Pharmacokinetics

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Areas of Pharmacology

Pharmacodynamics:

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

Areas of Pharmacology

Pharmacokinetics: "ADME"

- **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.**
2. **Distribution: Is the movement of drug molecules from the circulation to tissues and between different parts of the body.**

Areas of Pharmacology

3. **Biotransformation: Is conversion of the drug from one chemical structure into another by the action of metabolic enzymes (metabolism).**
4. **Excretion: Is the movement of drug molecules out of the body.**

Pharmacokinetics & Pharmacodynamics

Dosage form

↓

Disintegration

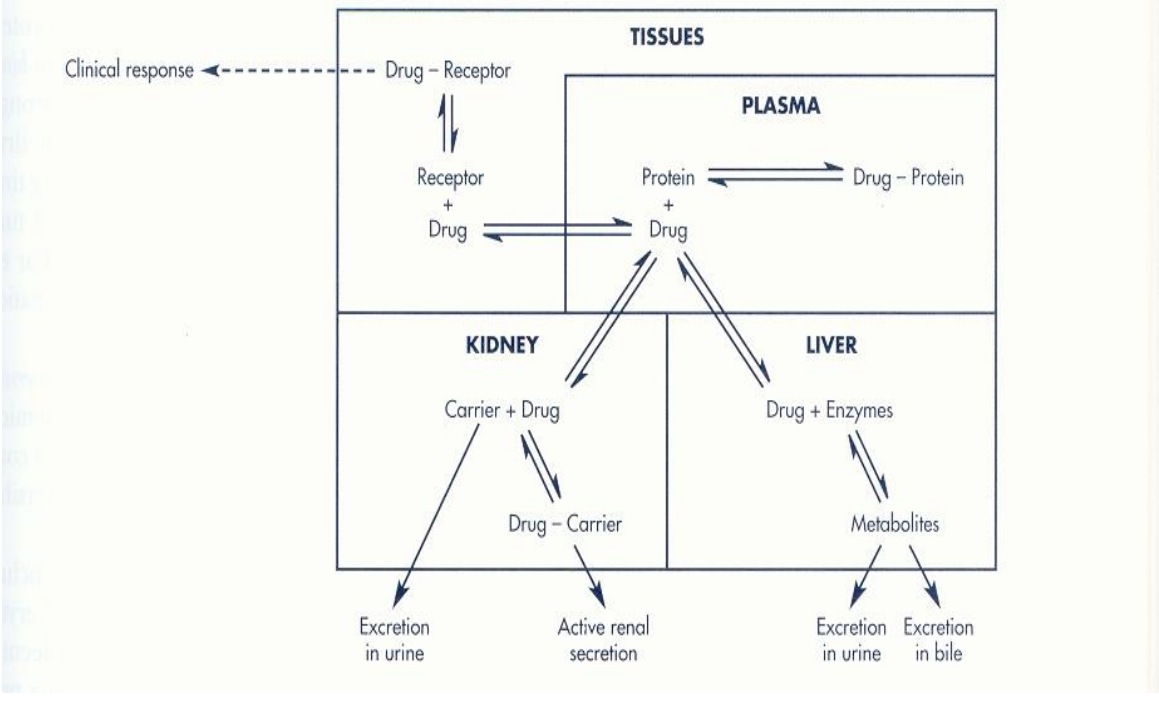
↓

Dissolution

↓ ***absorption***

Drug in the systemic circulation

Drug Disposition



Primary Principles

why do we need to study pharmacokinetics ?

- **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).**

- why do we need to study pharmacokinetics ?

"**to achieve a desired beneficial effect with the minimal adverse effects possible.**"

How is that related to pharmacokinetics ?

So the thing is pharmacokinetics let us know the concentration of the drug in the plasma which is proportional to the conc. at the action site which finally lead us to the therapeutic doses that is enough to treat the disease with the minimal adverse effect.

- mind you that we can't ever know the conc. at the action site because imagine how many receptors there is for a single drug.

P.K → plasma conc. → action site conc. →

therapeutic doses → beneficial effect

- "Anything that can be prevented, should be."

