Dr.Iman **Lec. 4**

Factors affect absorption

1- pH 2- Blood flow 3- Total surface area available 4- Contact time

.5 -. **Expression of P-glycoprotein**: P-glycoprotein is a multidrug transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes It is expressed throughout the body six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell, and its functions include:

- **In the liver**: transporting drugs into bile for elimination
- **In kidneys**: pumping drugs into urine for excretion
- **In the placenta**: transporting drugs back into maternal blood, thereby reducing fetal exposure to drugs
- **In the intestines**: transporting drugs into the intestinal lumen and reducing drug absorption into the blood
- **In the brain capillaries**: pumping drugs back into blood, limiting drug access to the brain

Thus, in areas of high expression, P-glycoprotein reduces drug absorption. In addition to transporting many drugs out of cells, it is also associated with **multidrug resistance**

Bioavailability

Definition:- Fraction of administrated drug that gains access to the systemic circulation in a chemically unchanged form.

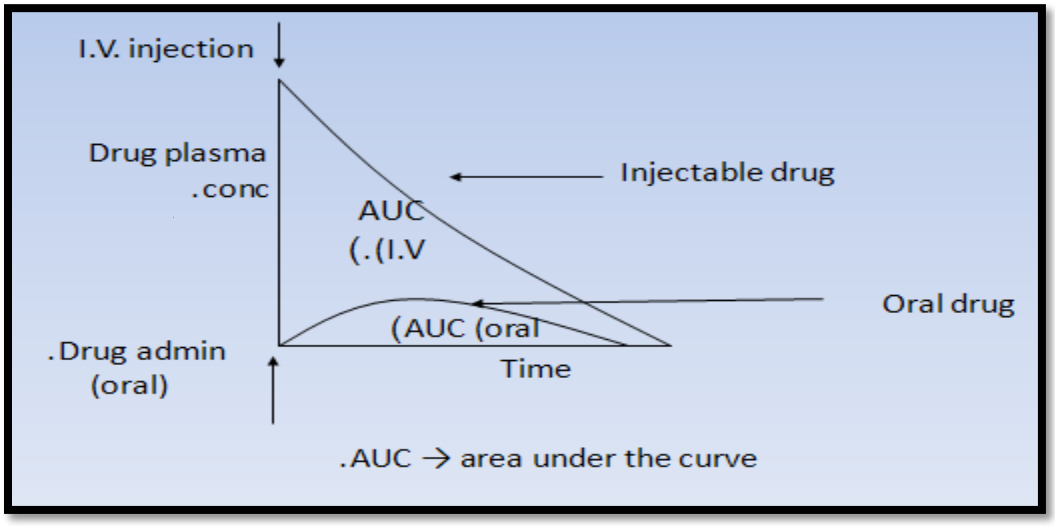
If the drug is given I.V., it is 100% available for therapeutic effect. (if 100mg of drug is given orally, 70mg → will reach the plasma unchanged , therefore bioavailability is 70% due to incomplete absorption and 1st pass metabolism.

Determination of bioavailability

Pharmacokinetic study must be done to obtain a plasma drug concentration VS time plot for the drug after both I.V. and non I.V. routes.

Bioavailability is the ratio of the area under plasma conc. Time curve (AUC) after a single oral dose to that obtained after I.V. admin. Of the same amount.

Bioavailability = { AUC after single oral dose / AUC after same I.V. dose }x100



Factors that influence bioavailability :-

1.**First - pass (hepatic) metabolism**: When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation .If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is decreased..: First-pass metabolism by the intestine or liver limits the efficacy of many oral medications. For example, more than 90% of *nitroglycerin* is cleared during first-pass metabolism. Hence, it is primarily administered via the sublingual or transdermal route. Drugs with high first-pass metabolism should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.

2.**Biological factors** :

Insulin :destroyed in the GI tract by degradative enzymes.

Binding to food e.g tetracycline and calcium in milk.

Penicillin G → unstable in gastric PH.

3.**Pharmaceutical factors (drug formulation)** : Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

4.**Solubility of drug :** Very hydrophilic drugs are poorly absorbed because of their inability to cross lipid-rich cell membranes. Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells.

For a drug to be readily absorbed, it must be largely lipophilic, yet have some solubility in aqueous solutions.

This is one reason why many drugs are either weak acids or weak bases. Drugs that are highly lipid soluble transported in aqueous solution by carrier proteins eg. Albumin

5.**Others**: like : intestinal motility, disease states affecting liver metabolism or gastrointestinal function.

