Doctor 021

PHARMACOLOGY

Sheet no. 2

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PHARMACOKINETICS

In the first lecture, we say that pharmacology has two areas:

***Pharmacodynamics:**

Is what the drug does to the body, which includes the biochemical and physiological effects of the drug, including the mechanism of action, and interaction with receptors as well as the adverse effects.

***Pharmacokinetics:**

Is what the body does to the drug.

In this lecture, we will study pharmacokinetics which is presented in 'ADME'

Deals with Absorption, Distribution, Metabolism (biotransformation), and Excretion of drugs:

***Absorption: This is the movement of drug molecules from the site of administration into circulation.**

***Distribution: This is the movement of drug molecules from circulation to tissues and between different parts of the body.**

***Biotransformation: This is the conversion of the drug from one chemical structure into another by the action of metabolic enzymes (metabolism).**

***Excretion: The movement of drug molecules out**

of the body.

PRIMARY PRINCIPLES

Why do we study pharmacokinetics?

The goal of therapeutics is to achieve the desired beneficial effect with the minimal adverse effects possible. Controlling the concentration of the drug provided that "the concentration of the drug in plasma is proportional to the concentration of the drug in the active site" as an assumption.

-active site where the drug should be functioning.

Notice that we don't measure the concentration in the active site, it is impossible to be measured because there are many receptors for one drug in the body as well as it is hard to know the total amount of it in its active site.

So pharmacokinetics is the use of the appropriate dose to produce the appropriate plasma concentration to have an appropriate concentration of the active form in the active site.

****GENERAL RULE****

WHAT CAN BE PREVENTED SHOULD BE PREVENTED

For ex, if we can prevent adverse effects, we should prevent them, by not exceeding the therapeutic concentration in the body which requires not exceeding the therapeutic dose.

-The clinician must determine the dose that most closely achieves this goal.

-A fundamental hypothesis of pharmacology is that a relationship exists between a beneficial or toxic effect of a drug and the concentration of the drug at the site of action (or in the blood).

MECHANISMS OF PERMEATION OF DRUG MOLECULES

-The drug has to reach the site of action to be effective.

-The movement of the drug between compartments requires passage through membranes.

-Permeation is the movement of drug molecules into and within

the biologic environment.

*drugs move from one site to another, so they have to cross the membrane, if it is given orally, it will cross several layers in the intestine to reach the circulation and then cross several layers to be distributed in the tissues and organs, also for metabolism they cross several layers to reach hepatic cells and the same for renal excretion.

*here are 4 diffusion Mechanisms: (lipid diffusion, aqueous diffusion, special carriers, and endocytosis, exocytosis).

1)Lipid diffusion (Passive diffusion):

-The most important mechanism, because the cell membrane is a phospholipid semi-liquid(semi-fluid) membrane.

-The drug dissolves in the membrane, if the drug is lipid soluble, it will dissolve in the membrane and then get out of it.

*lipid diffusion is passive diffusion!

-The more lipid soluble is a drug the more will be the passage across membranes and vice versa.

If the drug is very lipid soluble, then it won't cross the membrane, WHY???

The drug has to be sufficiently water soluble to reach the membrane. The main fluid in our body is water, so it has to be water soluble even if it is has low solubility to be able to reach the membrane. (it has to be water soluble to reach the membrane and lipid soluble to cross it)

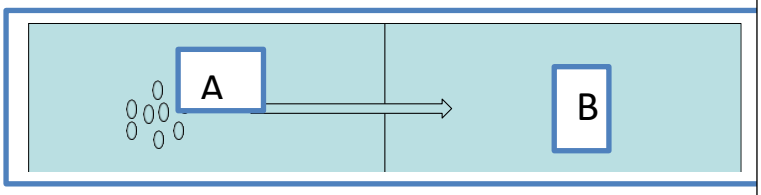
We conclude that the drug has to be partially water-soluble and partially lipid soluble, and of course, lipid solubility predominates.