So if you can prevent the adverse reaction then you should, by not exceeding the therapeutic concentration which requires not exceeding the therapeutic dose

Mechanisms of Permeation of Drug Molecules

- The drug has to reach the site of action in order to be effective. by crossing several membranes and layers from the site of administration → circulation → action site → metabolism → excretion
- The movement of the drug between compartments requires passage through membranes. How!

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

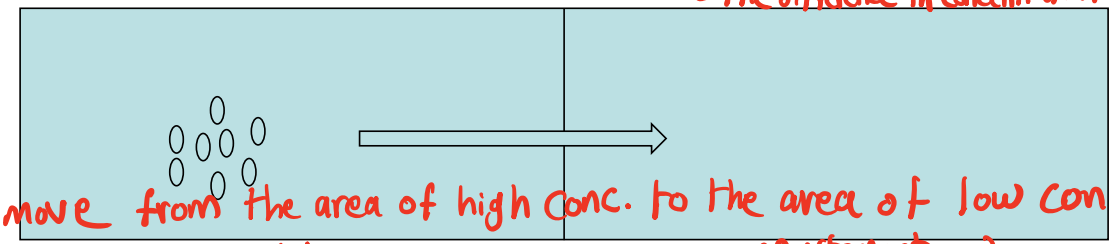
- The most important mechanism.
- The drug dissolves in the membrane.

• The cell membrane is a semifluid phospholipid membrane
• so if the drug is lipid soluble it will diffuse easily

Mechanisms of Permeation of Drug Molecules

- The more lipid soluble is a drug the more will be the passage across membranes, and vice versa. But if the drug is "very" lipid soluble ; it may not reach the membrane, why
- The drug has to be sufficiently water soluble to <u>reach</u> the membrane. so it should be partially lipid soluble and partially water soluble (with more of it being lipid soluble)
- The drug follows the concentration gradient.

↳ The difference in concentration across the membrane



The drug will move from the area of high conc. to the area of low conc.
There will never be equilibrium between the two compartements Because of the blood flow that washes the drug out to circulation (so there's always a conc. gradient)

Fick's Law of Diffusion

- **Governs passive flux of molecules across membranes.**
- **Flux (molecules/unit time) = C_1-C_2 x [(Area x Permeability coefficient)/ Thickness]**

• Flux: passage of the molecules per unit time

Constant

• $C_1 - C_2$: concentration gradient

↑ num. of layers
↑ Thickness
↓ absorption

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.

↑ Area ↑ absorption

That's why drugs are usually given orally rather than nasally considering the huge area of GI tract in comparison to the nasal cavity

Mechanisms of Permeation of Drug Molecules

Talking about the water and the lipid solubility of the drug, we should know:

- Most drugs are either weak acids or weak basis. So their ionization is mediated by pH of the medium and the value of pKa of the drug.
- 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.

As we said before, according to (pKa, pH) the drug will be partially ionized

doesn't cross the membrane X (it only reaches the membrane)

crosses the membrane ✓

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).**

donates protons

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

- Reversible reaction
- The direction of the reaction depends on the pH of the medium

Mechanisms of Permeation of Drug Molecules

accepts protons

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

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

Water soluble — ionized form

Lipid soluble — unionized

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:

$$\text{Log}_{10}[\text{protonated/unprotonated}] = \text{pKa} - \text{pH}$$

of the drug — of the medium

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

"These reactions move to the left in an acid environment (low pH) and to the right in an alkaline environment (high pH)."

The direction of the equilibrium in both acid and base ionization reaction move to the left at low pH value and to the right at high pH value.

