Medical Committee
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PHARMACOLOGY

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Pharmacokinetics

Mechanisms of Permeation of Drug Molecules

*What is pharmacokinetics? The movement of drugs from the site of administration to the circulation, and from the circulation to the rest of the organs of the body, and that requires the passage through membranes.

*What's the composition of the cell membrane? Lipid bilayer

So in order for the drug to cross the membrane it should be lipid soluble, so water soluble drugs will not pass through the membrane.

-The movement of drugs between compartments requires passage through membranes .the most important mechanism for the drugs to pass through these membranes is to be soluble in the membranes

**Lipid diffusion is the most common route of passage of a drug into the body and within the body.

*As we knew, the membrane is fluid so to a drug to pass in the fluid (membrane), it will dissolve and then and then it'll diffuse to the other side and then get reabsorbed or even distributed or excreted from the body because all require passage through membranes. We conclude that →the more lipid soluble the drug is, the more will be the passage through the membrane.

-So what decides lipid solubility? Polarity or Ionization. If the drug is polar (has polar chemical groups within the structure of the drug like hydroxyl, sulfhydryl, amino, carboxyl groups), the passage through the membranes will be less because that will make it water soluble but if it is ionized (has a charge) it will not pass at all through the membrane because the charge will not dissolve in the lipid.

-Lipid diffusion follows the concentration gradient so if the concentration inside is higher, the drug will certainly move in the direction showed in the picture below. If we take a membrane with chamber, the drug will move from the high concentration to the low concentration until reaching equilibrium but that will not happen in the body because of the circulation.

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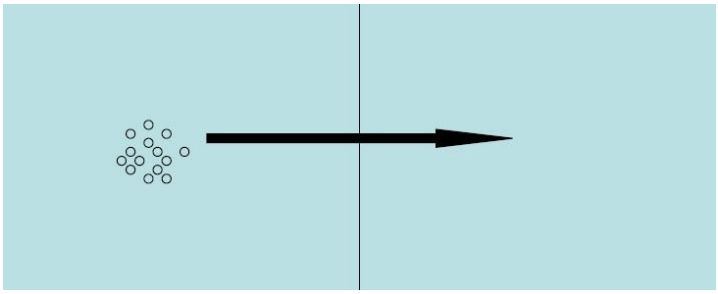

**Very important point: the drug has to have some water solubility to reach the membrane because we have a fluid within the GI tract so the drug has to pass and dissolve in the fluid then reach the membrane and when it reaches the membrane it will cross because it will dissolve in the membrane →SO very lipid soluble drugs will not be absorbed because they will not reach the membrane and they will not dissolve in body fluids which are aqueous.

In brief : The drug has to be lipid soluble to pass through the membrane and it should have some water solublity to reach the membrane

Fick's Law of Diffusion

*It governs passive flux of molecules across membranes.

*Flux (molecules/unit time) =

C1-C2 x [(Area x Permeability coefficient)/ Thickness]

**C1 is the higher concentration and C2 is the lower concentration (there should be a difference in the concentration on the two sides of membrane in order to the drug to pass from the area of high concentration to the area of low concentration); area is the area across which diffusion occurs (through which passage occurs); permeability coefficient is a measure of the mobility of drug molecules in the medium of diffusion path (it determines the physicochemical properties of the drug, lipid solubility...etc); and thickness is the thickness or length of diffusion path.

**The larger the surface area, the more is the absorption →For this reason the GI tract is the most suitable site for drug administration, So there will be absorption through the large area.

** The more the thickness the less is the absorption.

NOTE: Lipid diffusion is called passive diffusion because it doesn't require energy or carriers and this is the most common mechanism of passage of drugs to membranes

Note: the more polar the drug is, the less the absorption and the more ionization, the less the absorption.

*what govern polarity are the groups that we talked about.

*what governs ionization is the pKa of a drug and the pH of the medium and that is governed by Henderson-Hasselbalch Equation.

** Acid + Base = Salt + Water (usually the salt is ionized)

*The degree of ionization depends on the pH of the medium and the pKa of the drug therefore the pKa of the drug and the pH of the medium will affect lipid solubility of the drug.

