Pharmacokinetics of Drugs

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Absorption

- Is the transfer of a drug from its site of administration to the bloodstream.
- Absorption depend on the route of administration.
- IV delivery, absorption is complete; that is, the total dose of drug reaches the systemic circulation.
- Oral route requires that a drug dissolve in the GI fluid and then penetrate the epithelial cells of the intestinal mucosa ,disease states or the presence of food may affect this process.

Factors Affecting Drug Absorption

- Transport
- pH
- Physical factors

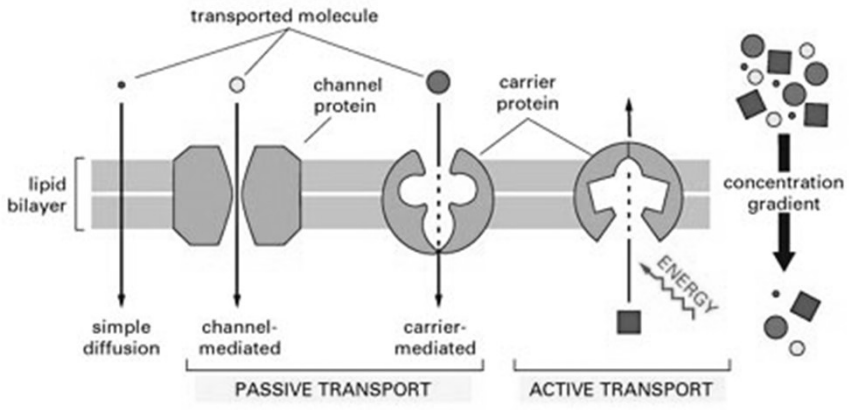
Transport of a drug from the GI tract

(Depending on their chemical properties)

- Passive diffusion
  The drug moves from a region of high concentration to one of lower concentration.
- Lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane bilayers.
- Water-soluble drugs penetrate the cell membrane through aqueous channels or pores

Active transport

- Drug entry involves specific carrier proteins that span the membrane
- Active transport is energy-dependent and is driven by the hydrolysis of adenosine triphosphate
- It is capable of moving drugs against a concentration gradient that is, from a region of low drug concentration to one of higher drug concentration.



- Endocytosis and exocytosis:
  This type of drug delivery transports drugs of large size across the cell membrane.
  Endocytosis involves engulfment of a drug molecule by the cell membrane and transport into the cell by pinching off the drug-filled vesicle (vitamin $B_{12)}$
  Exocytosis is the reverse of endocytosis and is used by cells to secrete many substances by a similar vesicle formation process. (norepinephrine).

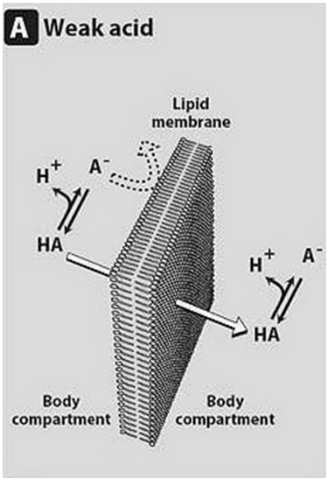
pH

Most drugs are either weak acids or weak bases

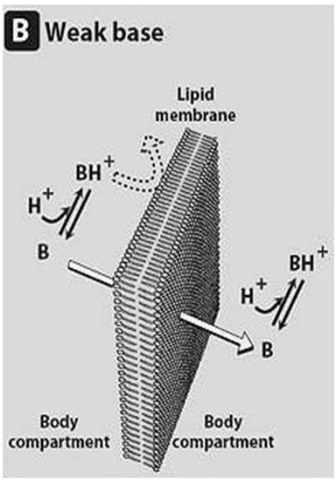
- Acidic drugs (HA) release an H^+ causing a charged anion (A^-) to form
  HA -------- $H^+ + A^-$
- Weak bases (BH^+) can also release an H^+. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):
  BH^+ --------- $B+H^+$

- A drug passes through membranes more readily if it is uncharged
- For a weak acid, the uncharged HA can permeate through membranes, and A^- cannot.
- For a weak base, the uncharged form, B, penetrates through the cell membrane, but BH^+ does not.

