◉Sheet ○Slides

number : 2

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Pharmacokinetics
-passage of a drug to the tissues

Pharmacokinetics refers to what the body does to a drug*(absorption, distribution, biotransformation and excretion),* whereas pharmacodynamics describaes what the drug does to the body, and inthis sheet we will talk about pharmacokinetics and specifically about what determines the passage of a drug to the tissues.

Pharmacokinetics*(pharma= drug, kinetic= movement)* is the movement of a drug within the body. When you take an oral drug for example, it will go to the GI tract, then it passes through the circulation, then to the tissues, then it goes to the liver to be metabolized or the kidney in which it passes through urine. All these process are movements of a drug.

Why is it important?To predict the concentration of a drug in the body after a given dose, as the pharmacological effect (therapeutic effect) is usually proportional to the concentration of the drug in the body at the site of action; hence, it is proportional to the dose. Doses are calculated according to pharmacokinetics.

In order for therapeutics to achieve its desired effect with minimum adverse effects we need a certain dose that gives a therapeutic concentration at the site of action. If it's lower than therapeutic concentration(subtherapeutic), it's useless. And if it's higher it will give more adverse effect until it reaches a toxic concentration.We know that by what we call **Dose-Response Relationship** or **Concentration-Response Relationship** which tells us the beneficial or toxic effect of a certain dose and the concentration at the site of action.

For some drugs we give the same dose for more than one patient , for others we must do Individualization and we call them drugs with low therapeutic index (drugs with small differences between therapeutic and toxic doses) so individualizationis a must.

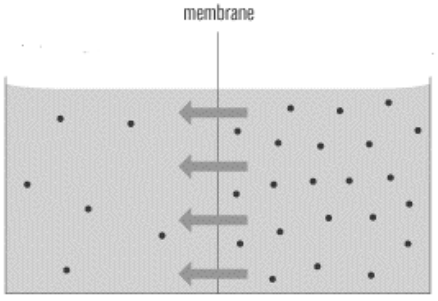
Actually, we cannot measure the drug concentration at the site of action unless by an invasive procedure, but suppose that a drug works on the heart can we take a sample from the heart tissue to measure it? It's even illegal. So we use its concentration in the accessible body fluids (mostly blood)*, as it is proportional to the concentration at the site of action (not equal but proportional).
*it may be from urine, saliva …etc

The drug has to reach the site of action to produce its effect; if it stays in the circulation it's not effective, but in order to move from the circulation to the site of action it has to pass through many layers of cells and traverse their membranes. So, the drug has to be lipid soluble **to pass through** the membrane and be absorbed; but it also has to have some water solubility **to reach** these membranes as most of our body is water.

Mechanismsof permeation: (how the drugs reach the site of action)

1-lipid diffusion

The most important mechanism for passage of drugs through the membrane is lipid diffusion, and it is a passive process that happens according to concentration gradient. In the figure below we have a membrane in a beaker with a higher concentration of a drug on the right side, so the drug will diffuse untill we have the same concentration on both sides.*(remember that the membrane is semi-solid or fluid which has many integral proteins that act as enzymes, transporters, ion channels,…)*



But in the body we do not reach equilibrium because the drug molecules that enter will soon be washed by blood flow, so we will always have a concentration gradient until the last molecule pass. Most drugs that are taken orally (by mouth) need 2 hours to be completely absorbed (may be more or less but mostly 2 hours) because we have a blood flow that will wash the drug molecules that pass.

0:00 – 12:00

The passive flux follows what we call **Fick's Law**

The flux (molecules per unit time) = Concentration gradient * Area * Permeability coefficient / Thickness if the membrane

The flux is directly proportional to the area and that what makes the oral administration of drugs is efficient as the area is large in the GI Tract. Actually the best absorption happensat theduodenum andthe upper jejunum because it has more blood vessels and more surface area as a result of folds,macrovilli and microvilli.

Permeability coefficient is a combination of many factors such as lipid water partition coefficient. (we know it by adding the drug to a test tube that contains a layer of water and a layer of oil and mixing them, and we leave them to settle to separate the two layers, then we measure the concentration of the drug in the two layers if the concentration of the drug is higher in the lipid the drug is lipid-soluble and vice versa).

The flux is inversely proportional to the thickness of the membrane, that's why the Blood Brain Barrier **BBB** which is thick prevents many drugs from entering the brain (in BBB the basement membranes are thick, we have glial cells"the connective tissue of the brain" that make it thicker and also the junctions are tight).

12:00-16:00

What governs this solubility? The chemical structure; they can be polar (Ionized or relatively polar by having a polar group such as: amino group, hydroxyl groups, sulfhydryl group …) and that makes them water soluble, if they are non polar then they are lipid soluble.
Other drugs can transform between both polar and non polar states according to their PKa and the PH of the medium (PKa is the PH at which 50% of the drug is ionized**remember Henderson–Hasselbalch equation*).*Most drugs are weak organic acids or weak organic bases (they are ionizable by donating or accepting protons, respectively).