The drug follows the concentration gradient,

Drug diffusion depends on the concentration gradient: which is the difference in concentration across the membrane

It diffuses from HIGH concentration to LOW concentration

Supposing the drug is in an artificial tube or chamber, it will diffuse from A to B across the semipermeable membrane until it achieves equilibrium.



الفكرة هون يا جماعة

انه كلما الدوا ينتقل من الاعلى تركيز للاقل الدم رح ياخده ويوزعه بالتالي رح ايضل في فرق تركيز فرح يضل ينتقل الدوا. بس هيك

البوكس انحط للتوضيح مش عشان تلخموا حالكم ☹

But this DOESN'T happen in our body, it continues to diffuse until the last molecule, because of the presence of blood flow which washes out the molecules continually from B site, look at the box again and imagine that A is the site of ingestion and B is the vessel, when the drug moves from A to B the blood flow will take it from B and distributes it so B will remain less concentrated than A.

FICK'S LAW OF DIFFUSION

Governs passive flux of molecules across membranes.

$$\text{Flux (molecules/unit time)} = C1\text{-}C2 \times [(\text{Area} \times \text{Permeability coefficient}) / \text{Thickness}]$$

*delta C: difference in concentration across the membrane, C1 is the higher concentration and C2 is the lower concentration

*area is the area across which diffusion occurs, the wider the area, the higher rate of absorption(flux),

That's why most drugs are given orally, the area of the GI tract is wide, so the absorption is higher, on the other hand, despite the absorption in the nose being like intravenous ingestion, it is a small area with low absorption efficiency.

*permeability coefficient is a measure of the mobility of drug molecules in the medium of the diffusion path(constant). The permeability coefficient describes how easily it is for the drug to move through the medium of diffusion.

*thickness is the thickness or length of the diffusion path. It represents a group of layers,

the thicker the membrane….the lower flux

the thinner the membrane…. The higher flux(thickness is the denominator)

MECHANISMS OF PERMEATION OF DRUG MOLECULES

We previously mentioned that the drug has to be lipid soluble to cross the membrane and retain certain water solubility to reach the membrane, that's why most drugs are weak acids or weak bases.

There is no NaOH, HCL,… or other strong bases and acids in the drug.

The ionization for weak acids and bases is governed by the PH of the medium and the PKa of the drug.

That's what Henderson-Hasselbalch Equation clarifies.

**IMPORTANT RULE:

A weak drug with certain PKa and in the medium of certain PH has:

Ionized fraction→ it is water soluble→ can reach the membrane but can not cross it

Unionized fraction→ it is lipid soluble→ can cross the membrane

-Most drugs are either weak acids or weak basis.

-Therefore the pKa of the drug and the pH of the medium will affect the lipid solubility of the drug and its passage across membranes.

---Ionized drug molecules are polar and water-soluble, whereas unionized drug molecules are nonpolar and lipid soluble.

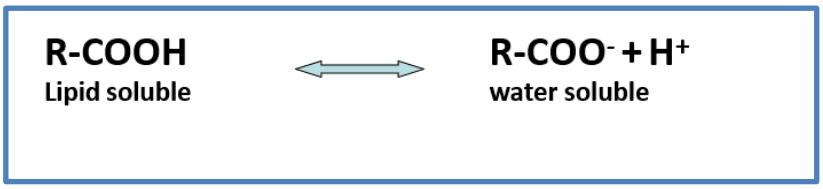
IONIZATION OF WEAK ACIDS AND BASIS

-They are reversible rxns!