A. Diffusion of the non-ionized form of a weak acid through a lipid membrane.



B. Diffusion of the nonionized form of a weak base through a lipid membrane.



The effective concentration of the permeable form of each drug at its absorption site is determined by pka

Pka
Is the ratio between charged and uncharged, it is determined by PH at site of absorption and by the strength of acid and base

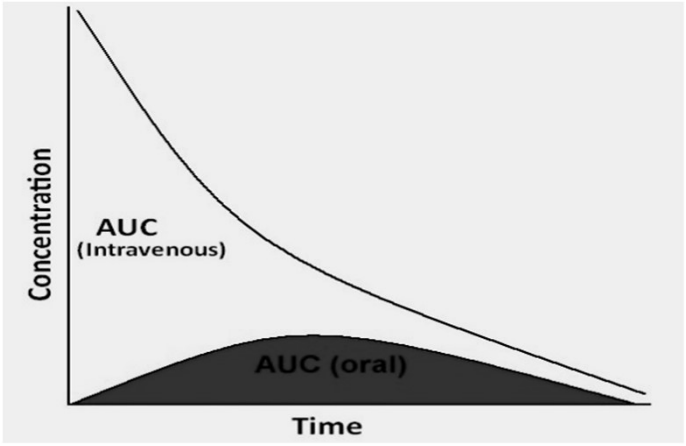
- e.g. acidic drug (aspirin) unionized at acid gastric PH and absorbed from stomach
- e.g. acidic drugs are ionized more in alkaline urine so not diffuse back in the kidney (faster excreation).

Physical factors influencing absorption

1. Blood flow to the absorption site: Blood flow to intestine is much greater than stomach thus absorption from intestine is favored over that from the stomach .
2. Total surface area: The intestine has a surface rich in microvilli thus the absorption of drug across the intestine is more efficient
3. Contact time at absorption surface: If drug moves through the GI tract very quickly, as in sever diarrhea ,it is not well absorption ,while the delay transport of the drug from the stomach to the intestine delays the rate of absorption of the drug.

Area under the curve (AUC)

- Represents the total amount of drug in the plasma during a certain time period.
- It is derived from the plot of drug concentration in blood or plasma as a function of time.



Area under the curve(AUC)

It is useful in the determination of other parameters including:

- Volume of distribution
- Clearance.
- Bioavailability.

Bioavailability:

It is the **amount of the drug** which reaches the circulation in an active form after oral administration, and ready to distribute and produce its effect and response

This amount is the fraction of dose absorbed **(F).**

Bioavailability= (AUC oral/AUC injected) x 100%

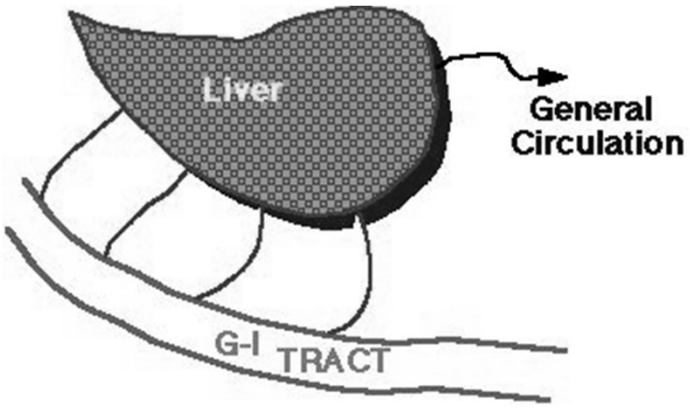
iv

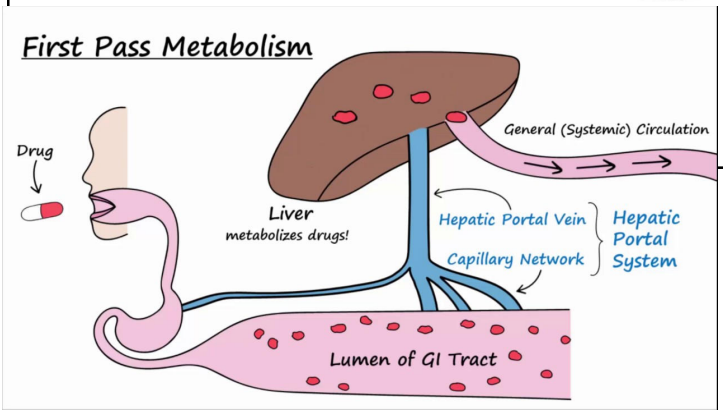
Factors which affect the bioavailability:

