Pharmacokinetics

Its study the effects of the body on the administered drug (*movement of drug inside the body*).
It represent four steps **A**bsorption, **D**istribution, **M**etabolism and **E**xcretion. [**ADME**]
Absorption: The transport of drug from the administration site to the blood stream crossing different biological membranes.
Distribution: The transfer of drug from bloodstream into the interstitial space of tissue and then into cell .
Metabolism: The enzymatic alteration in the structure of drug to more hydrophilic products to be easily excreted.
• **Excretion:** The movement of drugs and their metabolites outside the body by different routes of excretion.

❖ Application of pharmacokinetics in therapeutics

➢ Clinician can utilize the kinetic parameters to determine;
- The concentration of a drug at its sites of action
- The speed onset of drug action.
- Duration of drug action.
-Route of administration
- The intensity of drug action (dose, frequency of use & time course for required intensity). By applying knowledge of pharmacokinetics to drug therapy, we can help maximize beneficial effects and minimize harm. By selecting the most appropriate route, dosage, and timing (dose interval).

❖ Common factors affecting the absorption of drugs from GIT;

1- Drug dissolution and other physicochemical properties:
Before absorption the drug must be dissolved (dissolute). Drugs formulated for rapid dissolution have faster effect than formulations of slow dissolution.
2-Total surface area available for absorption
The *surface area* available for absorption is a major determinant of the *rate of absorption*. The *larger the surface area, the faster is the absorption*. For this reason, orally administered drugs are usually absorbed from the small intestine rather than from the stomach due to the presence of microvilli in brush borders of intestine (surface area about 1000-fold that of the stomach), so the absorption of the drug across the intestine is more efficient.
3- Blood flow to the absorption site
Drugs are absorbed most rapidly from sites where blood flow is high because such flow maintain a large gradient of drug concentration across vascular membrane , as blood containing absorbed drug replaced by drug free blood.
The intestines receive much more blood flow than does the stomach, so absorption from the intestine is favored over the stomach.

4- Concentration of drug and Contact time with the absorption surface:
The administered dose or concentration directly proportion with the amount of absorbed drug.
As well the contact time, if a drug moves through the GI tract very quickly, as can happen with diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the GIT delays the rate of absorption.
[Note: The presence of food in the stomach both dilutes the drug and slows gastric emptying.
Therefore, a drug taken with a meal is generally absorbed more slowly.
5-Lipid Solubility
As a rule, lipid-soluble drugs are absorbed more rapidly than drugs whose lipid solubility is low.
Because lipid soluble drugs can readily cross the membranes that separate them from the blood, whereas drugs of low lipid solubility cannot.
6- PH Partitioning
Most drugs are either weak acids or weak bases. Acidic drugs (HA) release a proton (H+), causing a charged anion (A-) to form:

$$HA \text{ (non -ionized)} \longleftrightarrow H^+ + A^- \text{ (ionized)}$$

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):

$$BH^+ \text{ (ionized)} \longleftrightarrow B \text{ (non-ionized)} + H^+$$

➢ All non-ionized drugs are lipid soluble and the ionized drug is water Soluble. So that the nonionized drug can be diffused through the lipid membrane by simple diffusion without energy.
Thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and A^- cannot.
For a weak base, the uncharged form B penetrates through the cell membrane, but the protonated form BH+ does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by *the relative concentrations of the charged and uncharged forms.*

The distribution ratio between the two forms (ionized and non-ionized) is determined by;
1- The pH at the site of absorption
2- The strength of the drug (weak acid or base), which is represented by the ionization constant, pKa.
PH=-Log [H+]. The **PH for the medium = un constant**.
pKa = -Log Ka. The **pKa for each drug is constant**

▪ **The weak acid drugs** are ***highly absorbed from acidic*** medium like ***stomach*** because *the non-ionized from greater than the ionized form*. While ***lower absorption*** occurs ***in alkaline medium like intestine*** because the ionized form greater than non-ionized form.

▪ **The weak base drugs** are ***high absorbed in alkaline medium like intestine*** because the *nonionized form greater than the ionized form*. While ***low absorbed in acidic medium like stomach*** because the *ionized form greater than non-ionized form*.