-as you know, we represent the reversible rxn with two opposing arrows, they don't have the same length, and one of them predominates to one direction according to the pH of the medium, if we don't know the PH, we could use this symbol ⟺

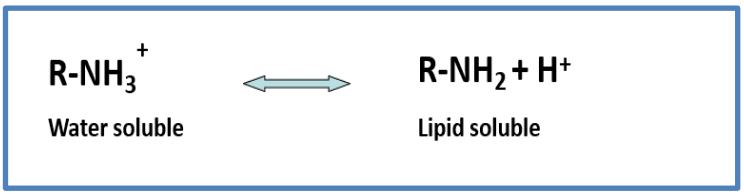
-A weak acid is a neutral molecule that can reversibly dissociate into an anion (negatively charged molecule) and a proton (a hydrogen ion).

It donates protons.



-A weak base is a neutral molecule that can form a cation (positively charged molecule) by combining with a proton.

It accepts protons.



The amine here accepts a proton and becomes ionized water-soluble(RNH3+)

-LET'S PAY MORE ATTENTION HERE!

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

A quick note:

Protonated acid: means it keeps H+ so it is unionized, it doesn't donate H+ yet

Protonated base: means it receives H+ so it is ionized.

A spare note for my MEDICAL colleagues :')

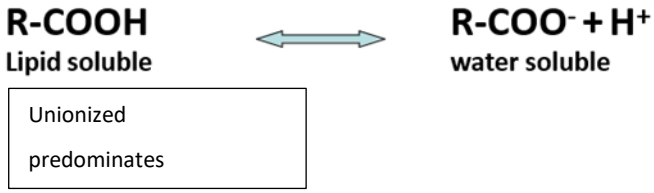
That's left ←

And that's right →

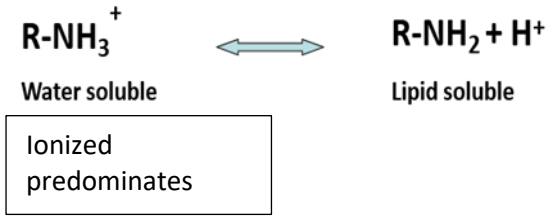
Now, let's start:

*IN AN ACIDIC environment, left predominates:

The acidic drug tends to be protonated, and the medium is the same to it, so it is unionized, and that's what predominates, which is to left

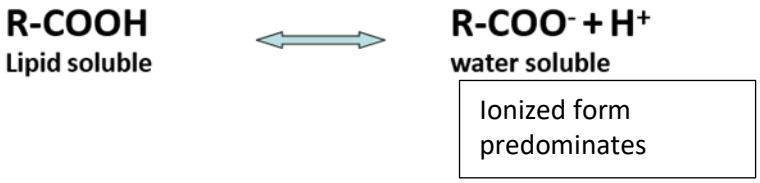


The basic drug tends to be ionized and protonated, so the left predominates

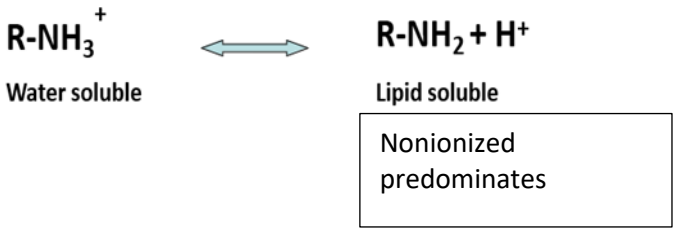


-IN BASIC environment, right predominates:

The acidic drug tends to donate the proton and becomes ionized, the right predominates



The basic drug tends to be unionized, the medium is the same to it, so there is no change, the right predominates



Acids in acidic environments and bases in basic environments are unionized

~~Acid + base → salt+ water~~

Ionized+ ionized ionized+water

Henderson-Hasselbalch Equation:

Log [protonated/unprotonated] = pKa – pH

Log: to base 10, ln: natural log

Protonated acid: unionized, protonated base: ionized

unprotonated acid: ionized, unprotonated base: unionized

This equation applies to both acidic and basic drugs.

Examples: (important for the exam):

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)?

