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PHARMACOLOGY

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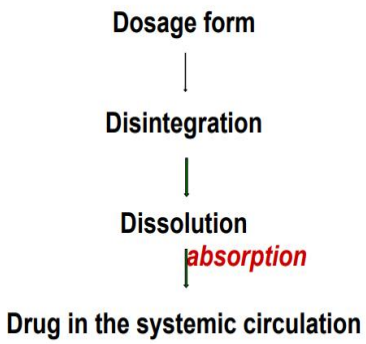
Pharmacokinetics

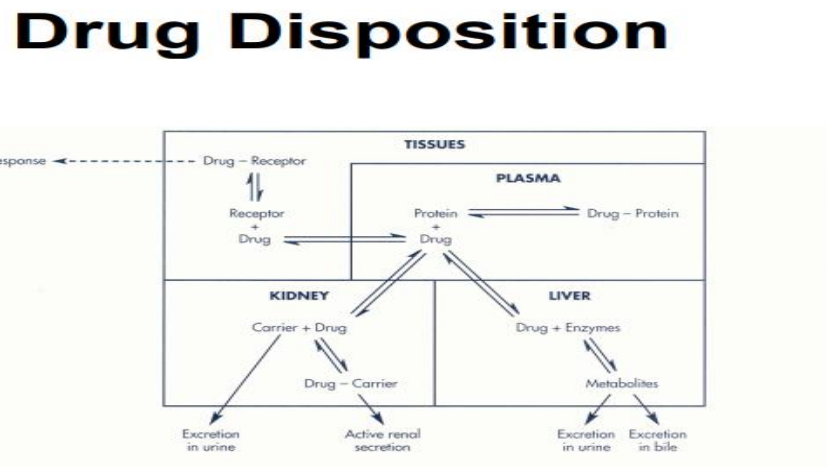
Pharmacology has two areas , PHARMACODYNAMICS which is concerned with the drug action and PHARMACOKINETICS which is how the body deals with the drug .

PHARMACOKINETICS 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 , ORAL DRUGS for example has to move from the small intestine to the circulation .**
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), The transformation is USUALLY from lipid soluble form to a more water soluble form , lipid and water solubility are the determinant of whether the drug will be metabolised in the liver or excreted with urine or in bile , lipid soluble will be metabolized and water soluble will be excreted .**
4) **Excretion: Is the movement of drug molecules out of the body , high molecular weight drugs will be excreted in bile (active process) and low molecular weight drugs will be excreted in urine by filtration mainly (the water soluble ones) and sometimes by active secretion like some antibiotics .**
    - **Orally taken solid drugs that are ingested as whole have to disintegrate then the active ingredients have to get out in to the fluid (dissolution) the it gets absorbed .**
    - **Whatever the route of administration is , the has to go into the plasma to get distributed to the organs of elimination and the site of action , in the plasma some drugs are bound to plasma proteins specifically albumin , so the drug is found in plasma in two forms one of them is free and the other is bounded to proteins and there is an equilibrium between these two forms ,THE ACTIVE DRUG IS THE FREE ONE because the bounded will become large and does not fit into receptors and other targets so it will not work .**

Pharmacokinetics & Pharmacodynamics





- ❖ **The goal of therapeutics is to achieve a desired beneficial effect with the minimal adverse effects possible. Clinically you can not measure the concentration of the drug at the site of action , so we depend on the proportionality between the plasma concentration of the drug and the concentration at the site of action of the drug .**
- ❖ **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).**

What is the difference between the adverse effect and the toxic effect ?

Adverse effect is the secondary side effect that may happen at a therapeutic dose while the toxic effect happens at over doses .

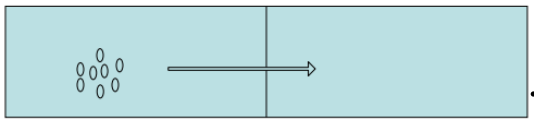
- **The drug has to pass through the membrane so it should have enough lipid solubility to be get into cells and the movement of the drug between compartments requires passage through membranes.**

Lipid diffusion (Passive diffusion):

It's a passive process so does not require energy and it depends in the concentration gradient (the concentration at the site of administration should be higher it in the circulation for the drug to be absorbed).

