بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | Lecture 7

Pharmacokinetics pt.1

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Pharmacokinetics

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'What the body do to the drugs'
Pharma = Drugs
Kinetics = Movement in the body

Pharmacokinetics

Drug moves from the **blood** to the **organ of elimination** or organ of metabolism (ex: liver/ kidneys)

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

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

Why didn't we say, "from the GI tract"? Because the drug can be taken subcutaneously or intramuscularly (not just orally by mouth)

Normally the drug passes through all four steps (**absorption-->distribution-->biotransformation-->excretion**), what if the drug is taken by IV (intravenously)? There will be no absorption as the drug directly enters the blood stream,, the last three steps (distribution, biotransformation, and excretion) are collectively called "the drug disposition" because they describe how the body handles the drug after it's absorbed

Pharmacokinetics

The drug goes in and out of the tissues continuously until it reaches **equilibrium**, because the drug crosses membranes

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).** Mostly In the **liver**

The term biotransformation is clearer than **metabolism.**

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

Mostly

Bile is for **larger molecules**; they will be secreted actively(using energy). On the other hand, kidneys get rid of smaller molecules easily by urine

Conclusion

As we said before, drugs pass through 4 main steps : (A - D - M - E)

Absorption : The process by which a drug moves from its site of administration into the bloodstream, for example a drug from the oral cavity to the bloodstream e.g. paracetamol.

Distribution : The movement of the drug from the bloodstream to various tissues and organs.

Biotransformation : The chemical alteration of the drug, usually in the liver, to make it easier to excrete, and it is the conversion of drug in one chemical substance into another by *metabolic enzymes*. Also can be called metabolism.

Excretion : The removal of the drug and its metabolites from the body usually from kidneys – Urine and/or pile.

Note :

The site of administration means where the patient took the drug, and they are :
Oral (Mouth) = Drug will pass through **4** steps !
Intramuscularly = Drug will pass through **4** steps !
Subcutaneous = Drug will pass through **4** steps !
Intravenously = Drug will move in **3** steps – No absorption step because it is already in the bloodstream !

Adverse effects :
undesirable effects (bad effects) this term is different from side effects as it includes both good and bad effects of the drug.

Primary Principles

- **The goal of therapeutics is to achieve a desired beneficial effect with the minimal adverse effects possible.** ➡ Is this achievable? No, explanation in the next slide...
- **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).**

- ✓ Drugs have adverse reactions(effects) it depends on how much the patient can tolerate them. Before prescribing any drug, as a physician you should calculate the benefit/risk ratio and if it turns out that the benefits outweigh the risk then you can prescribe the drug to your patient. **Are adverse reactions preventable?** Yes, but not 100% ,, **How can you prevent them?** By dose calibration (معايرة الجرعة) and monitoring of the dose regarding the effect. As a result of that, you will give the dose with the best therapeutic effect and least toxicity.

- **Why are we mentioning dose regulation and monitoring?** Because in most drugs there is a relationship between concentration and effect, if we increase the dose more than needed, we may reach toxicity as discussed previously (remember the dose response curves!)

- ✓ For the drug to be affective it must reach the site of action, for example if a patient is diagnosed with UTI (urinary tract infection) and it turns out that the bacteria causing this infection is sensitive to a certain antibiotic, but this antibiotic is not excreted in urine, **can this antibiotic be used in our case?** No. Another example, if a patient has a problem in the CNS and we have a drug that doesn't cross BBB(Blood Brain Barrier) , **can this drug be used?** No, it will not be effective.

Mechanisms of Permeation of Drug Molecules

- **The drug has to reach the site of action in order to be effective.**
- **The movement of the drug between compartments in the body requires passage through membranes.** **Mechanisms of drug movement :**

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

Passive: no energy/ carriers needed
Active: we need energy or carriers or both

- **The most important mechanism.**
- **The drug dissolves in the membrane.** Cell membranes are semi-liquid

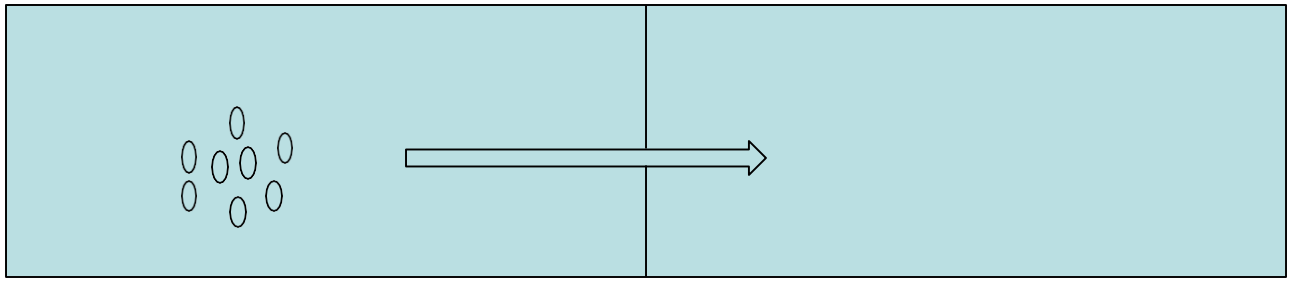
If a drug is ionized (ex: aminoglycoside antibiotics) then it will not cross membranes/ it will not be absorbed from the GI tract/ it will not be metabolized (doesn't reach the liver)/ but it will be excreted in urine by glomerular filtration , these drugs are not given orally

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.**

If the drug is very **highly lipid** soluble it will not get absorbed by the GI tract, why? Because the content of the GI tract is mostly watery and it is what carries the drug to the membrane

★ **The drug follows the concentration gradient.**



Moves from the area of high concentration--> low concentration

We took in chemistry that molecules diffuse following the concentration gradient until we reach a state of equilibrium where we have the same concentration of molecules in both compartments. Does this happen in the body when the drug is absorbed ?