Solution:

-Blood:

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

Prot/unprot = 10-0.4 = 0.4:1 = 0.4/1.4 (get rid of log by power to 10)

Notes:

It is a ratio, with 0.4(protonated particles) there are 1 unprotonated particles

There are no fractions, so for understanding multiply the ratio by 5

Getting 2:5 (for every 2 protonated particles, there are 5 unprotonated)

The unionized form of this drug in plasma predominates

We can represent this in a portion: ionized/total(ionized and unionized)= 0.4/(0.4+1)

Conclusion:

The basic drug in the basic environment: unionized

-Urine: the ph of urine is variable, almost it is given as acidic

Log (prot/unprot) = pKa – pH =7-6 =1

Prot/unpro = 101 = 10:1 = 10/11.

Conclusion:

The basic drug in the acidic environment: ionized, water-soluble

.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 =1/2

Half of this drug in the blood is ionized, and half is unionized.

-Urine:

Log (prot/unprotect) = pKa – pH

= 7.4 – 6 = 1.4

Prot/Unprot = 10^1.4 =25:1 = 25/26

It is an Acidic drug in acidic environment it should be unionized, unionized form is higher, which indicates that renal excretion isn't affecting the drug,because its unionized form predominates and the drug should be excreted by renal system so it needs to be ionized to be excreted faster.

If we want to get rid of this drug, supposing that the patient takes an overdose of this drug and it causes coma knowing that the drug's half-life is 4 days so after 16 days we get rid of it completely, in this case, we give the patient alkaline solution to make the urine more basic or alkaline solution, so acidic drug in alkaline will be more ionized and will be excreted faster PROVIDED THAT it is eliminated by renal system partially or completely.

This table isn't to memorize, just to show that every drug has PKA, so drugs can be prescribed accordingly:

TABLE 1–3 Ionization constants of some common drugs.

Drug	pK_a[1]	Drug	pK_a[1]	Drug	pK_a[1]
Weak acids		**Weak bases**		**Weak bases (cont'd)**	
Acetaminophen	9.5	Albuterol (salbutamol)	9.3	Isoproterenol	8.6
Acetazolamide	7.2	Allopurinol	9.4, 12.3[2]	Lidocaine	7.9
Ampicillin	2.5	Alprenolol	9.6	Metaraminol	8.6
Aspirin	3.5	Amiloride	8.7	Methadone	8.4
Chlorothiazide	6.8, 9.4[2]	Amiodarone	6.6	Methamphetamine	10.0
Chlorpropamide	5.0	Amphetamine	9.8	Methyldopa	10.6
Ciprofloxacin	6.1, 8.7[2]	Atropine	9.7	Metoprolol	9.8
Cromolyn	2.0	Bupivacaine	8.1	Morphine	7.9
Ethacrynic acid	2.5	Chlordiazepoxide	4.6	Nicotine	7.9, 3.1[2]
Furosemide	3.9	Chloroquine	10.8, 8.4	Norepinephrine	8.6
Ibuprofen	4.4, 5.2[2]	Chlorpheniramine	9.2	Pentazocine	7.9
Levodopa	2.3	Chlorpromazine	9.3	Phenylephrine	9.8
Methotrexate	4.8	Clonidine	8.3	Physostigmine	7.9, 1.8[2]
Methyldopa	2.2, 9.2[2]	Cocaine	8.5	Pilocarpine	6.9, 1.4[2]
Penicillamine	1.8	Codeine	8.2	Pindolol	8.6
Pentobarbital	8.1	Cyclizine	8.2	Procainamide	9.2
Phenobarbital	7.4	Desipramine	10.2	Procaine	9.0
Phenytoin	8.3	Diazepam	3.0	Promethazine	9.1
Propylthiouracil	8.3	Diphenhydramine	8.8	Propranolol	9.4
Salicylic acid	3.0	Diphenoxylate	7.1	Pseudoephedrine	9.8
Sulfadiazine	6.5	Ephedrine	9.6	Pyrimethamine	7.0–7.3[3]
Sulfapyridine	8.4	Epinephrine	8.7	Quinidine	8.5, 4.4[2]
Theophylline	8.8	Ergotamine	6.3	Scopolamine	8.1
Tolbutamide	5.3	Fluphenazine	8.0, 3.9[2]	Strychnine	8.0, 2.3[2]
Warfarin	5.0	Hydralazine	7.1	Terbutaline	10.1
		Imipramine	9.5	Thioridazine	9.5

[1]The pK_a is that pH at which the concentrations of the ionized and nonionized forms are equal.
[2]More than one ionizable group.
[3]Isoelectric point.

