PHARMACOLOGY

بسم الله الرحمن الرحيم

MID – Lecture 2

Pharmacokinetics

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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Pharmacokinetics

Quiz for the previous lecture

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Pharmacokinetics

- **Is what the body does to the drug.**
- **Deals with absorption, distribution, biotransformation and excretion of drugs:**

Metabolism

1. **Absorption: Is the movement of drug molecules from the site of administration into the circulation.**

Pharmacokinetics

2. **Distribution: Is the movement of drug molecules from the circulation to tissues and between different parts of the body.**
3. **Biotransformation: Is conversion of the drug from one chemical structure into another by the action of metabolic enzymes (metabolism).**

Biotransformation converts the drug to another or new chemical structure that can be excreted.

- **Now, what is the movement happening here?** 🤔

1. Movement of the drug to the site of metabolism.
2. Movement of the cofactors.
3. The drug move to the enzyme.

4. Excretion: Is the movement of drug molecules out of the body through urine and/or bile.

The drug is excreted mostly /mainly in the urine and some drugs go to the liver and is excreted in bile .

اللهم اعني على الدراسة ولا تجعل قلبي يمل منها وكن معي في كل لحظة ووفقني لما تحب وترضى وارزقني التوفيق والنجاح 🦋

Primary Principles

- **The goal of therapeutics is to achieve a desired beneficial effect with the minimal adverse effects possible.**

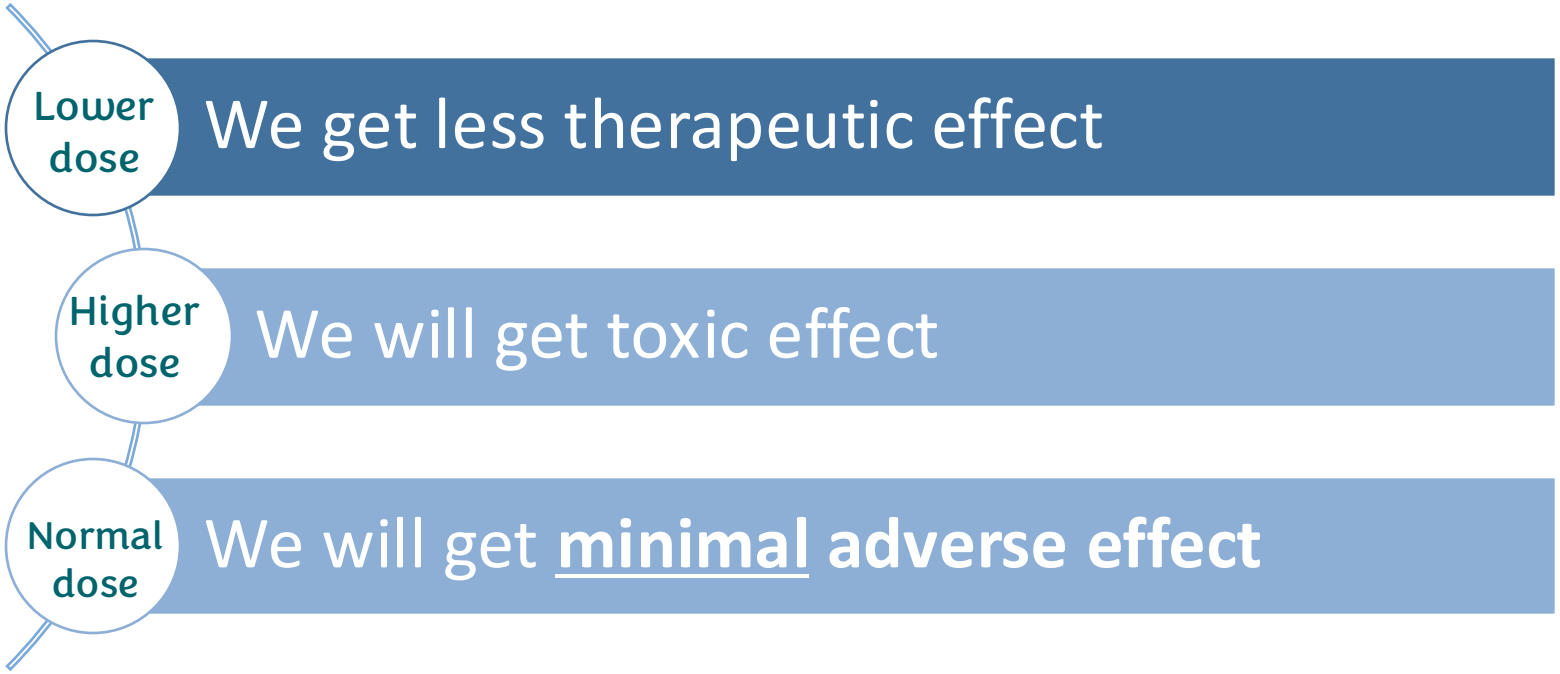
- **Common mistake :** 'Most people think that **adverse effects** and **side effects** have the same meaning.'