And this determine how much of drug will be found at each side of membrane.

The Henderson-Hasselbalch equation relates the ratio of the relationship of pKa and the ratio of protonated to un-protonated weak acid or weak base to the molecule's pKa and the pH of the

medium as follows PH = PKa+ Log	Un Protonated protonated

For acids: PH = pKa + Log [A-] / [HA-]

For base: PH = pKa + Log [B] / [HB+]

This equation is useful in determination of how much drug will be found on each side of membrane that separate two compartment that differ in PH for example:

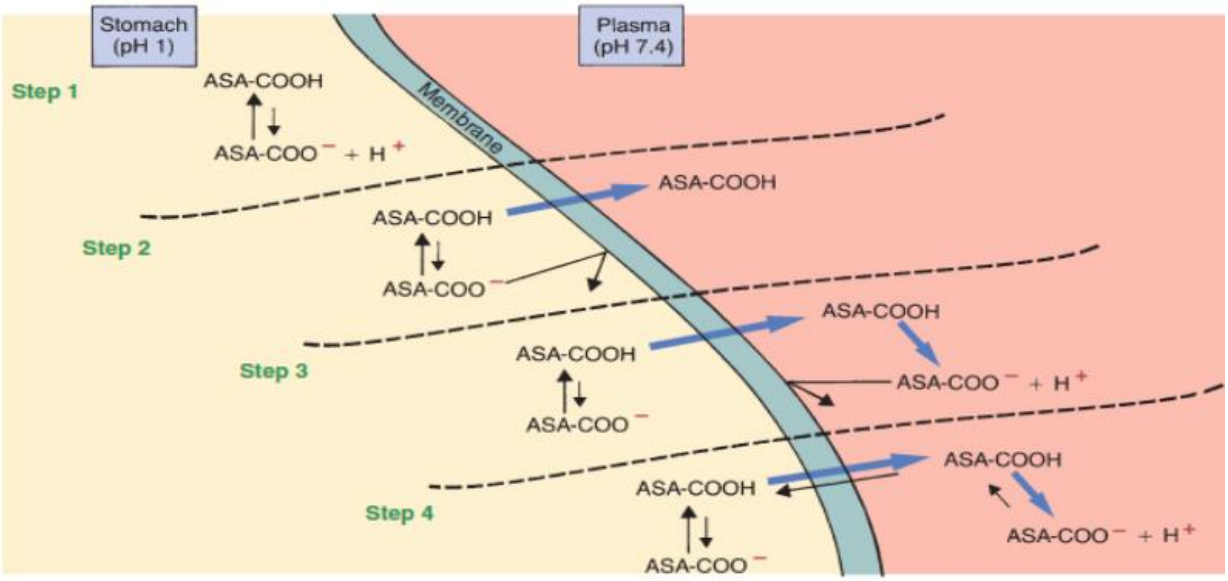
Stomach PH =1.0 -1.5 Blood plasma PH = 7.4

➢ **The lower the pH relative to the pKa**; the *greater will be the fraction of drug in the protonated form*. Because the uncharged form is the more lipid-soluble, more of a weak acid will be in the lipid-soluble form at acid pH, whereas more of a basic drug will be in the lipid soluble form at alkaline pH.

• **Ion Trapping (pH Partitioning)**

The process whereby a drug accumulates on the side of a membrane where the pH most favors its ionization. Acidic drugs ionize an accumulate in basic media, while basic drugs ionize and accumulate on acidic media. The ionization of aspirin (acidic) which give up its proton (become ionized) in basic media, and remains nonionized in acidic media.

Accordingly, when aspirin is in the stomach (an acidic environment), most of the aspirin molecules remain nonionized. So can be absorbed better from the small intestine, where the environment is relatively alkaline, at which being in ionized form. So aspirin is more efficiently absorbed from stomach but its completely absorbed from intestine.