Note:: protonated base is ionized and protonated weak acid is unionized.

***Summary:**

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

-Acids in an acid environment are unionized (non-polar).

-Bases in an alkaline environment are unionized (non-polar).

-The protonated weak acid is neutral and more lipid soluble.

-The unprotonated weak base is neutral and more lipid soluble.

-In an acid environment, the acidic drug is neutral while the basic drug is ionized.

-In an alkaline environment, the acidic drug is ionized while the basic drug is neutral.

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 the excretion of the drug from the body (in case of overdose), it is important to ionize the drug within the renal tubules to reduce reabsorption.

-This can be accomplished by changing urine pH.

-Weak acids are excreted faster in alkaline urine. Urine can be alkalinized by sodium bicarbonate (NaHCO3) given orally or intravenously.

-Weak basis are excreted faster in acidic urine. Urine can be acidified by ascorbic acid (vitamin C) or ammonium chloride (NH4Cl).

*if there is a toxic acidic organic drug that is excreted by urine then we will alkaline the urine making it ionizable so it will be excreted faster, we can use sodium bicarbonate NaHCO3 which is basic which can be given orally or intravenously.

*if there is a toxic basic drug and it is excreted in the urine, we can accelerate its excretion by urine acidification, using acidic agents like Ammonium chloride (NH4Cl) and vitamin C.

We don’t use vitamin C from its natural sources like oranges or lemons because they contain citrate that is alkaline so it will neutralize ascorbic acid(pure vitamin C) which is our target.

*if we want to prevent the secretion of a certain drug (transporting it from blood to urine), we inhibit its transporter so retention occurs(the drug remains in the blood)for ex: patients may be given penicillin with propellicin causing reduction of frequency administration of the drug, by inhibiting the active secreting process in the tubules by the carrier.

2)aqueous diffusion

-Through aqueous pores in membranes.

-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.

-Also driven by the concentration gradient.

-Drugs bound to plasma proteins do not permeate aqueous pores.

-If the drug is charged(ionized), its flux is influenced by electrical fields (membrane potentials).mainly driven by electrical potential however it depends on electrochemical gradient since it has both an electrical potential and concentration value.

**lipid diffusion depends on gradient concentration mainly, while aqueous diffusion depends on membrane potential mainly.

**aqueous solution depends on membrane potential if the drug is ionized, (not all water-soluble drugs are ionized!)

*water soluble molecules are either ionized(depend on both chemical gradient and membrane potential)or unionized
(depend on chemical gradient only)

3. Special carriers:

-The passive diffusion through these carriers is saturable, meaning that their transport rate(velocity) is proportional to concentration up to a certain limit and so they reach saturation state at it we achieve the maximum velocity of transport, it depends on amount and there's no constant ratio between transported molecules to the total molecules

As for diffusion, it is unsaturated so that when the difference in concentrations increases, the flux increases, and the ratio between the transported drug molecules and the total drug molecules remains constant

-They are less specific compared to active transport mechanisms that can transport sugar, AA…

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

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

-They are selective(partially), saturable and inhabitable.

Passive diffusion and lipid diffusion aren't inhibitable, while carriers are inhibitable, they can be inhibited, if we use something that hampers(prevents) their work.