  Adverse effects → The harmful effects
  Side effects → They do not have to be negative or harmful effects; they can be beneficial (the drug caused an effect other than the intended target).

  If we benefit of the action of the drug and the drug produces the desired effect, this effect is called **Therapeutic effect**

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

If we give the patient:



-The drug dose is written in the prescription in the form of a range like (ex. 250-500) and is called a **population dose** and ***not*** an **individual dose** because the response of individuals differs from one person to another, so you have to decide the appropriate dose for each patient **"selection of the correct dose".**
-Toxic effect refers to overdose; adverse effect refers to harmful effect at regular dose

- **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).**

There is a direct relationship between concentration and effect of the drug.

❑ **How can we measure the drug concentration at site of the action?** 🤔
We can not measure that, but it can be measured in blood.

Drug concentration of the blood is **not** necessarily equal to the drug concentration at site of action (if we have 5mg/L in blood that does not mean we have 5mg/L at the site of action) **but** the concentration of the drug at site of action **is proportional** to drug concentration in the blood.

Mechanisms of Permeation of Drug Molecules

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

❑ **How the drug reaches site of action?** 🤔

It has to diffuse through membrane of cells.

The drug must dissolve in cell membrane to be effective.

Example:

I can't give patient that have urinary tract infection antibiotic that does not get excreted in urine (the benefit = 0) and damage might even occur

This is similar to the case of a patient suffering from disease in brain and the drug can't cross through blood brain barrier, so the drug is useless.

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

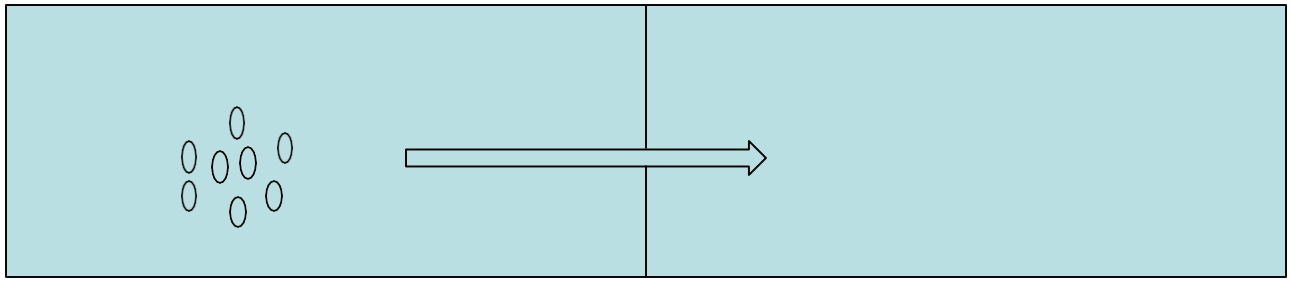
1. **Lipid diffusion (Passive diffusion):**

- **The most important mechanism.**
- **The drug dissolves in the membrane.**

The more lipid soluble the drug is, the better the permeation of the drug.

