Distribution, Metabolism, & Excretion

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Distribution
- Refers to the movement of the drug throughout the body to the various compartments
- These compartments include:
  - ______
  - ______
  - Cells (e.g., muscle, adipose, liver, kidney)
  - Excretory fluids (e.g., urine, bile, sweat)
  - Plasma fluid proteins (______)
- These compartments are separated by biologic membranes that let some substances to pass freely
Membrane Structure

- Cell membrane is composed primarily of ______ and __________.
- Actually called _______, composed of a polar, hydrophilic “head” and a lipid, hydrophobic “tail”
- Arranged in a __________
- Interspersed are membrane proteins

Cell Structure

- Lipid bilayer acts as a ________ barrier
- Lipid-soluble compounds are able to pass directly through the membrane by becoming dissolved in the lipid bilayer
- Non-lipid-soluble substances (water) may be able to pass through the membrane because of ________________
- Also find channel proteins, pore proteins, and cholesterol
Movement Across Membranes

- Drugs that pass through biologic membranes usually do so via:
  - Passive diffusion
  - Active transport
  - Facilitated diffusion

Passive Diffusion

- Drugs will pass through a membrane by way of diffusion with two criteria:
  1) __________ __________ exists
  2) Membrane is permeable to the diffusing substance
- Passive lipid diffusion is __________
  - Drug with high degree of lipid solubility can gain access to many tissues

Active Transport

- Involve using membrane proteins to transport substances across cell membrane
  - Protein carrier exhibits a degree of _________ for certain substances
  - Some compounds that resemble one another will be transported by the same carriers
  - Some energy (ATP) must be used to fuel the carrier system
  - May be able to carry substances against a concentration gradient (“_________”)
Facilitated Diffusion

- Similar features of both active transport and passive diffusion
  - Protein carrier is present in facilitated diffusion but _________ is expended
  - Inability to transport substances “_________”

Blood-Brain Barrier

- Sometimes...
  - Instead of diffusing across membranes, groups of cells join together to form a barrier that separates one body compartment from another
  - Cells form “_________” with each other and do not allow any appreciable space to exist between adjacent cells
  - Primary way drug diffusing is by diffusing first into and then out of the other side of the cells (No channel protein or pore protein)

Blood-Brain Barrier

- Capillary endothelium of the brain
  - Tight junctions
  - Lipid-soluble drugs are able to cross the BBB by
    - Some other substances (glucose) pass the BBB by facilitated diffusion
- Peripheral capillaries
  - Large gaps between adjacent cells
  - Large substances can diffuse across the barrier between the cells
Distribution

The extent that a drug distributes into a compartment depends on:

1) Tissue Permeability
   - A highly lipid-soluble drug can potentially reach all compartments
   - A large non-lipid-soluble compound will remain primarily in the compartment or tissue to which it is administered

2) ____________

3) Binding to plasma proteins
   - Certain drugs have a higher affinity to proteins such as albumin
   - The unbound or “free” drug is able to reach the target tissue and exert an effect

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Metabolism

- Also known as _______________
  - What is the primary site for this?
- Substrates & Metabolites
  - Drug reacting with the metabolizing enzyme is called the parent drug or _______________
  - Products of the reactions are called
  - Drug metabolism usually makes the drug inactive and more water soluble
  - See figure 2-12
Metabolism

- Occasionally…
  - Metabolite has a higher level of activity than the original compound (e.g., codeine)
  - If drug administered is in an inactive form, it is referred to as a “_________

- Biotransformation…
  - Creates a more polar compound
  - Polar compound is more water soluble and more easily transported to the kidneys

Metabolism

- Enzymes
  - Primary enzyme used to metabolize drugs are ____________ enzyme (CYP or P450)
  - There are about 50 CYPs found in man (to date)

- Enzyme induction
  - Prolonged use of certain drugs “induces” (increases) the body to be able to destroy drug more rapidly
  - Usually because more enzymes are being produced or less are being degraded

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**Excretion**

- Primary site for excretion is the kidneys
  - Only drugs that are relatively polar will be excreted in significant amounts
  - Nonpolar compounds are relatively ______ and can easily be passively diffused out of the nephron
- pH factors
  - When urine is more acidic, drugs that are_____ will be more highly ionized and be excreted faster (and vice versa)
  - Urinary pH can fluctuate between 5-8
    - Aspirin example: Excretion increased several fold if urine pH is 8 compared with pH of 6

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**Excretion**

- Other sites for excretion
  - Lungs for gaseous anesthetics
  - Liver and gallbladder via bile
    - most of the secreted bile is reabsorbed though
  - Sweat, saliva, and breast milk

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**Half-Life**

- Definition:
  - The amount of time required for _____ of the drug remaining in the body to be eliminated
  - E.g., Acetaminophen
    - Half-life \( t^{1/2} = 2 \) hours
    - What % of the drug is in your system?
- Drugs with a longer \( t^{1/2} \) have a longer duration of action
  - Naproxen vs. Ibuprofen
    - \( t^{1/2} = 14 \) hours vs. \( t^{1/2} = 2 \) hours
Variations in Drug Response & Metabolism

Factors responsible for variations include:

1. _____ factors – may result in abnormal or absent drug-metabolizing enzymes
2. _____ – diseases that cause altered blood flow or tissue function
3. Drug interaction – two compounds may act synergistically (barbituates and alcohol)
4. Age – older/young patients are more sensitive to most drugs

Variations in Drug Response & Metabolism

Factors responsible for variations include:

5. Diet – fermented cheese and wine should not be ingested with MAO inhibitors (increases catecholamines = hypertensive crisis)
6. _____ – hormone influence
7. Other factors
   1. Smoking / Alcohol consumption
   2. Obesity
   3. Spinal cord injuries – decreased ability of absorption in GI tract
   4. Burn injuries – increased GI absorption, increased bioavailability