- Acid in an acid environment

⇒ pKa of the drug > pH ⇒ more H^+ content ⇒ protonated ⇒ unionized

⇒ reaction moves to the left

$$\underset{\text{protonated}}{R\text{-}COOH} \longleftrightarrows R COO^- + H^+$$

- Base in an acid environment

⇒ pKa > pH ⇒ more H^+ content ⇒ protonated ⇒ ionized

⇒ reaction moves to the left

$$\underset{\text{protonated}}{RNH_3^+} \longleftrightarrows RNH_2 + H^+$$

- Acid in alkaline environment

pKa < pH ⟶ less H^+ content ⟶ deprotonated ⟶ ionized

⟶ to the right

$$RCOOH \rightleftharpoons RCOO^- + H^+$$

deprotonated

- Base in alkaline environment

pKa < pH ⟶ less H^+ content ⟶ deprotonated ⟶ unionized

⟶ to the right

$$RNH_3^+ \rightleftharpoons RNH_2 + H^+$$

deprotonated

* protonated acid ⟶ unionized deprotonated acid ⟶ ionized

* protonated Base ⟶ ionized deprotonated Base ⟶ unionized

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)?

Mechanisms of Permeation of Drug Molecules

- **Blood:** Alkaline env

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

  Prot/unprot = $10^{-0.4}$ = 0.4:1 = 0.4/1.4 (total molecules; 1 + 0.4)

  here there's more unprot (unionized) in the plasma so it can pass through membrane

- **Urine:** acidic env

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

  Prot/unprot = 10^{1} = 10:1 = 10/11. (total molecules; 1 + 10)

  more protonated (ionized) (water soluble) can't cross membrane

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)?

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 ionized half unionized

- **Urine:**

  Log (prot/unprot) = pKa – pH

  = 7.4 – 6 = 1.4

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

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.

NOT FOR MEMORIZATION

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.** true for both acids and Bases
- **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: in urine

- **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.**

in case of having acidic drug that is toxic and is excreted partially in urine, it can be eliminated by alkalization of urine using proper agent like ($NaHCO_3$).

in the case of toxic Basic drug, it's eliminated by acidification of urine

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).

Mechanisms of Permeation of Drug Molecules

depends on membrane potential mainly

2. **Aqueous diffusion:** specially for water soluble molecules and small molecules

- **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.**

Mechanisms of Permeation of Drug Molecules

- **Drugs bound to plasma proteins do not permeate aqueous pores.**
- **If the drug is charged, its flux is influenced by electrical fields (membrane potentials).** not by concentration gradient

* Not all water soluble molecules are ionized

Mechanisms of Permeation of Drug Molecules

3. Special carriers: for specific molecules

- **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.**

Mechanisms of Permeation of Drug Molecules

partially selective

- 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. it's an eflux transporter meaning that it prevents toxins from entering organs

Mechanisms of Permeation of Drug Molecules

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

- **They play a role in excretion of drugs and their metabolites into urine and bile.**
- **They mediate the resistance of some tumors to chemotherapeutic agents.**

Mechanisms of Permeation of Drug Molecules

C. The solute carrier families (SLC):

(membrane potentials)

- **They do not bind ATP but use ion gradients for transport energy.**
- **They are important in the transport or the uptake of neurotransmitters across nerve ending membranes.**

Mechanisms of Permeation of Drug Molecules

absorbing releasing

4. **Endocytosis and exocytosis:** for drugs that can't be absorbed by any mechanism mentioned before

- **Endocytosis is responsible for transport of vitamin B_{12} complexed with the intrinsic factor across the wall of the gut into the blood, and iron associated with transferrin into RBCs.** protein released from the stomach
- **Exocytosis is responsible for secretion of many substances from cells such as neurotransmitters and some hormones.**

Mechanisms of Permeation of Drug Molecules

- ***These principles of permeation of drug molecules apply to drug absorption, distribution and elimination.*** (passage through membranes)
- ***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 thick basement membrane at which endothelial cells lie. (thickness ↑ passage ↓)
3. The presence of connective tissue cells around endothelial cells (such as astrocytes in the brain).
4. The presence of drug export pumps. (Lipid pumps)

Barriers Against Drug Permeation & Transport

4. **The presence of intracellular and extracellular enzymes that metabolize drugs.** more in the placental Barrier
- **This occurs in endothelial cells of brain (blood-brain-barrier).**
- **It is present in other tissues such as 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.**