Pharmacokinetics

Yacoub Irshaid MD, PhD, ABCP
Department of Pharmacology

Pharmacokinetics

- **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.**

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).**

Cytochrome P_{450}

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

depends on MW

(↑ MW ⇒ moves through urine)

Primary Principles

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

All drugs have Adverse effects → Side effects

harmful effects

may be harmful, beneficial, no effect

toxic effect → Overdose (V. high Dose)

Adverse effect → Therapeutic Dose (normal Dose)

Dose of Drug cannot be measured at Site of Action (SOA)

But it can be measured in Blood ← Dose of Drug in bld is proportional to Dose at SOA (but it is not necessarily equal)

Drug must reach SOA to work

- Drug to treat UTI must pass Urinary Tract
- Drug that treats Brain injuries must pass BBB (Blood Brain Barrier)

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.**

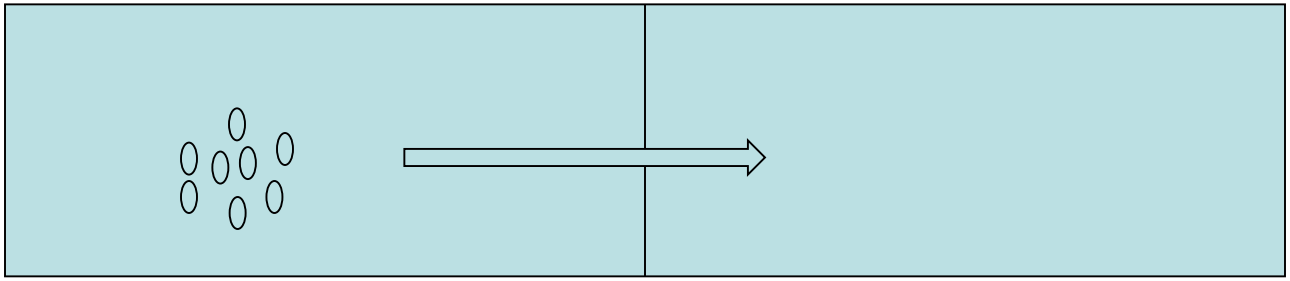
1. **Lipid diffusion (Passive diffusion):**

No transporter required

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

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.**



Why doesn't drug move back into blood after it is absorbed ?

Blood is constantly moving through body ... drug would be washed away and drug would be wasted.

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]

Obviously note ↑ Thickness ↓ Flux

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.**

depend on pH of medium and pKa of drug

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).** Lowry – Brønsted definition

R-COOH ⟷ **R-COO$^-$ + H$^+$**

Lipid soluble — **water soluble**

Can pass membrane — Doesn't cross membranes

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. Lowry – Brønsted definition

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

Water soluble

Cannot pass membrane

Lipid soluble

Can pass Membrane

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.**

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)?

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$$\log \frac{[\text{Protonated}]}{[\text{Unprotonated}]} = \text{pKa} - \text{pH}$$

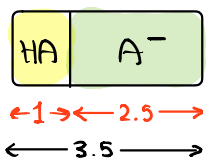
In Blood (pH = 7.4)

$$\log \frac{[\text{Protonated}]}{[\text{Unprotonated}]} = 7.0 - 7.4$$

$$\log \frac{[\text{Protonated}]}{[\text{Unprotonated}]} = -0.4$$

$$\frac{[\text{Protonated}]}{[\text{Unprotonated}]} = 10^{-0.4} = \frac{1}{10^{0.4}} < 1$$

$$\frac{1}{2.5} < 1$$



$$\frac{[HA]}{[HA]+[A^-]} = \frac{1}{3.5}$$

∴ Less protonated

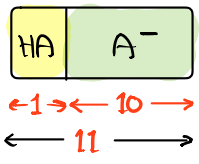
In Urine (pH = 6.0)

$$\log \frac{[\text{Protonated}]}{[\text{Unprotonated}]} = 7.0 - 6.0$$

$$\log \frac{[\text{Protonated}]}{[\text{Unprotonated}]} = 1.0$$

$$\frac{[\text{Protonated}]}{[\text{Unprotonated}]} = 10^{1.0} = 10^{1}$$

$$\frac{10}{1} > 1$$



$$\frac{[HA]}{[HA]+[A^-]} = \frac{1}{11}$$

∴ More protonated

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

- **Urine:**

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

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

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)?

Same idea as above

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

- **Urine:**

  Log (prot/unprot) = pKa – pH

  = 7.4 – 6 = 1.4

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

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

- 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).

releases HCl, NH_3

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

diameter of drug ↓ diameter of pores

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).**
- **They bring about drug movement by active transport or facilitated diffusion.** → no need for energy

needs energy ←

Tryptophan Transporter ⇒ facilitated diffusion.

Mechanisms of Permeation of Drug Molecules

- **They are selective, saturable and inhibitable.**
- **Many cells contain less selective membrane carriers that are specialized in expelling foreign molecules including drugs:**

A. ATP-binding cassette (ABC) family:

- **It includes P-glycoprotein or the multidrug-resistance type 1 (MDR1) transporter found in the brain, intestine, testes, neoplastic cells, and other tissues.**