction is so slow which often contributes to development of life-threatening ADRs as in case of chloramphenicol. [10]

XXI. EXCRETION OF DRUGS

It is an irreversible process of transferring Drugs and/or their metabolites from internal body environment to external environment through either kidneys (renal excretion) or lungs, intestine, biliary system, sweat and salivary glands, etc. (non-renal excretion). It is important that the complete intact drug or its metabolite must be passed out from body for bringing its pharmacological activity to a halt.

XXII. RENAL EXCRETION OF DRUGS

This is the most common route for excretion of a large number of drugs and their metabolites from the body in one way or the other. Some drugs such as gentamicin are so specific that they are excreted through kidneys only.

Following classes of agents are most commonly excreted through renal route in form of urine:

1. Water-soluble.
2. Non-volatile.
3. Small in molecular size (less than 500 Daltons).
4. The ones that are metabolized slowly.

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Nephron is the basic structural and functional unit of kidney which consists of glomerulus, PCT, DCT, loop of Henle and collecting duct. Approximately, one million nephrons are present in each kidney.

Three basic processes are involved in urinary excretion viz.

1. Glomerular filtration.
2. Active tubular secretion.
3. Active or passive tubular reabsorption.

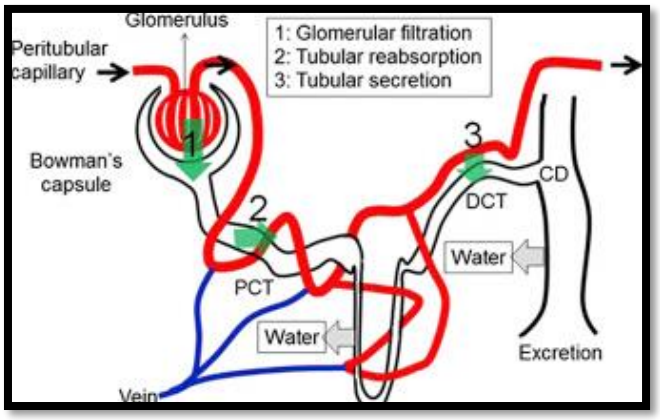

Figure 4: Urinary Excretion

XXIII. CONCEPT OF CLEARANCE

This term originally expresses the excretion of drugs and endogenous substrates through kidney as a measure of renal function. However, this term nowadays, has broader aspects including elimination of drugs through lungs (pulmonary clearance), liver (hepatic clearance), etc. which together are referred as non-renal clearance. Total systemic clearance compiles both renal as well as non-renal clearance. [11]

The drug containing hypothetical body fluid volume through which the drug has been completely removed in a specified time period is referred to as clearance (ml/min.) which is specific for given drug plasma concentration. Clearance denotes drug elimination rate as a function of plasma concentration in the similar way as amount of drug inside body is represented through apparent volume of distribution as a function of plasma drug concentration. [12]

$$\mathbf{Clearance(Cl)} = \frac{\boldsymbol{elimination\ rate}}{\boldsymbol{plasma\ drug\ concentration}}$$

Renal Clearance (Cl_R)

It is the volume of plasma that has been cleared completely from intact drug via kidneys as a function of time. Mathematically, it can be represented as:

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$$Cl_R = \frac{rate\ of\ urinary\ excretion}{plasma\ drug\ concentration}$$

Renal clearance, physiologicallycan be defined the ratio of "sum of rate of glomerular filtration and active secretion minus rate of reabsorption" to "plasma drug concentration C".

$$Cl_R = \frac{rate\ of\ filtration + rate\ of\ secretion - rate\ of\ reabsorption}{C}$$

Table 2: Relationship between Renal Clearance Values and Mechanism of Clearance

Renal Clearance (ml/min)	Renal Clearance Ratio	Mechanism of Renal Clearance	Example(s)
0 (least value)	0	Drug filtered and reabsorbed ompletely	Glucose
< 130	Above 0, Below 1	Drug filtered and reabsorbed partially	Lipophilic drugs
130 (GFR)	1	Drug is filtered only	Creatinine, Inulin
> 130	>1	Drug filtered as well as secreted actively	Polar, ionic drugs
650 (Highest value)	5	Clearance equal to renal plasma flow rate	Iodopyracet, PAH

Influence from each of the above physiological process on drug clearance cannot be directly measured. However, compounds getting cleared through glomerular filtration only may be used for comparing values of clearance so obtained such as creatinine, inulin, etc. which is referred to as renal clearance or excretion ratio.

$$\textbf{Renal Clearance Ratio} = \frac{Cl_R\ of\ drug}{Cl_R\ of\ creatinine}$$

The clearance ratio will differ according to the type of process whether the drug is only filtered, filtered and secreted or filtered and reabsorbed. The values for renal clearance ranges from 0 to 650 ml/min and for clearance ratio, these varies from 0 to 5.[13]

XXIV. FACTORS AFFECTING RENAL EXCRETION / RENAL CLEARANCE

Renal clearance of drugs depends on several factors apart from three physiological processes discussed above which in turn influence urinary excretion viz.

1. Physicochemical properties of the drug
2. Plasma concentration of the drug
3. Distribution and binding characteristics of the drug
4. Urine pH
5. Blood flow to the kidneys
6. Biological factors
7. Drug interactions
8. Disease states

XXV. RENAL FUNCTION AND RENAL FAILURE

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Values obtained for GFR using markers of both endogenous and exogenous origin indicates about renal function indirectly such as renal dysfunction or chronic renal disease. The marker agent used for determining GFR must be pharmacologically and physiologically inert. It must be cleared in its intact form through glomerular filtration only.

Examples of such markers which have been exploited largely in determining GFR and hence, renal function includes inulin (exogenous polysaccharide made up of fructose) and serum creatinine (endogenous amine generated through muscle catabolism). However, out of these two, creatinine clearance is widely used over inulin as the latter involves tedious process while the former has several advantages such as there is no need of performing urinary studiesand can be directly correlated to steady state plasma creatinine concentration. However, the generation of creatinine in body is a metabolic process which in turn depends on several factors such as age, gender, weight, etc. Hence, creatinine clearance in different individuals based on age, gender, weight, etc. is calculated using different formulas such as [14] :-

For Children (between 1 to 20 years),

$$\boldsymbol{Cl_{cr} = \frac{0.48\,H}{S_{cr}}\left[\frac{W}{70}\right]^{0.7}}$$

For Adults (above 20 years),

- males

$$\boldsymbol{Cl_{cr} = \frac{(40 - age)W}{72 S_{cr}}}$$

- females

$$\boldsymbol{Cl_{cr} = \frac{(40 - age)W}{85 S_{cr}}}$$

$$\boldsymbol{= 0.9\, Cl_{cr}\ of\ Male}$$

Where,
Clcr = creatinine clearance in ml/min,
Scr = serum creatinine in mg%,
H = height in cms, and
W = weight in Kg
Age is measured in years.

Creatinine clearance can also be measured through another direct method involving determination of excretion rate of creatinine in 24 hours and simultaneously calculating the mean of readings for serum creatinine levels before and after collecting urine at specified interval (for urine collection)

Creatinine clearance using this method can be calculated from the following formula :-

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$$Cl_R = \frac{rate\ of\ creatinine\ excretion}{serum\ creatinine}$$

The normal value for creatinine clearance ranges from 120 to 130 ml/min using this formula. If its value lies between 20 to 50 ml/min indicates moderate renal failure. Severe renal impairment results if its value approaches below 10 ml/min..

The renal function, RF can be calculated from followingequation :-

$$RF = \frac{Cl_{cr}\ of\ patient}{Cl_{cr}\ of\ a\ normal\ person}$$

Dose Adjustment in Renal Failure

Patients with problem of renal failure exhibits alteration in their pharmacokinetic profile which corresponds to reduction in drug elimination rate and simultaneously, renal clearance which corresponds to increase in drug's elimination half life and alteration in apparent V_d.It is very important to adjust dose of the drug based on renal function especially for those possessing narrow therapeutic index to avoid any severe drug toxicity.[15]

There is no requisite for changeing dosage regimen of a drug if

- The fraction of drug getting excreted remains unchangedi.e. f_u is$\leq$ 0.3, and
- The value for renal function (RF) is $\geq$ 0.7 i.e. normal.

The points mentioned holds true only when the metabolites generated are inactive and the binding property of the drug and its bioavailability is unchanged. Also, the renal function as well in case of renal failure situation. Elimination of drug gets extremely diminished when values of f_u and RF are unity and zero respectively. In such conditions, non-renal clearance of drugs gets enhanced substantially.

Following formula can be used to determine the amount of dose required for a patient suffering from renal impairment problem:-

$$\textbf{Drug dose in renal impairment} = \textbf{Normal dose x RF}$$

Following equation is employed for determining dosing interval of a drug in hours :-

$$\textbf{Dosing interval} = \frac{normal\ interval\ in\ hours}{RF}$$

The dose for a drug which has elimination from both renal as well as non-renal routes can be determined from the following equation :-

$$Drug\ dose = normal\ dose\ (RF \times fraction\ excreted\ in\ urine + fraction\ eliminated\ non-renally)$$

Dialysis and Haemoperfusion

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Dialysis is the process of removing out accumulated toxic excretory products such as potent drugs and their metabolites from blood plasma in case of serious injury to kidney or renal failure via diffusion across semi-permeable membrane either throughPeritoneal dialysis or Hemodialysis. The former involves filtration of blood through natural membrane present in peritoneal cavity of abdomen by introducing catheter and draining fluid into abdomen which is discarded after a span of time while in the latter case, system situated exterior to the body containing artificial membrane is employed. This is also widely used in case of drug poisoning situations as a result of overdosage. Since, the equipment has such a wide application for renal failure patients, it is also often called as artificial kidney. The hemodialysis using hemodialyzer takes around 3-4 hours and must be repeated every 2 days.[16]

The removal of toxic metabolites and other substances by hemodialysis is governed through several factors which are:

Water Solubility: a substance to get dialyzed must be water soluble. Drugs such as glutethimide can't be dialyzed because of their hydrophobicity.

Molecular Weight: dialysis can be more effective for molecules having low molecular weights below 500 Da. Vancomycin owing to its high molecular weight cannot be dialyzed.

Protein Binding: since, dialysis involves mere diffusion process (passive), hence, plasma protein bound drugs cannot be dialyzed.

Volume of Distribution: drugs such as digoxin possessing large V_d can't be dialyzed owing to their wider distribution in the body.

Hemodialyzer basically consists of a dialyzing fluid containing potassium, sodium, dextrose, chloride, calcium and acetate ions which is isotonic to blood plasma. Toxic metabolites and other excretory products such as uric acid, creatinine, urea, etc. present in patients' plasma are removed through diffusion process along semipermeable membrane into the dialysate fluid until establishment of equilibrium. However, it is possible to make plasma rid of toxic metabolites completely by replenishing the dialysate with fresh fluid. Drugs such as aminoglycosides, barbiturates, lithium, chloral hydrate, etc. can be extensively separated from plasma using hemodialyzer.

The machine's ability to make plasma free from drug and their toxic metabolites is expressed by dialysance (dialysis clearance) and rate of dialysis is determined by blood flow rate to it which often affects its performance. Dialysis clearance can be calculated from the following equation :-

$$\boldsymbol{Cl_d = \frac{Q\,(C_{in} - C_{out})}{C_{in}}}$$

Where, Cl_d = dialysance or dialysis clearance
Q = rate of blood flow to dialyzer
C_{in}= drug concentration in blood while entering the dialyzer
C_{out} = drug concentration in blood while leaving the dialyzer

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Hemoperfusion involves passage of blood through bed/layers of charcoal or any other resin used as adsorbent. This method does purifies blood from toxic metabolites via adsorption process but has serious drawback of retaining WBCs, platelets and other endogenous steroids on the adsorbent surface. This method find its wide application in severe toxicity of any drug.

NON-RENAL ROUTES OF DRUG EXCRETION

All the routes of drug and/or their metaboiltes excretion other than kidneys comprises **extrarenal** or **non-renalroutes of drug excretion**such as:-

1. Biliary excretion
2. Pulmonary excretion
3. Salivary excretion
4. Mammary excretion
5. Skin/dermal excretion
6. Gastrointestinal excretion
7. Genital excretion [3]

Table 3: Excretion Routes, Mechanisms and Drug Excreted

Route of Excretion	Mechanism of Excretion	Type of drug excreted
Renal Excretion	Glomerular filteration, Active Secretion, Active/ Passive reabsorption	Free, Hydrophilic, Unchanged drugs
Billiary Excretion	Active Secretion	Hydrophillic, Unchanged drugs/metabolites/Conjugates of molecular weight > 500
Pulmonary Excretion	Passive Diffusion	Gaseous and volatile, blood and tissue insoluble drugs
Salivary excretion	Passive Diffusion, Active Transport	Free, unionized, lipophilic drugs, some polar drugs
Mammary excretion	Passive Diffusion	Free, unionized, lipophilic drugs (Some basic drugs)
Dermal excretion	Passive Diffusion	Free, unionized, lipophilic drugs

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