PHARMACOKINETICS

Pharmacokinetics

A dequate drug doses must be delivered to the target organ to get therapeutic but not toxic levels.

So, pharmacokinetic examines the movement of drug over time through the body. Therefore, four pharmacokinetic properties determine the onset, intensity, and the duration of drug action

Pharmacokinetic involves:

1-Absorption from site of administration (input).

2-Distribution (drug reversibly leaves blood stream and distribute into the interstitial and intracellular fluid).

3-Metabolism (liver, kidney, ...).

4-Elimination: Drug and its metabolites are eliminated from the body (output) in urine, bile, feces.

Routes of drug administrations *determined by:*

Properties of drug: water soluble, lipid soluble, ionized .....

Therapeutic objectives: rapid onset, local effect, long term administration.

There are 2 major routes of administration: A- Enteral. B-Parenteral.

Absorption: is the transfer of a drug from its site of administration to blood stream. The rate and efficiency of absorption depend on drug properties & the route of administration E.g. I.V. → complete absorption, other routes → partial absorption (oral route → drug dissolves in G.I. fluid, penetrates the epithelial cells --- any disease or food may effect this process)

Transport of drugs across cell membrane

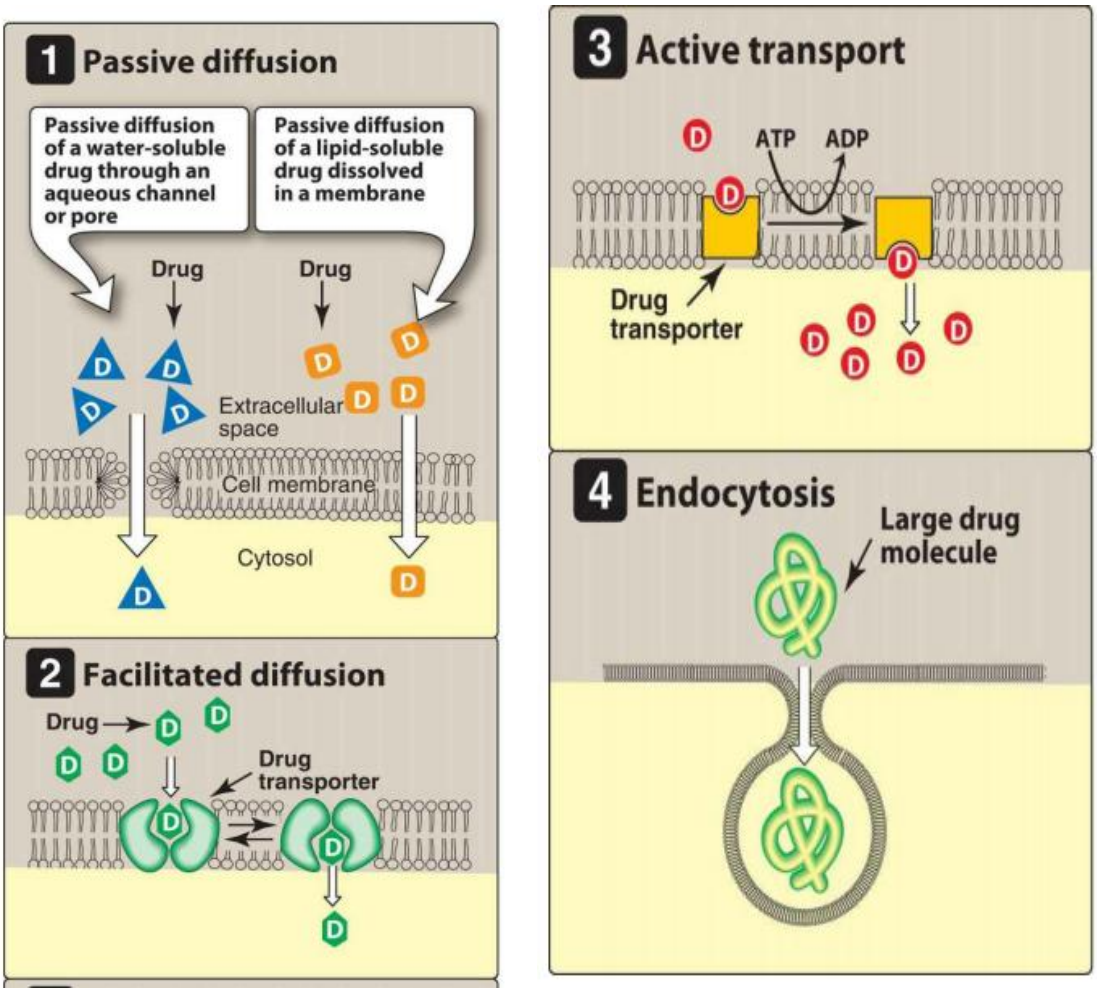
biological membrane: - lipid bilayers with island of protein molecules