*The more the drug is ionized the less the absorption and vice versa. Ionized drug molecules are polar and water soluble, whereas, Unionized drug molecules are non polar and lipid soluble →SO the drugs that are either weak acids or weak bases depending on their pka and the PH of the medium are NOT totally ionized or unionized BUT a portion is ionized and a portion is unionized →the portion that is unionized is the one that passes through the membranes and get absorbed or distributed and because it is a constant percentage, so as far as certain molecules pass, the percentage will get back so some of the ionized will be unionized and will get absorbed.

Henderson-Hasselbalch Equation

*Weak acid: is a neutral molecule that can reversibly dissociate into an anion (negatively charged) and a proton.

R-COOH ⟷ R-COO- + H+

Lipid soluble water soluble

*If we put the acid (R-COOH) in an environment, depending on the PH and the Pka, it will dissociate to (R-COO- + H+)

R-COOH is neutral (lipid soluble), it passes through membrane.

R-COO- is ionized, it does not pass through membrane.

* It is bidirectional so with excess acid, acid+acid will not be ionized, whereas acid+base will be ionized (it gives you salt). You can affect absorption by changing PH, we can't change the Pka (it's a characteristic of the molecule).

*Weak base: is a neutral molecule that can form a cation (positively charged) and a proton.

R-NH3+  R-NH2 + H+

Water soluble Lipid soluble

*This base if combined with a proton, it can produce the charged molecule.

*If you add acid to any substance containing amino group, the amino group become ionized and will be positively charged so this is a base.

*These reactions move to the left in acid environment and to the right in alkaline environment.

*Log [protonated/unprotonated] = pKa – pH

*This equation applies to both acidic and basic drugs.

*we use this to know the percentage or the portion of the drug given and how much is ionized and how much is unionized (The unionized fraction will easily pass through the membrane but the ionized will not)

*More unionized→more passage

*Less unionized→ less passage

Examples:

Example (1): Pyrimethamine is a weak base drug with a pKa of 7.0. What is the proportion of ionized and unionized drug in blood (pH = 7.4) and urine (pH = 6)?

- Blood:

Log (prot/unprot) = pKa – pH =7 – 7.4 = - 0.4

Prot/unprot = 10-0.4 = 0.4:1

Percentage= 0.4/1 (Its almost 1/3 or less)

1.4= the sum of the two molecules

*That means: For each molecule that is unprotonated which is lipid soluble we have 0.4 ionized molecules (We have 4 protonated molecules in every 10 unprotonated molecules. Which means: For every 10 molecules that can pass, 4 molecules can't. It's a ratio not percentage and this ratio remains constant so the drug continues to move after some of it get absorbed and the ratio of what remain will be also the same.

Urine:

Log (prot/unprot) = pKa – pH =7 - 6 =1

Prot/unprot = 101 = 10:1

That means 10 will not pass through the membrane and 1 will.

-What does that mean? When talk about urine, we talk about the reabsorption to the body→ as a result→ for every 11 molecules there are 10 molecules that will NOT pass through the membranes and will NOT go back (they'll stay in the urine) and one molecule only will pass and will get reabsorb back)

-A student asked: Should people who have acidosis or alkalosis take different drugs?

-Answer: This will be taken into account because the drug in the circulation will be different because the PH is different (The passage, the distribution and the absorption from the GI tract will be different).

*When PH=Pka → a half is ionized and a half is no ionized.

Note: you can change the pH of the urine to make the drug benefit.

It's a base drug, the protonated portion is ionized, which is less in the plasma (blood), but the protonated portion is more in urine, when the drug is in urine it will not get back (it'll not be absorbed)

Example (2): Phenobarbital is a weak acid with a pKa of 7.4. What is the proportion of ionized and unionized drug in blood (pH = 7.4) and urine (pH = 6)?

- Blood:

  Log (prot/unprot) = pKa – pH

  = 7.4-7.4 = 0

  Prot/Unprot = 100 = 1:1 (A half is ionized and a half is unionized)

→ It will pass through the membranes

- Urine:

  Log (prot/unprot) = pKa – pH

  = 7.4 – 6 = 1.4

  Prot/Unprot = 101.4 =25:1 (The unionized =25,

The ionized molecules=1) →this drug will be reabsorbed in the urine.

<u>From the question you have to know:</u>

1) What is the fraction of the ionized is and no ionized molecules.