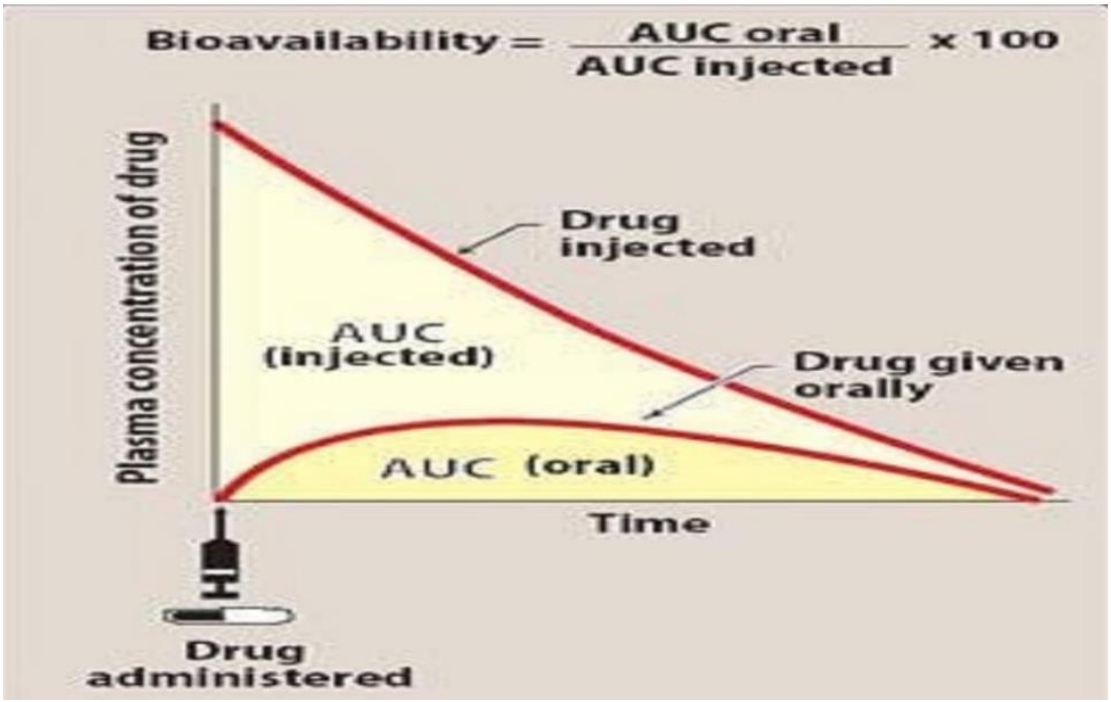
Bioavailability:

Bioavailability is *the fraction of administrated drug reaches the systemic circulation as chemically unchanged form.*

e.g;, If 100mg of drug is administered orally and 70mg is absorbed unchanged, the bioavailability is 0.7 or 70%.

Bioavailability determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with levels achieved by IV administration which 100% bioavailable .

Bioavailability usually affected by any factor which can affect the absorption process.



II- Drug DISTRIBUTION

Reversible movement of drugs from the blood to the interstitial space, then pass into the cells to reach the site of action.

❖ Factors affecting the drug distribution

- Blood flow and tissue perfusion
- Capillary permeability
- Binding to plasma and/or tissue proteins
- Drug solubility (water or lipid solubility)

1-Blood Flow to Tissues

The drug distributed to areas of rich in blood vessels (Brain, heart, liver & kidney) . Therefore, these organs receive significant amount of drug on a short time. While slow distribution of drug occur to the sites of low blood vessels (Fat, skin , muscle and bone).

2- Drug's solubility – (water or lipid) soluble:

Lipophilic drugs readily move across most biologic membranes, and widely distributed throughout the body.

3- Capillary permeability

The *passage of drug to across* blood vessels determined by ***Capillary structure*** and ***physicochemical properties of the drug*.**

Capillary structure varies in different organs;

- *In the liver and spleen*, there is ***discontinuous*** capillaries through which large molecules can pass, while intestinal and renal capillaries have smaller size of fenestrate within endothelium.

The capillary structure of CNS is ***continuous,*** and there are *no slit junctions*. So only Lipid soluble & non-ionized drugs can enter into the CNS, and cross the blood brain barriers (BBB).

The newborns are vulnerable to CNS affected drugs , because BBB is not fully developed at birth.

III- Metabolism (biotransformation)

Metabolism ; refer to the enzymatic alteration of drug structure to more polar products that easily excreted from the body, and this process mainly occur in the liver.

The metabolic process was occur by two of hepatic reactions named as phase I and phase II reactions *to form more hydrophilic product and accelerate the rate of drug excretion*.

Phase I reactions include (***reduction, oxidation or hydrolysis***) that convert lipophilic drugs into more polar molecules. Drug metabolism mainly occur by hepatic microsomal enzyme system, known as the Cytochrome P450 that catalyze metabolism of wide range of drugs.

Phase II reactions:

This phase consists of **conjugation reactions** with endogenous substrate, such as glucuronic acid, sulfurate, acetate, …. to produce more polar and water-soluble products to be excreted with urine or bile and these metabolites are therapeutically inactive. A notable exception is morphine-6- glucuronide, which is more potent than morphine.

Factors affecting the rate of metabolism:

a- Age **b- Genetic Variability** ***c-Nutritional status***
d-Competition between drugs **e- Enzyme induction or inhibition**

IV- Excretion

The process by which drugs and their metabolites irreversibly removed from the body to the outside through major renal route (with *urine) and* less extent through minor non renal routes, *as* with *bile, sweat, saliva, tears, skin, breast milk,* and expired air**.**

Renal elimination of a drug

Excretion of drugs by the kidney into the urine include three processes:
1- Glomerular filtration 2- Tubular secretion 3- Tubular reabsorption

Factors that modify renal drug excretion:

1- Age of patient
2- competition for active transport
3- PH dependent ionization of drugs

➢ Always the nurse must consider the patient's kidney function and urine acidity before administering a drug. Because kidney dysfunction can lead to toxic levels of a drug in the body because the drug cannot be excreted.

Half Life t1/2

The **time** required to **reduce** plasma concentration of drug to the **half.** The concept of half-life is clinically useful for determining the drug duration, dosing interval and plateau steady state concentration *level.*

Example

If the initial plasma concentration of given drug (2000 mg/L). Calculate the plasma concentration of this after 12 hrs from administration, knowing that half-life of the drug is 4 hrs?

4hrs --After first t1/2 : 2000/ 2= 1000mg/L
8 hrs-After second t1/2 : 1000/2= 500 mg/L
12hrs---after third t1/2 : 500/2= 250 mg/L

Factors that prolong the half-life of drugs
- Decrease renal and hepatic blood flow as with shock or heart failure
- Decrease rate of excretion or metabolism
- Increase protein binding
- Increase volume of distribution

❖ The course of drug response**:**
Plasma drug level

1- *Minimum Effective Concentration (MEC).*
The plasma drug level below which therapeutic effects will not occur.
2- *Toxic Concentration (TC).*
The plasma level at which toxic effects begin is termed the *toxic concentration.*
3- **Therapeutic Range (Window)**
It is the range of plasma drug levels, falling between the MEC and the toxic concentration. When plasma levels are within the therapeutic range, there is enough drug present to produce therapeutic responses but not so much that toxicity results. *The objective of drug dosing is to maintain plasma drug levels within the therapeutic range.*

- **Drug's onset**: The time required for the drug to give a therapeutic response.
- **Drug's Peak time**: The time required for a drug to reach its maximum therapeutic response.
- **Drug's Duration of action**: The length of time of therapeutic response, at which the drug concentration maintained above MEC and below toxic concentration.

Drug Levels Produced
With IV infusion & Repeated Doses
(steady state level) ***which the amount of drug removed by elimination is equal to the amount of drug absorbed with each drug dose***.

To reduce fluctuations in drug levels, achieve by;
1- *administer drugs by continuous infusion.*
2- Another is to *administer a depot preparation,* which releases the drug slowly and steadily.
3- *Reduce both the size of each dose and the dosing interval* (keeping the total daily dose constant)