1. Presystemic factors (first pass metabolism in the liver).
2. Solubility of the drug
3. Chemical instability
4. Nature of the drug formulation

1. **First pass effect**: it is term used for the hepatic metabolism of pharmacological agent when it is absorbed from the gut and delivered to the liver via the portal circulation.
   The greater the first pass effect, the less the agent reaches to the circulation when the agent is administrated orally

First pass metabolism in the liver





2. Solubility

- Very hydrophilic drugs are poorly absorbed because of their inability to cross the lipid rich cell membranes
- Highly lipid soluble drugs easily cross cell membranes

3. Instability

- Some drug such as Penicillin G, are unstable in PH of the gastric content
- Insulin destroyed in the GIT by enzymes

4. Nature of drug formation

Drug absorption may altered by factor unrelated to the chemistry of the drug

e.g. particle size, enteric coated agents

Volume of distribution (V_d)

Term used to quantify the distribution of the drug through out the body after an oral or iv dosing.

Is a hypothetical volume of fluid into which the drug is dispersed.

Factors Affect Distribution

1. Blood flow in brain,liver, kidney is grater than the skeletal muscle

2. Capillary permeability
   Capillary permeability is determined by capillary structure and by the chemical nature of the drug

Factors Affecting Drug Distribution

1. Tissue Permeability of the drug .
   a. Physiochemical properties of drugs like (molecular size , Pka , Partition coefficient).
   b. Physiological barriers to diffusion drug.
2. Organ/tissue Size and Perfusion Rate.
3. Binding of Drugs to Tissue Components.
4- Miscellaneous factors

age , pregnancy , diet , obesity ,disease and drug interaction).

- The basement membrane in liver allows drug to exchange
- The chemical structure of drug influences its ability to cross cell membranes .
  e.g. hydrophobic drugs , no net charge, readily move across most biologic membrane

3. Binding to proteins

Reversible binding to plasma proteins slows their transfer out of the vascular compartment .

Plasma albumin is the major drug binding portions and may act as a drug reservoir(when the concentration of the free drug decreases, the bound drug dissociates from protein this maintains the free- drug concentration as a constant fraction of the total drug in plasma

Water compartments in the body

1.Plasma compartment:

If a drug has a very large molecular weight or binds extensively to plasma proteins, it is too large to move out through the endothelial slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment.

2.Interstitial Fluid (extracellular fluid)

If drug has a low molecular weight but its hydrophilic , it can move through the endothelial slit junctions of the capillaries into the Interstitial Fluid. e.g. aminoglycoside antibiotic

3. Intracellular Fluid

If a drug has a low molecular weight and hydrophobic , not only can move into interstitium through the slit junction , but it can also move through the cell membranes into the Intracellular Fluid e.g. ethanol

4.Other site

In pregnancy the fetus may take up drugs and thus increase the volume of distribution

Volume of distribution (V_d)

$V_d = D/C_0$

- Drugs that are highly lipid soluble, such as digoxin, have a very high volume of distribution .
- Drugs which are lipid insoluble, such as neuromuscular blockers, remain in the blood, and have a low V_d.

Volume of distribution (V_D)

$$V_D = \frac{amount\ of\ drug\ in\ the\ body}{plasma\ drug\ concentration}$$

Volume of distribution (V_d)

$V_d = D/C_0$

D = dose, C_0 = concentration at t_0

Example:

A 500 µgm dose of digoxin was given to a patient, after which the plasma concentration of digoxin was measured and found to be 0.7 ng /ml. calculate V_d

Volume of distribution: (V_d)

V_d=500/0.0007=714L

Clinical importance of V_d

1. Drugs with high **V_d** usually have **high lipid solubility** which makes them having a **long half life**.
2. **V_d** is used to estimate the **initial dose** of the drug needed to achieve therapeutic pl. con. at the beginning of treatment (**loading dose**).

Loading dose =V_d x Target concentration

Metabolism

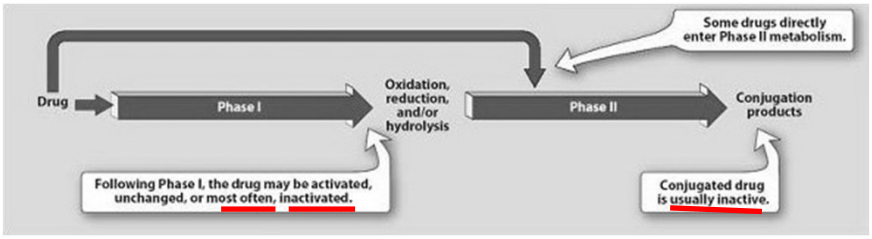
Is the irreversible transformation of substances and its metabolites.