Mechanisms of Permeation of Drug Molecules

- **The more lipid soluble is a drug the more will be the 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 molecules tend to move from the left to right to reach the equilibrium depending on the concentration gradient and the permeability of the membrane , which is not the case in the body , the drug will keep moving because of the circulation , it always goes away from the site of administration so its always the site of low concentration .

- **The absorption happens usually in the small intestine and sometimes in the stomach (for the acidic ones).**

So the small intestine is the major site for absorption ,WHY? Fick's law will explain the matter :

Fick's Law of Diffusion :

Governs passive flux of molecules across membranes.

- **Flux (molecules/unit time) = C1 -C2 x [(Area x Permeability coefficient)/ Thickness]**

C1 : higher concentration

C2 : lower concentration (because the circulation will always push the drug away)

The more the thickness , the lower the absorption (remember the blood brain barrier that is very thick preventing any diffusion to the brain).

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 bases.

- **Therefore the pKa of the drug and the pH of the medium will affect lipid solubility of the drug and its passage across membranes because they determine the ratio of ionized and non ionized molecules.**

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

The unionized molecules should be enough to allow the passage of significant molecules through the membrane .

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).

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

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

$$\underset{\text{Water soluble}}{R\text{-}NH_3^+} \rightleftharpoons \underset{\text{Lipid soluble}}{R\text{-}NH_2 + H^+}$$

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**

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)?(extra info for you , the PH of the urine is different due to the food administration (vegetarians have more alkaline urine) .**

   Blood:
   Log (prot/unprot) = pKa – pH =7-7.4 = - 0.4
   Prot/unprot = $10^{-0.4}$= 0.4:1 = 0.4/1.4 (most of the drug is lipid soluble (unprotonated)so can pass the membrane)
   Urine:
   Log (prot/unprot) = pKa – pH =7-6 =1
   Prot/unprot = 10^{1} = 10:1 = 10/11 (most of the drug is water soluble in urine so it will be excreted).
   So if there is a basic toxic drug in the body we acidify the urine so it will be excreted without getting reabsorbed back .

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 = 10^{0} = 1:1 =1/2 (still there will be a movement but the equilibrium will keep shifting).

   - **Urine: Log (prot/unprot) = pKa – pH = 7.4 – 6 = 1.4**

   Prot/Unprot = $10^{1.4}$ =25:1 = 25/26 (the drug will be reabsorbed because the major is lipid soluble , so the urine should be alkalinized so the drug will be excreted)

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

Different drugs have different pka values :

>>>>absolutely not required >>>

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:

1) 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.**

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).**

So should we give the patient a vitamin C or tell them to eat foods that contain acid ? they should take vitamin C because the acid that found in fruits is citric acid which turns to alkaline substance (potassium citrate and sodium citrate),so urine doesn't acidify in the latter situation.

2)Aqueous diffusion:

3) Special carriers:

These two will be discussed in the next lecture ….

Study questions :

1) **Chlorothiazide is a weakly acidic drug with a pKa of 6.5. If administered orally, at which of the following sites of absorption will the drug be able to readily pass through the membrane?**

A. Mouth (pH approximately 7.0).

B. Stomach (pH of 2.5).

C. Duodenum (pH approximately 6.1)

D. Jejunum (pH approximately 8.0). E. Ileum (pH approximately 7.0)

ANSWER : B

Because chlorothiazide is a weakly acidic drug (pKa = 6.5), it will be predominantly in nonionized form in the stomach (pH of 2.5). For weak acids, the nonionized form will permeate through cell membrane readily

2) Alkalization of urine by giving bicarbonate is used to treat patients presenting with phenobarbital (weak acid) overdose. Which of the following best describes the rationale for alkalization of urine in this setting?

A. To reduce tubular reabsorption of phenobarbital.

B. To decrease ionization of phenobarbital.

C. To increase glomerular filtration of phenobarbital.

D. To decrease proximal tubular secretion.

E. To increase tubular reabsorption of phenobarbital.

ANSWER: A

As a general rule, weak acid drugs such as phenobarbital can be eliminated faster by alkalization of the urine. Bicarbonate alkalizes urine and keeps phenobarbital ionized, thus decreasing its reabsorption .

3) Which does the term pharmacokinetics not include? (what the body does to the drug or how the drug gets in, around and out of the body)

A. Clinical response to a drug; toxicity & efficacy

B. Drug concentration at site of action

C. Dose of drug administered

D. Drug metabolized or excreted

ANSWER: A