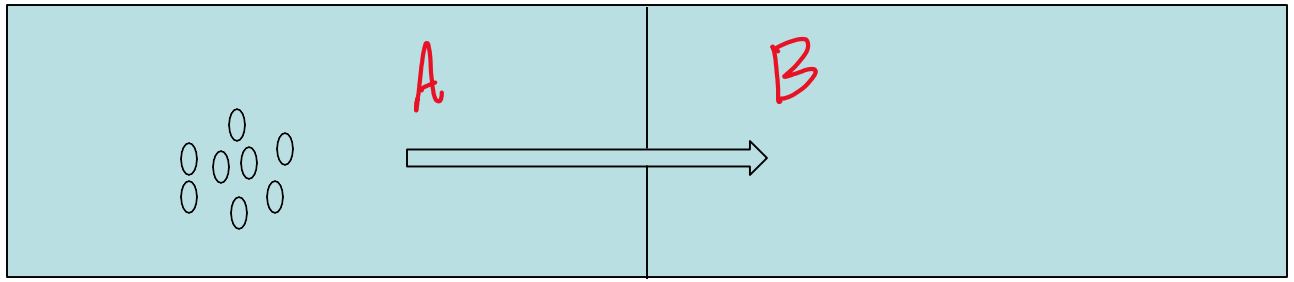
Mechanisms of Permeation of Drug Molecules

- **The more lipid soluble is a drug, the more will be its passage across membranes and vice versa.**
- **The drug has to be sufficiently water soluble to reach the membrane.**
- **The drug follows the concentration gradient.** → The concentration across the membrane



The drug is lipid soluble, but it should have some water solubility to reach membrane.
If the drug is very very lipid soluble in intestine and doesn't reach the wall of the intestine, the drug won't be absorbed, so there should be at least partial water solubility to reach the membrane.

There are drugs that are very lipid soluble that can't be given orally unless it was a huge dose because the rest will not be absorbed.
But most drugs (fortunately) are partially water soluble and partially lipid soluble.



The drug move from high concentration to low concentration.

In picture above :
The molecules cross through membrane from high concentration to low (A→B) until the concentrations are equal, but in our bodies all molecules cross from (A→B) to the last molecule, **why** ? 🤔

Because of blood flow.

Fick's Law of Diffusion

- **It governs the passive flux of molecules across membranes.**
- **Flux (molecules/unit time) =**

  C_1-C_2 x [(Area x Permeability coefficient)/ Thickness]

-When the surface area is larger, the absorption is greater. Therefore, most of the Drugs we take are taken orally because their absorption occurs in the intestines, which are characterized by a large surface area. Therefore, we obtain more effective absorption.

-When thickness is large, it lowers diffusion which happens in thick membranes in our body like the blood brain barrier, placental barrier, and prostate.

C_1 is the higher concentration and C_2 is the lower concentration; area is the area across which diffusion occurs; permeability coefficient is a measure of the mobility of drug molecules in the medium of diffusion path; and thickness is the thickness or length of diffusion path.

Mechanisms of Permeation of Drug Molecules

- **Most drugs are either weak acids or weak basis.**
- **Therefore, the pKa of the drug and the pH of the medium will affect 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.**

Mechanisms of Permeation of Drug Molecules

Ionization of weak acids and basis:

(Organic)