2) The ionized fraction is water soluble and doesn't pass through membranes and the unionized fraction is the one that passes through the membrane

3) The direction depends on the process (absorption, distribution, elimination) and in the urine usually they reverse because of the absorption for example: In the intestine we wanted the urine to be unionized to get absorbed. It all depends on what you want.

The half life of this drug =4 days →One dose will stay in the body for 16 days → Over dose is toxic

SO how can we accelerate its elimination from the body? We must alkalize the urine because the drug is an acid and the urine is alkaline so it will

become ionized so it doesn't pass through the membrane and it will get excreted from the body.

-We conclude that we can change the urine's PH to affect the excretion of the drugs

BUT! How can we alkalinize the urine in a patient body? We give him Sodium bicarbonate orally or intravenously, SO the urine becomes alkaline and I will enhance the elimination of acidic drugs.

*If w want to make the base mostly ionized, we should acidify the urine but HOW? By giving the patient vitamin C (the ascorbic acid) OR we can use ammonium chloride (NH4Cl) because it releases small amount of HCl to acidify the urine and the ammonia can be metabolized in the body but we don't need to use NH4Cl , We can use only the ascorbic acid

All In All:

**The lower the pH relative to the pKa, the greater will be the fraction of the drug in the protonated form.

**More of a weak acid will be in a lipid soluble form in acidic pH; and more of a weak base will be lipid soluble at an alkaline pH.

Application:

Manipulation of drug excretion by the kidney:

If the drug is filtered in urine in unionized form, it will be reabsorbed by renal tubules. If we want to accelerate excretion from the body (in case of overdose), it is important to ionize the drug within the renal tubules to reduce reabsorption.

-The drug should normally be excreted in the urine →if the drug normally is not excreted in the urine, Manipulation of urine PH will NOT affect its elimination from the body. It has to go to the urine naturally in order to modify its excretion from the body.

Note: usually the drug in the urine should be ionized to be eliminated, but in the intestines it should be unionized to be absorbed.

Aqueous diffusion

-How some molecules (proteins or ionized molecues) are going to get in the body?

They can pass through aqueous pores in membranes. When we say that water soluble molecules don't pass through the membrane, this is NOT absolute. It very rarely can pass through the pores but it has to be small in size.

-Occurs within the larger aqueous compartments of the body (Interstitial space, cytosol, etc), across epithelial membranes tight junctions, and the endothelial lining of blood vessels (aqueous diffusion can occur through capillaries because there are spaces between cells) →for this reason we will have edema (which is passage of water from the blood in the capillaries to the interstitial and that will carry drug with it also).

-Anything in the plasma will go through this, BUT this is not significant portion of passage of drugs to membranes and you can't depend on.

- Also driven by the concentration gradient.

-Drugs bound to plasma proteins do not permeate aqueous pores (If the drug is bound to plasma proteins the molecule will be large and can't pass through the membrane which is lipid and also can't enter through these pores because they are smaller than the size of the protein bound drug. The drug should be free in order to pass these pores)

-If the drug is charged, its flux is influenced by electrical fields (membrane potentials).

Special carriers

-Some of them are specific for certain molecules (like glucose, amino acids, etc) and some of them are not specific so they can carry drugs from one side to another side and also in both sides which means that one carrier can allow the drug to enter into cell and another carrier can expel it from the cell.

-Exist for substances that are important for cell function and are too large or too insoluble in lipids to diffuse passively though membranes (peptides, amino acids, glucose, etc).

-They are saturable (they have a limited capacity). Some of them require energy. Some depend on the electrical potential.

-They bring about drug movement by active transport or facilitated diffusion.

-What is the difference between these two types of diffusion?

Both are carrier mediator and saturable (have capacity) but the active requires energy, whereas the facilitated does not.

-They are selective, saturable and inhibitable.

-What's the meaning of saturable?

In passive diffusion, we talked about ratios but in carrier mediated it's amount per time.

For example: In passive diffusion →1/10 of the amount per hour (ratio), as much as you go it's 1/10 (specific ratio).

BUT in carrier mediated → If you have 100 mg , you need 5 hours (amount per time), if you have 1000 mg you need how much? devide it by 5 you get 200 hours.

**Capacity→ is the passage amount per time (carrier mediated) .It doesn't relate to the amount you put.

→In passive diffusion it is a ratio that is independent on the amount you put.

Best Wishes: Areej Mosleh ☺

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