•**Acidic drugs** $HA \rightleftharpoons H^+ + A^-$

(Protonated acid= unionized acid= lipid soluble, so it will traverse membranes)
(Nonprotonated acid= ionized acid= water-soluble, so it will be excreted with urine)

In acidic environments they are unionized, because we have a high concentration of H^+ and the reaction will shift to the left, that means they are nonpolar →so they are absorbable.
In alkaline environments they are ionized (polar) → non-absorbable.

•**Basic drugs** $NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^-$
*this example shows the same principle but that doesn't mean it's a drug

Protonated base is ionized … unprotonated base is unionized

In alkaline environments, the reaction will shift to the left and the drug is nonionized (nonpolar) →absorbable.
In acidic environments they are ionized (polar) → non-absorbable

(Acid + acid) or (base + base) → absorbable
Acid + base → non-absorbable

In our body, we have different PH levels (in GI Tract it varies from 1.2 to 8, in the blood it's 7.4, in the urine it depends on the diet; if you eat a lot of meat the urine will be more acidic and if you are vegetarian the urine

is alkaline but in normal people it's slightly acidic pH=6), so the ionization state and hence the absorption will change according to the PH.
In the urine, if the drug is ionized it will be excreted and we will get rid of it; we utilize this in increasing the elimination of a toxin by changing the PH of the urine. (Also we can keep the drug in the body by making it more ionized thus more reabsorption occur)
Vitamin c and NH^+Cl make the urine acidic whereas sodium bicarbonatemakes it alkaline. *Note: we don't use hydroxyl or HCl in ordernot to damage the tissues.

We get rid of the acid by alkalinizing the urine and we get rid of bases by acidifying it

Can we change the PH of the plasma? No, it's very controlled by buffers.

16:00 – 25:50

Henderson–Hasselbalch equation

$PH = Pka + Log (A^-/HA)$

→ $-Log (A^-/HA) = Pka - PH$

→ $Log (HA/A^-) = Pka - PH$

→ **$Log (protonated/unprotonated) = Pka – PH$**

Example: APyrimethamine is a weak base drug has a Pka of 7, what is the proportion of ionized and unionized drug in the blood and urine? (PH in urine = 6)

In blood,
Log (protonated/unprotonated) = Pka - PH
Log (protonated/unprotonated) = 7 – 7.4 = -0.4
Protonated/unprotonated = $10^{-0.4}$ = 0.4
Ionized/unionized = 0.4(for each 1 unionized there is 0.4 ionized)
Unionized is more → more lipid soluble → absorption

In urine,
Log (protonated/unprotonated) = 7 – 6 = 1
Ionized/unnionized = 10 (for each 1 unionized there are 10 ionized)

Ionized is more → less lipid soluble → excretion

(If I want to absorb it more I have to increase the pH of the urine ... making it more alkaline and if I want to get rid of it faster the PH has to be decreased)

Example: Phenobarbital is a weak acid drug has a Pka of 7.4, what is the proportion of ionized and unionized drug in the blood and urine? (PH in urine = 6)

In blood,
Log (protonated/unprotonated) = 7.4 – 7.4 = 0
unionized/ionized = 1 (50% is ionized)
** it will pass toward the tissues because a part is nonpolar and then half of the ionized remaining will be unionized to maintain the ratio 1:1 , so it will be distributed to tissues but it takes longer time.
In urine,
Log (protonated/unprotonated) = 7.4 – 6
Unionized/ionized = 25

Most of it is unionized → more lipid soluble → reabsorption

*Note: if we give the patient such a drug (which half-life is 4 days and needs 16 days to be washed of the body) it will stay long in the body so we alkali the urine, therefore the drug will be ionized and we get rid of it faster.

**The lower the PH relative to the Pka the greater will be the fraction of the drug in the protonated form (protonated acid = unionized, protonated base = ionized).

25:00-37:00

2-Aqueos diffusion(a minor method of crossing the membrane)

The entrance of the drug dissolved in water through protein pores in the membrane (the least important form of transport of drugs).
It is unsaturable which means that increasing the concentration will always increase the diffusion.

3-Carrier mediated transport

a- **Active transport**
- needs energy
- against concentration gradient

b- **Facilitated diffusion**
- doesn't need energy
- following concentration gradient

* Both for molecules that are too large or too insoluble in lipid to diffuse passively through the membrane.
* Although drugs are xenobiotics(foreign to the body) they can utilize the already existing transporters (which we assume to be very selective) to enter the cells by having similar structure to the substance they transport (similarity in electrical spatial distribution or in geometry).

* Both are saturable which means they have maximum capacityto move molecules per unit time.

* Both are inhibitable by competition of substrates.So if we have 2 drugs that use the same carrier they will inhibit each other.

* Some carriers work in the opposite direction which means they pump foreign substances outside of the cell to protect the body (Example: P-glycoprotein in the GI Tract). So some drugs will not be absorbed not because it's not lipid soluble but because P-glycoprotein pumps it outside.

How to overcome this?We give the drug intravenously or inhibit this carrier.