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

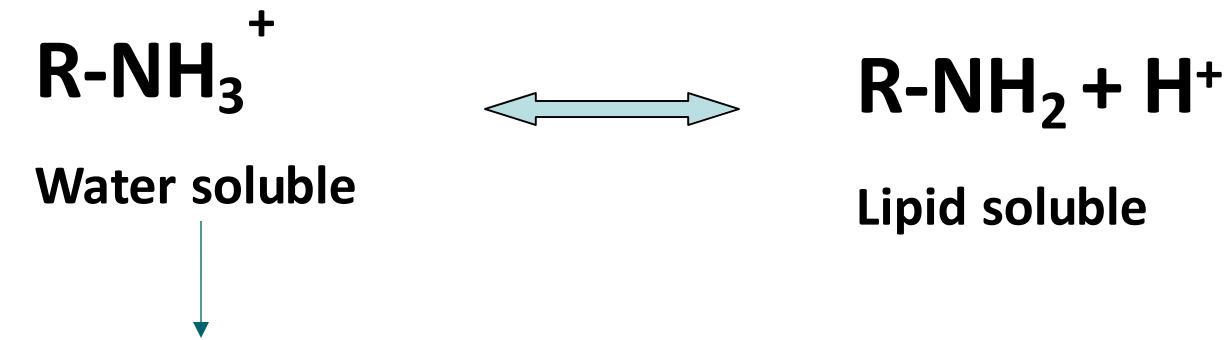
$$\underset{\text{Lipid soluble}}{R\text{-}COOH} \rightleftharpoons \underset{\text{water soluble}}{R\text{-}COO^- + H^+}$$

What do you think will happen if we put this molecule in an acidic medium?
The environment will have a higher concentration of H+ which will cause the equilibrium to shift to the left favoring the formation of the unionized form (lipid soluble)

Mechanisms of Permeation of Drug Molecules

(Organic)

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



Mechanisms of Permeation of Drug Molecules

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

Henderson-Hasselbalch Equation:

Log [protonated/unprotonated] = pKa – pH

- **This equation applies to both acidic and basic drugs.**

✓ General rule:
- In weak acids the protonated form is the lipid soluble (unionized)
- In weak bases the protonated form is the water soluble (ionized)

Mechanisms of Permeation of Drug Molecules

Examples:

1. **Pyrimethamine as a weak base drug with a pKa of 7.0.**

   What is the proportion of ionized and unionized drug in blood (pH = 7.4, it's fixed) and urine (pH = 6, it changes according to our meals)?

Mechanisms of Permeation of Drug Molecules

- **Blood:**

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

  Prot/unprot = $10^{-0.4}$ = 0.4:1 = 0.4/1.4

Explanation for the answers:

1. There is no 0.4 molecule, so we multiply the ratio with 10
2. This is a ratio which means that for each 10 unprotonated molecules (lipid soluble as it's a weak base) have 4 molecules protonated (water soluble)
3. If we wanted to get a percentage from the ratio we will do as the following

0.4:1 → 0.4 will remain the same (the numerator)

→ We will add 0.4 to the 1 (the denominator) then we will multiply them by 100 which will give us 28.6%

Explanation for the previous slide:

- Now after we got the percentage of the protonated form we can do the same to get the percentage to the unprotonated form as the following :

0.4:1 → We will put (1) as the numerator

→ The denominator will stay the same (1.4) giving us 71.4% as the unprotonated form percentage

- After that we can tell the drug will be mostly unprotonated (lipid soluble) resulting in its distribution from blood to the tissues (more lipid soluble molecules than water soluble)
- With time, the equilibrium will be shifted to the lipid soluble formation side because of the distribution to tissues resulting in more distribution of it through the tissues (as once the drug enters the body it's available at both forms but only the lipid soluble form pass through the cell membrane and after some time the body will start converting the remaining water soluble to the lipid soluble form)

Mechanisms of Permeation of Drug Molecules

- **Urine:**

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

  Prot/unprot = 10^1 = 10:1 = 10/11.

The protonated is the ionized form which cannot be reabsorbed through the proximal convoluted tubule in the kidney but it can reabsorb the unionized form, the kidney filters the molecules then reabsorbs them including this drug, that's why we won't see the unionized form in urine

Mechanisms of Permeation of Drug Molecules

- 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)?