No. All the drug molecules are absorbed from the intestinal lumen --> blood circulation, why? Because when the drug enters circulation, it will be washed away/ diluted thus no equilibrium is achieved (always the concentration of the drug in the intestinal lumen is higher than in the blood)

Fick's Law of Diffusion

- **It governs the passive flux of molecules across membranes.** In the bodies
- **Flux** is measured by : **(molecules/unit time)**

Depends on the concentration gradient

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

C1 : concentration at one side (side of administration)

C2 : concentration in the circulation

At the beginning it will be zero

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.

- As we learned before about Fick's law (in diffusion box) : bring glass box, divide it into 2 parts , put a semi permeable membrane , 2 fluids , chemical substance in one part, then the chemical substance will start to diffuse until it reaches **equilibrium** (equal concentrations).

✓ In our body : any substance that enter the blood will be diluted by the circulation and go away , **so always there will be concentration gradient .**

❖ More concentration gradient = more passage

❖ More area = more passage and absorption (that's why most drugs are taken orally, because the surface area of the GI tract is very large (from the stomach to the terminal ileum which is the last part of small intestine) (usually the colon isn't a side of absorption)

- Examples of surface area: long tubes, fold shaped mucosa (in the upper intestine they have villi).

❖ More membrane thickness = slower passage (so it's a **reverse factor**).

There are a lot of drugs that get absorbed by the GI tract ,then go to the circulation, then to organs **BUT** do not across the blood brain barrier and do not reach the brain **AND** this related to **THICKNESS.**

We have a **permeability coefficient** , it tell us how easily a substance can cross a membrane (the ease of diffusion).

Mechanisms of Permeation of Drug Molecules

At surgical PH , these weak acids and basis will be partially dissociated . So, it's partially ionized and partially unionized.

- **Most drugs are either weak organic acids or weak organic 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.**
- pKa of the drug and PH of the medium will determine the solubility in lipids and water.
- **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:

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

Weak acid always have carboxyl group whatever the structure is.

The reaction will move to the left in an acid environment. The H+ made a neutral compound. In weak acid the longer arrow will refer to **unionized.**

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

The weak acid donates protons when it's in water solution.

Proportion is how much it's ionized and how much it's unionized , is determined by the pKa of the drug and the PH of the medium.

Mechanisms of Permeation of Drug Molecules

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

Both reactions (weak acid and base) are reversible but the arrows aren't equal.

Amine group means weak base.

$R\text{-}NH_3^+$ ⟷ $R\text{-}NH_2 + H^+$

Water soluble

Lipid soluble

The reaction will move to the left in an acid environment. The H+ made an ion NH3+ . In weak basis the longer arrow will refer to ionized.

It's lipid soluble because it doesn't have charge . Add to it a proton it will become ionized.

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.**

Protonated acid is unionized+ lipid soluble,
Protonated base is ionized + water soluble.

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) and urine (pH = 6)?

We don't treat pKa as PH,
(more PH means more basic and lesser means acidic, this is wrong in pKa).

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

  (it's a ratio)

We have more unionized(lipid soluble) this means that the drug can easily diffuse through membrane.

This means that FOR EACH 10 UNIONIZED MOLECULE , WE HAVE 4 IONIZED.
So it has a lipid solubility to pass the membrane and water solubility to reach the membrane. So it can be distributed to other tissues, excreted by the urine and so on.

- **Urine:**

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

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

This means that 10 IONIZED AND 1 UNIONIZED.
Most of the drug is ionized , so it cannot be reabsorbed , so it excrete out through urine.

Mechanisms of Permeation of Drug Molecules

Half life = 4 days
Because any filtered amount will be reabsorbed.

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)?

If someone took overdose of phenobarbital and toxicity happens , how can the body get rid of that?
Through **changing the pH** of the urine to make the drug ionized in urine, How??

Increase the PH to make it alkaline = more ionization = accelerate the elimination from the body.
There are more ways to get rid of drug toxicity !
- for **weak acid** make the urine **alkaline .**
- for **weak base** make the urine **acidic .**

Mechanisms of Permeation of Drug Molecules

- **Blood:**

  Log (prot/unprot) = pKa – pH

  = 7.4-7.4 = 0

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

  Half is ionized and the other isn't . It can be pass membranes and get distributed in the body.

- **Urine:**

  Log (prot/unprot) = pKa – pH

  = 7.4 – 6 = 1.4

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

  Lipid soluble. This drug will be extensive reabsorbed.

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).**

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:

- **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

What will happen if we give the patient with phenobarbital toxicity CaOH instead of giving NaHCO3 ?
Absolutely not because it's strong base and will burn everything. Very dangerous !

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

Can the patient eat a lot of حمضيات?

Absolutely no because they contain citric acid and citric acid will convert to base in the body, and this will form basis like sodium citrate / potassium citrate. So, we should buy vitamin C in pharmaceutical form.

Additional Resources:

رسالة من الفريق العلمي:

Extra References :

Youtube :

1- Ninja Nerd : Pharmacokinetics (40 minutes)
HIGHLY recommended !!
2- Simple Nursing : Pharmacokinetics
Explains the ADME system in 7 minutes !!

Legan Aldofat App :

Past Papers

Did you study well ? Go to chat GPT :

Generate MCQ's to be a NERD and solve them right !

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