Reactions of drug metabolism

The kidney cannot eliminate lipophilic drugs

Therefore, lipid-soluble agents must first be metabolized in the liver using two general sets of reactions, called Phase I and Phase II

The biotransformation of drugs



Phase I (oxidation, reduction, hydrolysis)

Phase I reactions function to convert lipophilic molecules (oxidized or reduced) into more polar molecules by introducing or unmasking a polar functional group (OH, $-NH_2$, -SH)

exposing

- Phase I reactions most frequently involved in drug metabolism by the cytochrome P450 system (also called microsomal mixed function oxidase)
- The P450 system is important for the metabolism of many endogenous compounds (steroids, lipids, etc) and for exogenous substances .

Cytochromes P450 are a superfamily of enzymes containing heme as a cofactor that function as monooxygenases.

Enzyme induction

- The drug called(inducer)
- A drug may induce the enzyme that is responsible for the metabolism of another drug or even itself e.g:

• Carbamazepine (antiepileptic drug) increases its own metabolism

• Phenytoin increases hepatic metabolism of oral Contraceptives Leading to decreased level

Reduced action and Unplanned Pregnancy

•Phenobarbital + warfarin

metabolism of warfarin (danger of thrombosis)

How is cytochrome P450 induced?

The most common mechanism of CYP enzyme induction is transcriptional gene activation. Nuclear receptors, such as the aryl hydrocarbon receptor (AhR), pregnane X receptor (PXR) and constitutive androstane receptor (CAR), mediate drug-induced changes in the expression of phase I and phase II enzymes and transporters.

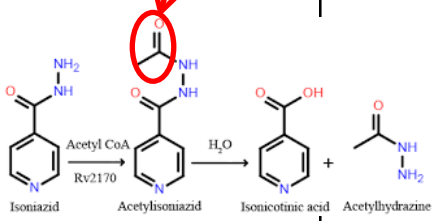
Enzyme inhibition:

- It is the decrease of the rate of metabolism of a drug by another one.
- This will lead to the Increase of the concentration of the target drug and leading to the increase of its toxicity .

Cimetidine + Theophylline

cimetidine reduces the clearance of theophylline causing an increase in adverse effects

Acetyl



Phase II

- This involves coupling the drug metabolite with an endogenous substrate (glucuronic acid, sulfate, glycine, or amino acids) results in polar, usually more water –soluble compounds
- Some parent drugs may already possess a functional group that may form a conjugate directly without prior Phase I reaction
- Not all drugs undergo Phase I and II reactions in that order. For example, isoniazid is first acetylated (a Phase II reaction) and then hydrolyzed to isonicotinic acid (a Phase I reaction)

Anti TB drug

Phase I reactions not involving the P450 system: These include amine oxidation (for example, oxidation of catecholamines or histamine), alcohol dehydrogenation (for example, ethanol oxidation), esterases (for example, metabolism of pravastatin in liver)

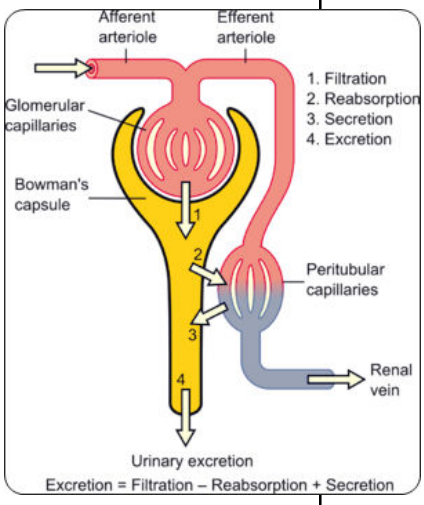
Drug Elimination

Removal of a drug from the body occurs via a number of routes, the most important being through the kidney into the urine. Other routes include the bile, intestine, lung, or milk in nursing mothers

Kidney is responsible for excreating all water souble substances

Net renal excretion =
glomerular filtration+tubular secreation-tubular reabsorption

- All non protein bound drugs presented to the glomerulus is filtered , thus glomerular filtration of drug depends on it is plasma protein binding and renal blood flow **& particle size**



Distal tubular reabsorption

- The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation.
- Manipulating the pH of the urine to increase the ionized form of the drug in the lumen may be used to minimize the amount of back-diffusion(increase the clearance of an undesirable drug
- Weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine

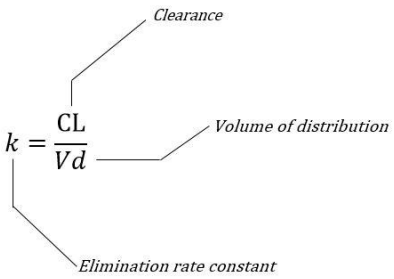
Proximal tubular secretion

- Secretion primarily occurs in the proximal tubules by two energy-requiring active transport (carrier-requiring) systems, one for anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms of weak bases).

A-

BH+

- Clearance (CL): It represents the volume of blood or plasma which is completely cleared from the drug per unit time.
- CL = k x V_d



In clinical practice clearance can be used to calculate the maintenance dose of some important drugs.

A maintenance dose is the maintenance rate [mg/h] of drug administration equal to the rate of elimination at steady state.

Example of maintenance dose calculation:
A target plasma theophylline concentration of 10mg/liter is desired to relieve acute bronchial asthma in a patient, if theophylline clearance=2.8L/h, what is the maintenance dose?

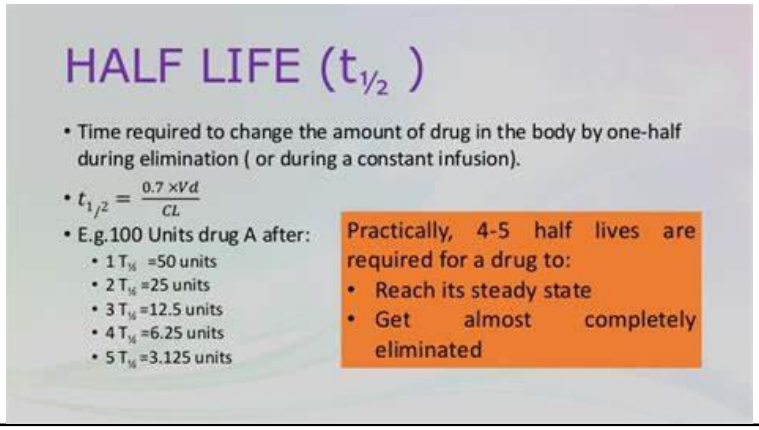
Clearance **Conc. at steady state**

Dosing rate = CL ×C_{ss} = 2.8 × 10 = 28 mg/hour
Therefore in this patient the proper intravenous infusion rate
would be 28 mg/hour.
The attack was relieved and the physician wants to maintain the treatment with theophlline which is given every 12 hours, what would be the dose of theophylline?
Maintenance dose = dosing rate × dosing interval
= 28×12 hours = 336 mg every 12 hours

Half life ($t_{1/2}$)

- The time it takes for plasma levels of drug to decrease by half (50%) is called the half-life
- $t1/2 = 0.693 \times V_d / cl$

Clearance



Concentration at steady state:

- It is the concentration of the drug which is reach after specific time of drug administration; usually the period reach to this state is 5× half life time, the half life time is the time which is needed for the original concentration of the drug in the blood to be half.
- Steady state usually occurs when a drug is given by constant i. v. infusion or repeatedly by other routes, the amount of the drug in the body and with it the plasma concentration rise until reached this state

Concentration of steady state (Css)
At steady state
1. Drug input = drug output
2. Maximum effect
3. Neither toxicity nor decline of effect
4. The amount of the drug in the body is constant

First order kinetics

- The processes of absorption, metabolism and elimination are proportional to the concentration o of the drug present in the body at that time
- The majority of drugs used therapeutically follow first order kinetics.

Zero order kinetics :saturated kinetics

Some processes of pharmacokinetic are independent of the concentration of drug.

- For some drugs as ethanol, phenytoin and salicylates which are inactivated by metabolism, the drug is removed at constant rate that is independent of plasma concentration.
- The explanation for this is that the rate of metabolism of these drugs reaches a maximum behind it no increase in the metabolism of the drug; this is because there is a limited amount of the enzymes which are responsible for drug metabolism.