✓ Extra information from the doctor:

- When you take a phenobarbital, you need two weeks to get rid of it because we usually need 4 half-lives to eliminate 93% of the drug

Mechanisms of Permeation of Drug Molecules

- **Blood:**

  Log) prot/unprot = (pKa –pH

  0 = 7.4-7.4 =

Lipid soluble

  Prot/Unprot1/2= 1:1 = 10^0 =

It can be distributed as half the molecules are lipid soluble

- **Urine:**

  Log) prot/unprot = (pKa –pH

  1.4 = 6 – 7.4 =

  Prot/Unprot25/26 = 25:1= $10^{1.4}$ =

In each 26 molecules there is 25 lipid soluble that get reabsorbed which means if someone took an overdose from this drug, he will be in a coma for a long period but how can we help??

We will change the pH of the urine making it alkaline till the drug is ionized so it won't be reabsorbed, and this will be done by sodium bicarbonate solution

Mechanisms of Permeation of Drug Molecules

- **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).** But acid in an alkaline environment will be ionized and vice versa

Mechanisms of Permeation of Drug Molecules

- **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.**

Mechanisms of Permeation of Drug Molecules

Application:

Manipulation of drug excretion by the kidney:

By changing the ph of the urine to facilitate the ionization of the drug

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

Mechanisms of Permeation of Drug Molecules

- **This can be accomplished by changing urine pH.**
- **Weak acids are excreted faster in alkaline urine. Urine can be alkalinized by sodium bicarbonate ($NaHCO_3$) given orally or intravenously**

- This sodium bicarbonate is absorbed in the blood then released to the urine and makes urine alkaline, so does blood get alkalized too?
- Not really, we can control the amount of alkaline given without harm and there is a buffer system in the blood, and it gets excreted in the urine faster.

Mechanisms of Permeation of Drug Molecules

- **Weak basis are excreted faster in acidic urine. Urine can be acidified by ascorbic acid (vitamin C) or ammonium chloride (NH_4Cl).**

Preferred

If the patient has problems in the liver like hepatic failure using it won't be good for him as ammonia will be metabolized and may make it worse

- we can't eat oranges instead of taking vitamin c because the citric acid in oranges will bind to Na or K and turn into alkaline but in VitC we will get ascorbic acid directly
- What controls the unionized molecules that will pass through the cell membrane is the fick's law and the Ph of the medium and pka of the drug

Mechanisms of Permeation of Drug Molecules

2. Aqueous diffusion:

- **Through aqueous pores in membranes.**
- **Also driven by the concentration gradient.**
- **Drugs bound to plasma proteins do not permeate aqueous pores.** We need to make sure that the diameter of the drug is smaller than the pores
- **If the drug is charged, its flux is influenced by electrical fields (membrane potentials).**

Mechanisms of Permeation of Drug Molecules

3. **Special carriers (carrier-mediated transport):**

- **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).**

If it needs energy, it's active transport and if not, it's facilitated diffusion, and they can take the drugs against the concentration gradient