Bioequivalence

Two drug formulations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations

Therapeutic equivalence

Two drug formulations are therapeutically equivalent if they are pharmaceutically equivalent (, they have the same dosage form, contain the same active ingredient, and use the same route of administration) with similar clinical and safety profiles.Clinical effectiveness often depends on both the maximam serum drug concentration &on time needed to reach peak conc.So, two drugs that are bioequivalent may not be therapeutically equivalent.

Distribution of drug

. is the process by which a drug reversibly leaves the blood stream and enters the interstitium (extracellular fluid) and the tissues. For drugs administered IV, absorption is not a factor, and the initial phase represents the distribution phase, during which the drug rapidly leaves the circulation and enters the tissues

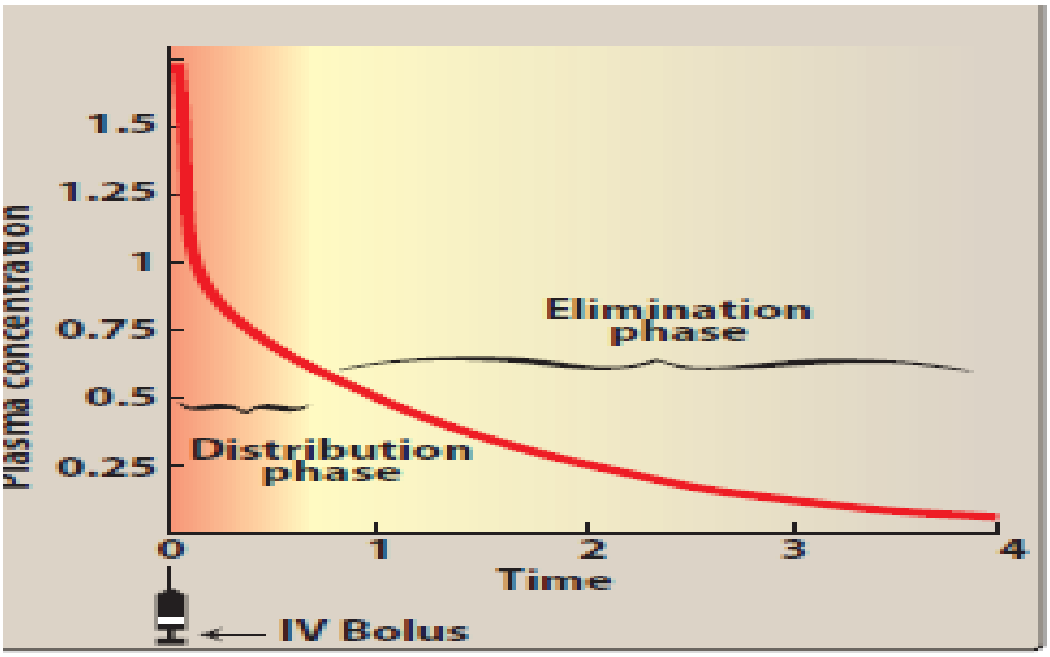


Figure 1.12
Drug concentrations in serum after a single injection of drug. Assume that the drug distributes and is subsequently eliminated.

Distribution depends on :

1-Blood flow :- The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to the "vessel-rich organs" (brain, liver, and kidney)is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow. Variation in blood flow partly explains the short duration of hypnosis produced by an IV bolus of *propofol* .High blood flow, together with high lipophilicity of *propofol,* permits rapid distribution into the CNS and produces anesthesia. A subsequent slower distribution to skeletal muscles and adipose tissues lowers the plasma concentration so that the drug diffuses out of the CNS, down the concentration gradient ,and consciousness is regained.

a-Capillary structure: presence or absence of slit junctions in the basement membrane between endothelial cells of capillaries. To enter the brain, drugs must pass through the endothelial cells of the CNS capillaries or be actively transported. For example, a specific transporter carries *levodopa* into the brain.

b-Drug structure: non ionised (lipid soluble) or ionised (water soluble). , lipid-soluble drugs readily penetrate the CNS because they dissolve in the endothelial cell membrane. Ionized or polar drugs generally fail to enter the CNS because they cannot pass through the endothelial cells that have no slit junctions

3-Binding: to plasma proteins. The binding of a drug to P.P. will slow its transfer out of the vascular compartment.

Binding to tissue proteins: Many drugs accumulate in tissues,leading to higher concentrations in tissues than in the extracellular fluid and blood. Drugs may accumulate as a result of binding to lipids, proteins, or nucleic acids. Drugs may also be actively transported into tissues. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity. (For example, acrolein, the metabolite of *cyclophosphamide* can cause hemorrhagic cystitis because it accumulates in the bladder.)

Volume of distribution (Vd) (apparent volume)

- A hypothetical volume of fluid into which a drug is disseminated with a concentration equal to that in the plasma.
- Lipid soluble drugs diffuse freely and have larger Vde.gparacetamol.
- If the drug remains mostly in the plasma (bound) → small Vd.
- Non lipid soluble → small Vd.
- Drugs stored in the tissues → ↑ Vd.
- ↑Vd will ↑ t ½ & the duration of action.

Calculation of Vd:

$Vd = d / c_0$

d = total amount of drug in the body (dose).

c = plasma concentration of the drug at zero time.

e.g : dose = 25mg , plasma concentration = 1mg/L
Vd = 25mg / 1mg/L=25L

Practical value of Vd

- E.g. salicylate has small Vd ,major proportion of drug in plasma, can be removed by haemodialysis in cases of intoxication.
- Chloroquine has larger Vd ,haemodialysis is inappropriate treatment of overdose.

Plasma protein and tissue binding

1. Drugs may bind to plasma protein (P.P.) reversibly. They circulate in a protein – bound and free state and in dynamic equilibrium.
2. The free fraction is pharmacologically active and can diffuse through capillary wall, produce it's systemic effects, metabolized, dialysed or excreted.
3. The protein – bound fraction is a reservoir of inactive drug.
4. Most drugs are associated with plasma components such as albumin, globulins, transferrin, glycoprotiens, and α and β – lipoproteins.

5. **Albumin:**-is the main binding protein for drugs and many natural substances.

Albumin has high capacity (a number of drug molecules bind to a single albumin molecule), and low affinity for many basic drugsi.e a lot is bound but it is readily released.
And has low capacity (1 :1) (one molecule of drug + one molecule of albumin) with high affinity for acidic drug& hydrophobic drugs.

6. Saturation of binding sites is unlikely in therapeutic doses.
7. Acidic drugs bound to albumin, basic drugs bound to albumin, lipoprotein and α_1 – glycoprotein.
8. Drugs may interact competitively at plasma protein binding site **e.gtolbutamide**, 95% bound to P.P. and 5% free, if **sulfonamide***** is given, it displace tolbutamide from P.P. so free (active) form of tolbutamide↑ in plasma. Drug – drug interaction can take place at P.P. binding sites.
9. Reduction of P.P. (albumin) e.g : in renal failure and in liver disease may increase the free fraction of some drugs (need dose monitoring)

Tissue binding

Many drugs accumulate in tissues,leading to higher concentrations in tissues than in the extra cellularfluid and blood. Drugs may accumulate as a result of binding to lipids, proteins, or nucleic acids. Or may also be actively transported into tissues. Tissue reservoirs may serve as a major source of the drug and prolong its actions , delays elimination and prolongs half life (t 1/2) of the drug or cause local drug toxicity. (For example, acrolein, the metabolite of *cyclophosphamide*, can cause hemorrhagic cystitis because it accumulates in the bladder.)

-benzodiazepines enter fat stores, **chloroquine** binds to a melanin – containing tissues.

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-Displacement from tissue binding site may be a mechanism for pharmacokinetic interaction, **e.g : digoxin and quinidine.**-Free plasma digoxin will be **doubled** because quinidine will displace digoxin from tissue binding and impair, renal excretion of digoxin.

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Order of reaction (or kinetic)

Rate at which movement and changes of drug molecules take place across cell membrane and during metabolism and elimination.

First order kinetics :-

1. Constant fraction of drug is transported / metabolised unit time e.g : 10% of drug / unit time.
2. Rate of absorption, distribution and excretion of a drug are directly proportional to it's concentration in the body.
3. The process follows Law of Mass Action.↑ concentration of drug → ↑ rate of reaction (absorption, metabolism, excretion).
4. In doses used clinically, most drugs are subjected to first order kinetics.

Zero order kinetics :-

1. Constant amount of drug is transported, metabolised, eliminated / unit of time, independent of the concentration of the material.
2. Metabolic process that has limited capacity becomes saturated as the amount of the drug rises in body.
3. Enzyme mediated metabolic process are the most likely to show rate – limitation because the amount of enzyme can become saturated.
4. Rate of the process reaches it's maximum where it stay constant; rate limited = zero order = saturation kinetics.

e.g : alcohol (ethanol) is subjected to 1st order kinetics at plasma concentration < 10 mg/100ml; t 1/2 = 1hour

alcohol alcohol dehydrogenase acetaldehyde

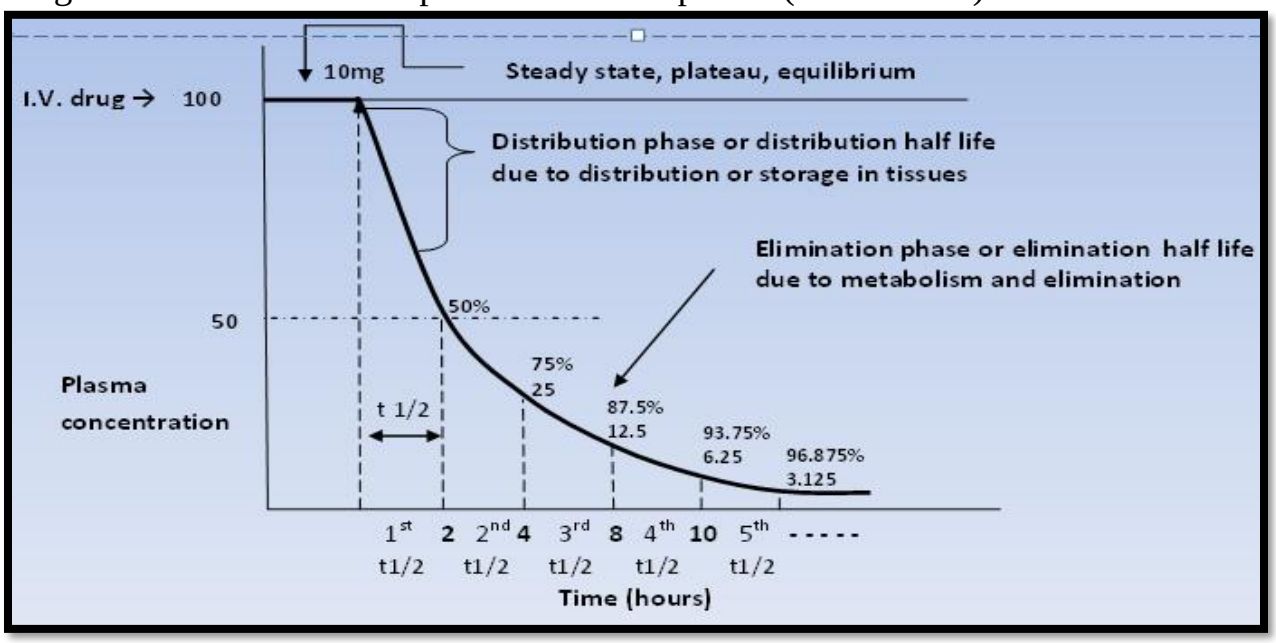
at ↑ concentration, the enzyme alcohol dehydrogenase becomes saturated and the rate of metabolism becomes constant **i.e** zero order kinetic**; increasing t 1/2** leads to alcohol accumulation

other**e.g phenytoin and salicylate.**

Time course of drug concentration and effect

Plasma half life (t 1/2) :-

Time taken for plasma concentration to fall by half, it is constant if elimination processes are first order kinetic. And ↑ with increase in the dose in zero order kinetic. A drug is eliminated from the plasma in 5 t 1/2 period (Rule of five).



Rule of five

Generally, the elimination 1/2life = time at which the drug is "completely" (97%) eliminated from the body (assuming that the drug was given in a **single** original dose)

1. First t1/2life – 50% of the original drug removed.
2. Second t1/2life – 75%
3. Third t1/2life – 87.5%
4. Forth t1/2life – 93.75%
5. Fifth t1/2life – 96.875%

Clinical situations resulting in changes in drug half-life

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required.

. The half life of a drug is increased by 1) diminished renal or hepatic plasma flow ,e g; , in cardiogenic shock, heart failure, or hemorrhage; 2) decreased ability to extract drug from plasma, for example, as
seen in renal disease; and 3) decreased metabolism, for example, when another drug inhibits its biotransformation or in hepatic insufficiency as with cirrhosis.

. On the other hand, the half-life of a drug may decrease
by 1) increased hepatic blood flow, 2) decreased protein binding, and3) increased metabolism

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Steady state

-Plasma concentration when the amount of the drug in the body remains constant, i.e plasma concentration is on the plateau and the rate of administration is exactly equal to it's rate of elimination.

-Stable drug effect.

-When drug is given at a stable – constant – dose approximately **five half – lives** are required to achieve steady – state concentration.

-With each t1/2 plasma concentration ↑ by half the difference between the ultimate steady state (100%) concentration and the current concentration.

-Maximal **therapeutic effect** do not occur until equilibrium is established, when drug dose is changed, an additional 5 t 1/2 are needed to re – establish equilibrium.

-When a drug is discontinued, it is eliminated gradually over several t1/2 (usually 5).

Calculation of steady state concentration :-

1) t1/2 100/2 = 50% =(ultimate conc."100" – actual conc. "0")/2 = 100/2
2) t1/2 50% + 50/2 = 75%
3) t1/2 75% + 25/2 = 87.5%
4) t1/2 87.5% + 12.5/2 = 93.75%
5) t1/2 93.75% + 6.25/2 = 96.875%