****Many cells contain less selective membrane carriers that are specialized in expelling foreign molecules including drugs:**

A. ATP-binding cassette (ABC) family:

(expulsion and effluxion)

It includes P-glycoprotein(efflux transporter) or the multidrug-resistance type 1 (MDR1) transporter found in the brain, intestine, testes, neoplastic cells(cancer cells), and other tissues(bile, kidney, …)

-P-glycoprotein: the most important, it effluxes the drug from the organ it is found in to protect it, for clarification:

The ones in the intestines prevent the entry of drugs into the body

The ones in the brain protect it from their entry

The ones in the liver efflux the drug from it.

-the second and least important is MDR1: they are the reasons why the patient doesn't respond to his drug because they are active, resist, efflux, and expel the drug.

B. The multidrug-resistance associated protein (MRP) transporters (also from the ABC family):

-They play a role in the excretion of drugs and their metabolites into urine and bile.

-They mediate the resistance of some tumors to chemotherapeutic agents.

*ABC family expel, MRP excretes

C. The solute carrier families (SLC):

-They do not bind ATP but use ion gradients for transport energy. (secondary active transport).

-They are important in the transport or the uptake of neurotransmitters across nerve-ending membranes.

In CNS the neurotransmitter in neurons endings do their effect, so to inhibit the effect these SLCs **reuptake** the neurotransmitter.

4)endocytosis and exocytosis:

There are some drugs cant be transported only by endo and exocytosis.

*endocytosis: to engulf.

-Endocytosis is responsible for the transport of vitamin B12 complexed with the intrinsic factor across the wall of the gut into the blood, and iron is associated with transferrin into RBCs.

*B12 is taken orally then it binds with a protein of the stomach called (intrinsic factor), they move after that to the terminal ilium where absorption happens by receptor mediator endocytosis

If the intrinsic factor is deficient, then B12 is taken by injection.

*B12 deficiency is a common deficiency due to long-term antiacid use, stomach infections, usage of metformin(diabetes drug) to save weight, and other causes.

-Exocytosis is responsible for the secretion of many substances from cells such as neurotransmitters and some hormones.

-These principles of permeation of drug molecules apply to drug absorption, distribution, and elimination.

-These processes determine how rapidly and for how long the drug will appear in the target organ, the site of action, and organs of elimination.

BARRIERS AGAINST DRUG PERMEATION & TRANSPORT

1)Tight junctions between endothelial cells and absence of pores.

2)The presence of a thick basement membrane at which endothelial cells lie.

3)The presence of connective tissue cells around endothelial cells (such as astrocytes in the brain). (more absorption, less excretion)

4)The presence of drug export pumps. (efflux pump),

5)The presence of intracellular and extracellular enzymes that metabolize drugs.

--This occurs in endothelial cells of the brain (blood-brain-barrier). It is present in other tissues such as the testis

PLACENTAL BARRIER

-A semipermeable membrane made up of placental tissues, where the maternal and fetal circulations remain completely separated.

-Between cells, there are tight junctions that allow slow passage of ions and small molecules but restrict movement of larger molecules and certain drugs, but not accurate100% some pathogens can reach the fetus.

PAST PAPER

1) the following about passive absorption is true EXCEPT:

a- The driving force is a concentration gradient

b- Does not involve a carrier

c- The process is saturable

d- The process shows a low structural specificity

e- The process is suitable for lipid-soluble drugs

2)All of the following are general mechanisms of drug permeation Except

a) Aqueous diffusion

b) Aqueous hydrolysis

c) Lipid diffusion

d) Pinocytosis or endocytosis

e) Special carrier transport

3)What is the proportion of the nonionized form of weak base (pka = 9.4)when put

in a media (pH = 7.4)

a) 99%

b) 1%

c) 0.1%

d) 50%

4)Which of the following acids has the highest degree of ionization in an aqueous solution?

a) Aspirin pKa = 3.5

b) Indomethacin pKa = 4.5

c) Warfarin pKa = 5.1

d) Ibuprofen pKa = 5.2

e) Phenobarbital pKa = 7.4

C

B

B

A