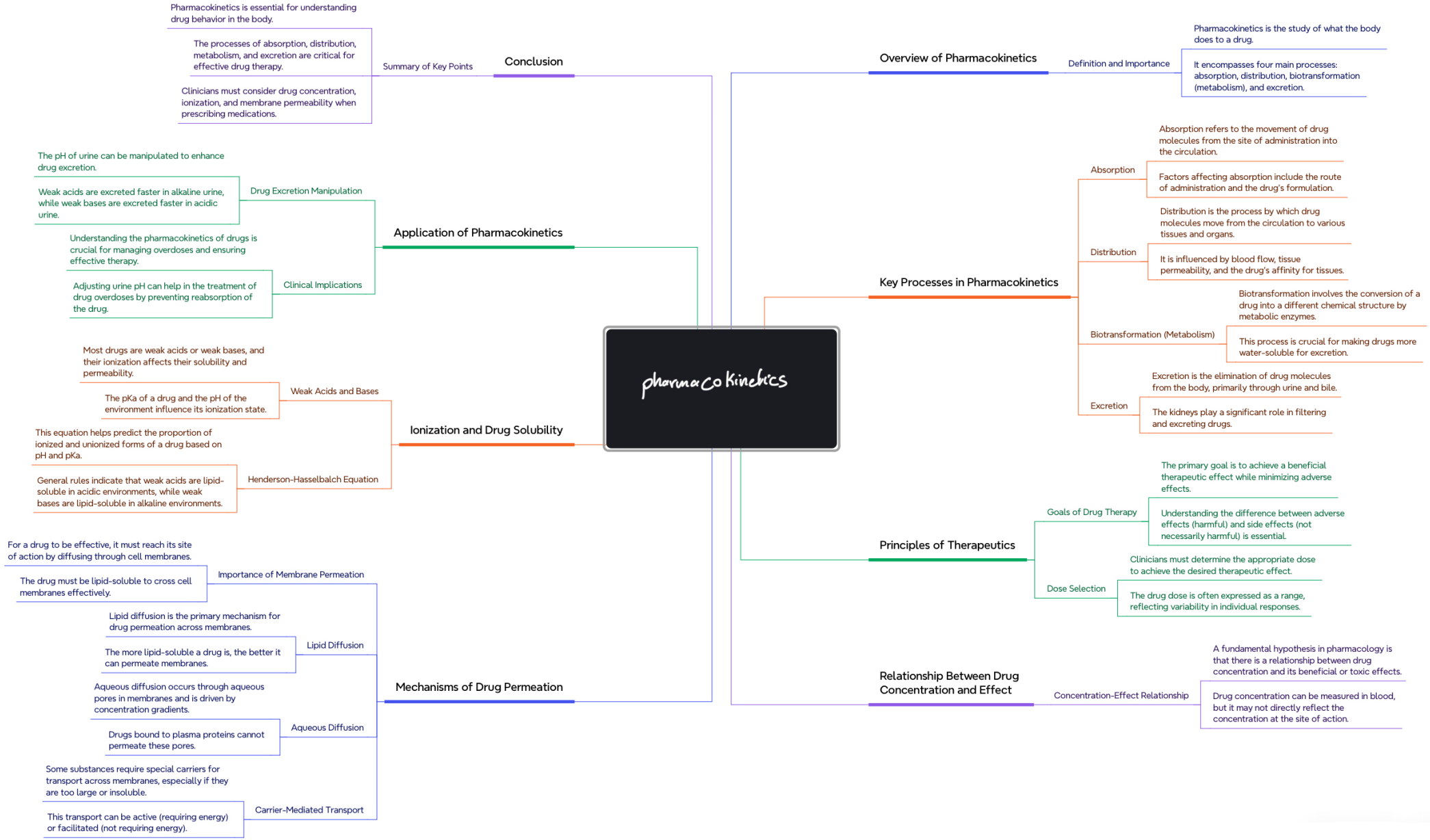
- **They bring about drug movement by active transport or facilitated diffusion.**

Mechanisms of Permeation of Drug Molecules

- **They are selective, saturable and inhibitable.**

It's not totally selective as it can pass some other molecules that are similar in structure