Lipid soluble substances diffuse readily into cells since, they cross the cell membrane more easily than water soluble substances most drugs therefore are lipid soluble.

Tight junctions link adjacent epithelial or endothelial Cells, some tight junctions – as in jejunum and proximal renal tubular epithelium – are traversed by water filled channels through which water soluble substances of small molecular wt. may filter, this epithelium. Called Leaky epithelium.

But, in stomach and urinary bladder there is no leaky epithelium., but tight epithelium, so water soluble substances cannot pass (no water channels)

Special protein molecules within the membrane. Allow specific substances to enter or leave the cell preferentially (carrier protein)



I-Passive diffusion

The most common mechanism by which drug enter tissues and distributed through them.

The driving force is the concentration Gradient across the membrane between the compartments. (from area of high conc. → low concentration)

No need for energy or carrier

The process does not become saturated and not inhibited by other substances

The rate of drug movement is proportional to the concentration difference across the cell membrane

(Stomach ↑→↓blood ↑→↓tissue↑)

II-Filtration

Water-soluble drugs pass through aqueous channels in tight junctions

Plays minor role in drug transfer e.g. Na^+ (except for glomerular filtration)

The rate of filtration depend on both, pressure gradient as driving force, and on the size of the compound relative to the size of the pore.

III-Bulk flow

Most substances, lipid or water soluble, cross the capillary wall at rates rapid in comparison with their rates of passage across other body membrane.

Bulk flow of liquid occurs through intercellular pores – major mechanism of passage of drugs across most capillary endothelial Membrane, except those in CNS.

IV-Carrier mediated transport

1-**Active transport:**

Drug entry involves specific carrier protein present on the cell membranes

The process is energy – dependent, driven by hydrolysis of ATP $\rightarrow$ ADP.

Capable of moving drugs against conc. Gradient and the process shows saturation kinetics e.g. iron absorption.

Active transport systems are selective and may be competitively inhibited by other cotransported substances.

2-Facilitated diffusion:

-Carrier mediated transport that does not require energy e.g. vit. B12 absorption. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecule into the interior of cells and moving them from an area of high concentration to an area of low concentration. The process shows saturation and may be inhibited by compounds that compete -for the carrier

V-Ion- pair transport

Absorption of highly ionized compounds e.g. sulfonic acid from GIT.

These compounds penetrate the lipid membrane Despite their low lipid- water partition coefficients by combination with endogenous compound-mucin in the GIT forming neutral ion-pair complexes which will penetrate lipid membrane By passive diffusion

VI- Endocytosis and exocytosis(for large molecules eg: noradrenaline stored in membrane bound vesicles in nerve terminals &released by exocytosis.

Placental blood barrier :

chorionic villi, consisting a layer of trophoblastic cells enclosing fetal capillaries, bathed in maternal blood. Allows only lipid soluble compounds.

Blood brain barrier:-

the capillaries of cerebral circulation differ from those in most other parts of the body, they lack the filtration channels between endothelial cells, this tight junction between cap. Endothelial Cells, together with their basement membrane and astrocyte processes, form this barrier, this barrier separates blood from brain tissues

lipid soluble substances enter brain tissues only e.g. alcohol, diazepam

Factors influencing absorption

A-Effect of pH on drug absorption

most drugs are weak electrolytes (acid or base)

Present partly in the ionised and partly in unionised forms

The degree of ionisation influence, lipid solubility → diffusion → absorption →metabolism and elimination

Acidic drug (HA) $HA \rightarrow H^+ + A^-$

In acidic environment (has free H^+) acidic group tends to retain H^+ ion and remains unionised.

In basic environment (deficit of free H^+) this favours loss of H^+ ions from an acidic group, thus becomes ionised.

The opposite is the case for a basic drug.

Basic drugs (BH^+) $BH^+ \rightarrow B + H^+$

can release H^+ in basic environment and retained H^+ in acidic environment.

The ratio between ionised and non ionised forms depends on pH at site of absorption and on strength of weak acid or weak base, represented by PKa

PKa: negative log of Ka (dissociation or ionization constant) which is the measure of the strength of interaction of a compound with a proton, the lower the pka the more acidic compound &vice versa. A drug passes through membranes more readily if it is uncharged.

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.

Henderson- Hasselbach equation:

pH = pKa + Log [non protonated] / [protonated]

If pH = pKa of the drug → unionised / ionised is 1:1

For acids: pH = pKa +log[ionised (A^-)/ non ionised (HA)]

For bases: pH= pKa + log [non ionised (B) / ionised (BH^+)]

<u>E.g aspirin (acetylsalicylic acid) pKa = 3.5</u>

in stomach (pH=1.5) aspirin is non – ionised (lipid soluble)

In gastric epithelial Cell (pH= 7.4) ionised (trapped) causing gastric cell damage

Body (pH=7.4) aspirin is metabolised to salicylic acid pKa =3 highly ionised remain in ECF, then filtered by glomeruli to the tubular fluid (more acidic) unionised, passes into tubular cells.

If urine alkalinized, more salicylic acid ionised ad remains in tubular fluid →<u>excreted</u>

Permanently ionised drugs:(polar drug)

E.g. heparin – negatively charged acidic- ipratropium, T- curarine, +ve charged basic

Contain groups which dissociated so strongly and remain permanently ionised

Limited capacity to cross cell membrane disadvantage in case of heparin → given by injection, but during pregnancy, it is useful anticoagulant since, it does not cross placental barrier

Drugs incapable of becoming ionised (non-polar drugs)

*e.g steroids, digoxin

Lacking any ionisable group.

Unaffected by pH.

Lipid soluble , diffuse readily across cell membrane.

B-Blood flow to the absorption site (greater in intestine) , in shock, blood flow to cutaneous tissue is severely reduced →minimizing the absorption from subcutaneous administration

C-Total surface areafor absorption

The intestine has a surface area rich in micro-villi and about 1000 fold that of stomach Absorption From intestine is more efficient.

D-Contact time

Drug moves quickly through GIT in diarrhea→ not well absorbed

While anything delays the transport of drug from stomach to intestine will delay absorption e.g. food or drugs like parasympatholytic agent.

E- Expression of P-glycoprotein:

P-glycoprotein is a multidrug transmembran transporter proteins responsible for transporting various molecules, including drugs, across cell membranes (It is expressed throughout the body, 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

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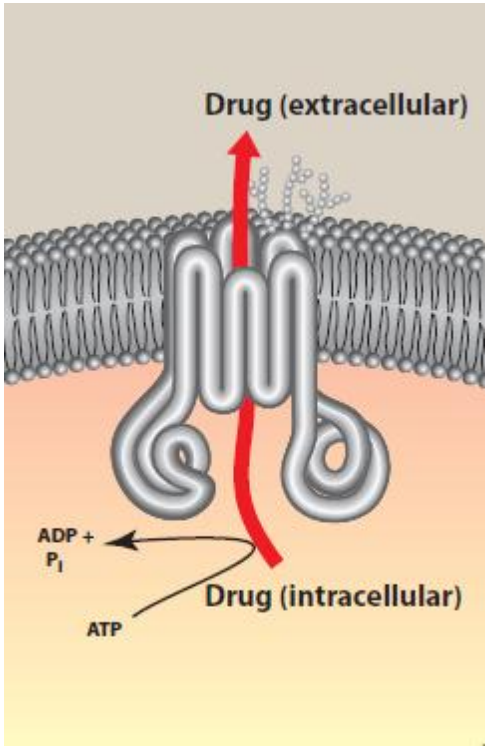

(Fig) the six membrane-spanning loops of the P-glycoprotin from a central channel for the ATP-dependent pumping of drugs from the cell