Extra slide


pharmacokinetics
Overview of Pharmacokinetics
Definition and Importance
Pharmacokinetics is the study of what the body does to a drug.
It encompasses four main processes: absorption, distribution, biotransformation (metabolism), and excretion.
Key Processes in Pharmacokinetics
Absorption
Absorption refers to the movement of drug molecules from the site of administration into the circulation.
Factors affecting absorption include the route of administration and the drug's formulation.
Distribution
Distribution is the process by which drug molecules move from the circulation to various tissues and organs.
It is influenced by blood flow, tissue permeability, and the drug's affinity for tissues.
Biotransformation (Metabolism)
Biotransformation involves the conversion of a drug into a different chemical structure by metabolic enzymes.
This process is crucial for making drugs more water-soluble for excretion.
Excretion
Excretion is the elimination of drug molecules from the body, primarily through urine and bile.
The kidneys play a significant role in filtering and excreting drugs.
Principles of Therapeutics
Goals of Drug Therapy
The primary goal is to achieve a beneficial therapeutic effect while minimizing adverse effects.
Understanding the difference between adverse effects (harmful) and side effects (not necessarily harmful) is essential.
Dose Selection
Clinicians must determine the appropriate dose to achieve the desired therapeutic effect.
The drug dose is often expressed as a range, reflecting variability in individual responses.
Relationship Between Drug Concentration and Effect
Concentration-Effect Relationship
A fundamental hypothesis in pharmacology is that there is a relationship between drug concentration and its beneficial or toxic effects.
Drug concentration can be measured in blood, but it may not directly reflect the concentration at the site of action.
Conclusion
Summary of Key Points
Pharmacokinetics is essential for understanding drug behavior in the body.
The processes of absorption, distribution, metabolism, and excretion are critical for effective drug therapy.
Clinicians must consider drug concentration, ionization, and membrane permeability when prescribing medications.
Application of Pharmacokinetics
Drug Excretion Manipulation
The pH of urine can be manipulated to enhance drug excretion.
Weak acids are excreted faster in alkaline urine, while weak bases are excreted faster in acidic urine.
Clinical Implications
Understanding the pharmacokinetics of drugs is crucial for managing overdoses and ensuring effective therapy.
Adjusting urine pH can help in the treatment of drug overdoses by preventing reabsorption of the drug.
Ionization and Drug Solubility
Weak Acids and Bases
Most drugs are weak acids or weak bases, and their ionization affects their solubility and permeability.
The pKa of a drug and the pH of the environment influence its ionization state.
Henderson-Hasselbalch Equation
This equation helps predict the proportion of ionized and unionized forms of a drug based on pH and pKa.
General rules indicate that weak acids are lipid-soluble in acidic environments, while weak bases are lipid-soluble in alkaline environments.
Mechanisms of Drug Permeation
Importance of Membrane Permeation
For a drug to be effective, it must reach its site of action by diffusing through cell membranes.
The drug must be lipid-soluble to cross cell membranes effectively.
Lipid Diffusion
Lipid diffusion is the primary mechanism for drug permeation across membranes.
The more lipid-soluble a drug is, the better it can permeate membranes.
Aqueous Diffusion
Aqueous diffusion occurs through aqueous pores in membranes and is driven by concentration gradients.
Drugs bound to plasma proteins cannot permeate these pores.
Carrier-Mediated Transport
Some substances require special carriers for transport across membranes, especially if they are too large or insoluble.
This transport can be active (requiring energy) or facilitated (not requiring energy).

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide #19 Slide #20 Slide #21 Slide #7	We will add 0.4 to the 1 (the denominator) then we will multiply them by 100 which will give us 60%-65% The protonated is the ionized form which cannot be reabsorbed through the proximal convoluted tubule in the kidney, the kidney filters the molecules then reabsorbs them including this drug, that's why we won't see it in urine at high concentration We will get adverse effect (toxic effect) **(just to be clear, this is not completely wrong, we searched about adverse effects and found out it could be used here but decided to change it because the doctor mentioned you should differentiate toxic effect (overdose) & adverse effect (normal dose)**	We will add 0.4 to the 1 (the denominator) then we will multiply them by 100 which will give us 28.6% **Added information** The protonated is the ionized form which cannot be reabsorbed through the proximal convoluted tubule in the kidney but it can reabsorb the unionized form, the kidney filters the molecules then reabsorbs them including this drug, that's why we won't see the unionized form in urine We will get toxic effect
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي: