Pharmacokinetics & Pharmacodynamics

Reed Halterman, DNP, CRNA
Associate Professor
Assistant Program Director
Augusta University

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Objectives

- Participants will understand the idea and examples of pharmacokinetics.
- Participants will understand the idea and examples of pharmacodynamics.
- Participants will be able to apply the concepts of pKa, elimination, and others.

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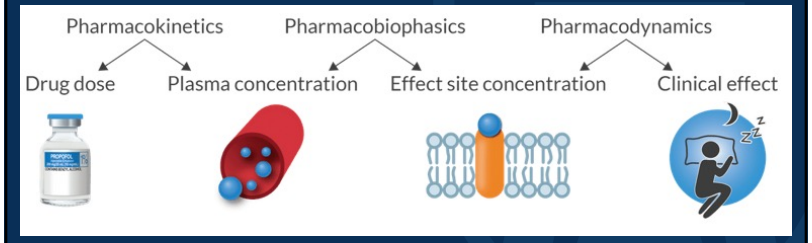

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Pharmacokinetics

What the body does to the drug

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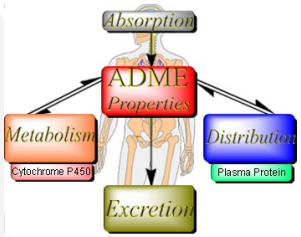
Pharmacokinetics



- Absorption
- Distribution
- Metabolism
- Elimination

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Absorption

- Routes of Administration
  - Enteral
  - Parenteral
  - Other

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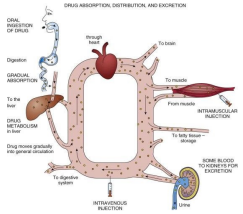
Routes of Administration

- Goal – transport drug to site of action
- Considerations
  - Drug's
    - Solubility
    - Charge
    - Molecule size
    - Protein binding
  - Physiologic conditions
  - Blood flow



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Oral Route

- Disadvantages
  - GI upset
  - Drug breakdown by gut
  - Absorption irregularities
  - First Pass Effect
  - Hard to get patients to swallow pills when asleep

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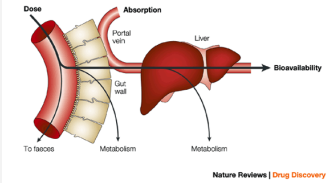
First Pass Effect of the Liver



- Venous blood from the GI tract drains into the liver via the portal system
- Often requires increased dose for P.O. meds

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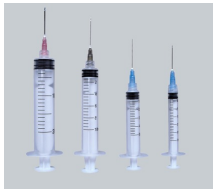
Parenteral Route

- Ensures more reliable absorption
- Doesn't require pt participation
- Faster & more predictable
- Can give GI irritating drugs
- Invasive
- IM/SQ absorption can be unpredictable



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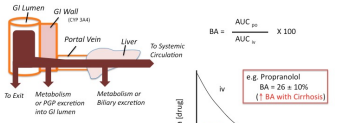
Distribution

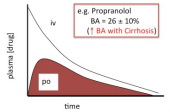
- Bioavailability - the fraction of drug that reaches the circulation
- Distribution primarily determined by
  - Perfusion
  - Concentration gradients
  - Ability of drug to cross membranes

Bioavailability

- the fraction absorbed into the systemic circulation is the drug's bioavailability



$$BA = \frac{AUC_{po}}{AUC_{iv}} \times 100$$



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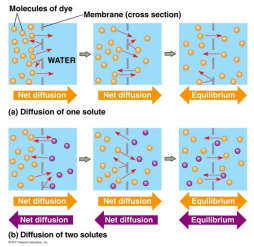
Absorption Into The Body

- Drugs must cross membranes to enter the cells they target
- Transportation across membranes can be from
  - Diffusion
  - Active transport by carrier proteins



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Factors Affecting Diffusion

Diffusion is the movement of particles via random motion from an area of concentration to an area of lower concentration

Fick's Law:

$$DiffusionRate = \frac{(\Delta Conc)(MembraneArea)(Solubility)}{MembraneThickness\sqrt{MolecularWeight}}$$

Fick's Law applies only to uncharged particles

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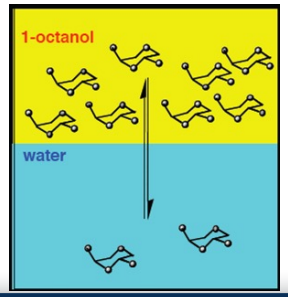
Measures Of Solubility

- More lipid soluble a drug the faster it will be absorbed
  - Partition coefficients reflect the relative solubility of a drug between two substances
    - Oil-to-water
    - Blood-to-gas
    - Tissue-to-blood



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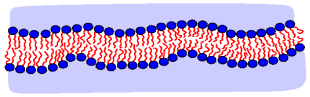
Movement Across Membranes

- Lipid membranes create barriers separating compartments
- Diffusion across lipid membranes is dependent upon the state of charge on the drug molecule
  - Ionized molecules cross slower
  - Unionized molecules will cross faster



How do we know what state the drug will be in????

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Henderson-Hasselbalch Equation

Weak Acid

$HA + H_2O \Leftrightarrow A^- + H_3O^+$

Weak Base

$HB^+ + H_2O \Leftrightarrow B + H_3O^+$

$HA \Leftrightarrow A^- + H^+$

$HB^+ \Leftrightarrow B + H^+$

- Most drugs are weak acids or weak bases
- In solution these compounds disassociate to some extent
- Weak acids dissociate into charged particles and weak bases into uncharged particles
- Remember uncharged particles can cross lipid membranes faster

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Henderson-Hasselbalch Equation

$$pH = pK_a + \log\frac{[nonprotonated]}{[protonated]}$$

$HB^+ \Leftrightarrow B + H^+$ $\qquad$ $HA \Leftrightarrow A^- + H^+$

(Protonated is bound to hydrogen)

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Henderson-Hasselbalch Equation

- pKa is the hydrogen ion concentration (pH) at which 50% of the drug is ionized and 50% is unionized
- When pH equals the pKa
  - 50% drug is ionized
  - 50% drug is unionized
- Use pKa & pH to determine if most of the drug is ionized or unionized

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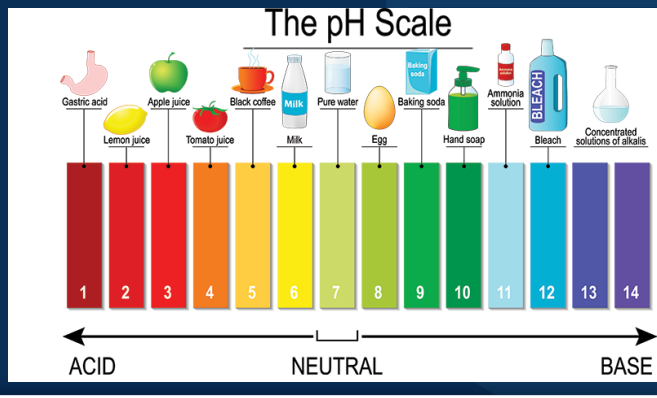

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Henderson-Hasselbalch Equation

- Examples
  - Weak acid with a pKa of 8.1 in a solution with a pH of 10.0
  - Weak base (lidocaine) with a pKa of 7.9 in a solution with a pH of 4.0
- Will the drug be mostly ionized or unionized?

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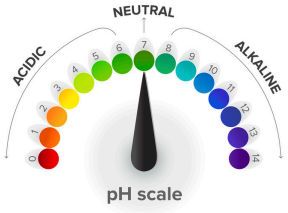
"Like Dissolves Like"

- Acid + Acid = non-ionized
- Base + Base = non-ionized



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Drug Preparations

- Most of the drugs that we give are weak acids and bases
  - Weak acid paired with positive ion
    - Sodium
    - Calcium
    - Magnesium
    - Example: Sodium thiopental
  - Weak base paired with negative ion
    - Chloride
    - Sulfate
    - Example: Lidocaine hydrochloride

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Drugs We Use

- Weak bases
  - LAs
    - Lidocaine **hydrochloride**
  - Ketamine **hydrochloride**
  - Opioids
    - Morphine **sulfate**
    - Fentanyl **citrate**
  - Benzos
    - Midazolam **hydrochloride**
- Weak acid
  - Barb
    - **Sodium** thiopental
  - Propofol
    - soybean oil, glycerol, egg lecithin, disodium edetate, and **sodium hydroxide**

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	Ionized	Unionized
Solubility	Water • Hydrophilic • Lipophobic	Lipid • Hydrophobic • Lipophilic
Pharmacologic Effect	Not active	Active
Hepatic Biotransformation	Less likely	More likely
Renal Elimination	More likely	Less likely
Diffuses Across Lipid Bilayer • **Blood-brain barrier** • **GI tract** • **Placenta**	 No No No	 Yes Yes Yes

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Example

- Propofol
  - pKa of 11

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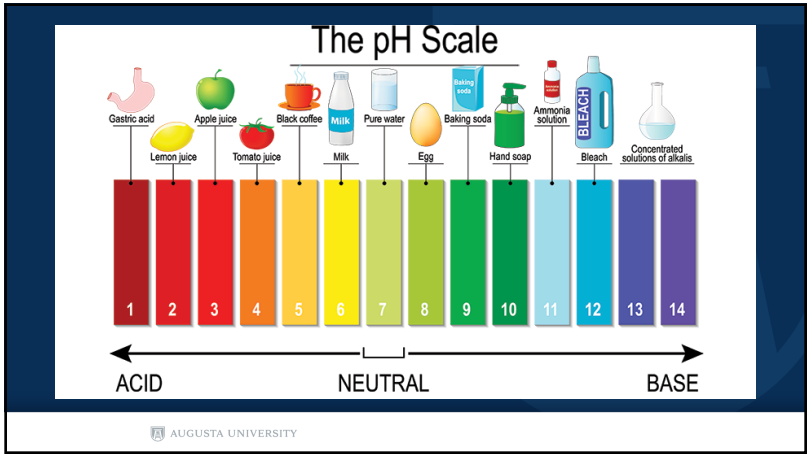

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Locals

- At pH 7.4
- Lidocaine (pKa **7.7**) is 35% non-ionized
- Bupivacaine (pKa **8.4**) is 12–13% non-ionized

- Which has faster onset?

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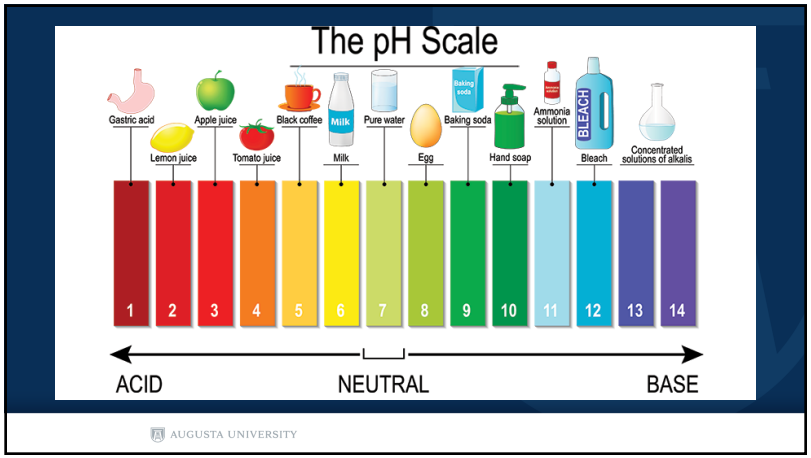

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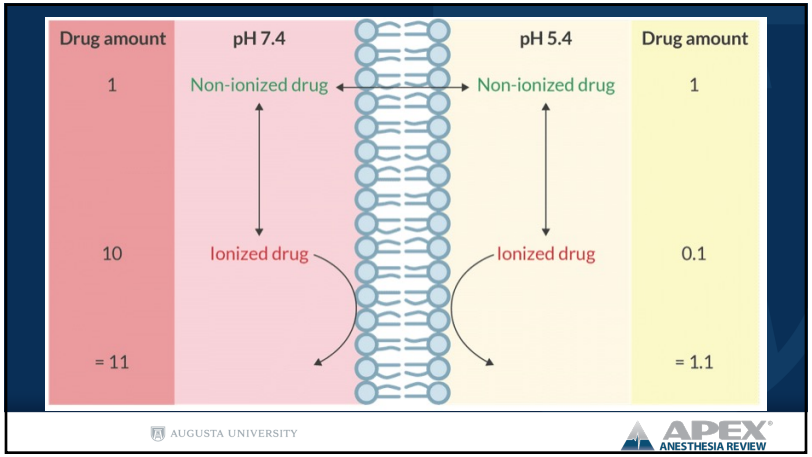

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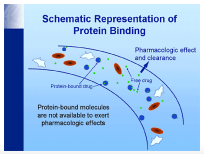
Protein Binding

- Most drugs bind to some degree to protein
- Protein molecules are too large to cross membranes
  - Bound drug stay in circulation
  - Unbound drug is pharmacologically active
- Binding is influenced by
  - Chemical nature of the drug
  - Conc. of plasma protein & drug
  - Competition from other drugs
  - Kidney & liver failure



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	Key Facts	Cp Increased By:	Cp Decreased By:
Albumin	Most plentiful plasma protein Primary determinant of plasma oncotic pressure T1/2 = 3 weeks Carries a negative charge Primarily binds with acidic drugs Also binds with neutral and basic drugs	n/a	Liver disease Renal disease Old age Malnutrition Pregnancy
α1-Acid Glycoprotein	Binds with basic drugs	Surgical stress Myocardial infarction Chronic pain Rheumatoid arthritis Advanced age	Neonates Pregnancy
Beta-globulin	Binds with basic drugs	n/a	n/a

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	Before Displacement	After Displacement	% Increase of Unbound Fraction
Drug 1			
% Bound	98	96	
% Unbound	2	4	100% increase
Drug 2			
% Bound	50	48	
% Unbound	50	52	4% increase

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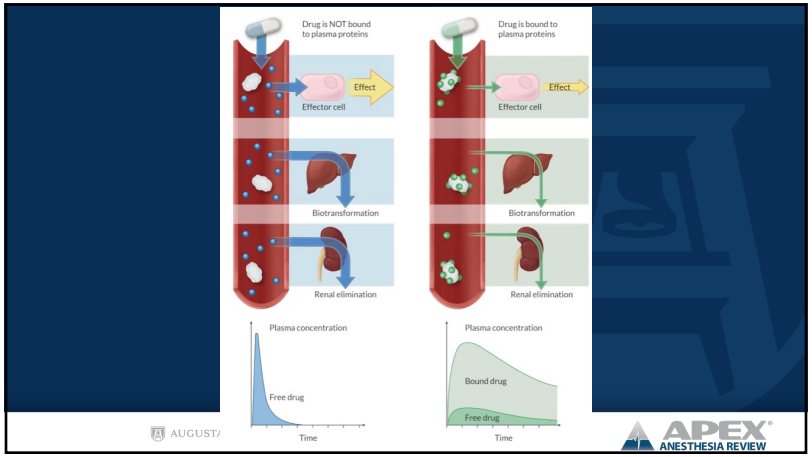

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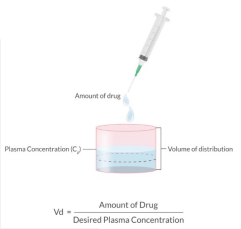
Volume of Distribution (Vd)



- Relationship between administered dose and plasma concentration that results
- Assumes
  - Drug distribution is spontaneous
  - Dug does not transform or get eliminated

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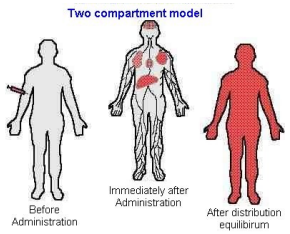
Compartment Models

- Models are used to explain and predict the behavior of drugs in the body



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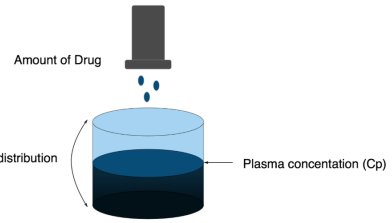
One Compartment Model

- Simplest
- Compartment made up of entire body
- Assumes
  - Instant distribution
  - Uniform distribution
  - Uniform elimination
- Least representative of real life



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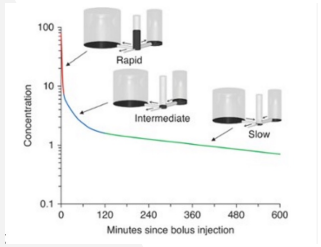
Two (Three) Compartment Model



- Plasma Compartment
- Vessel Rich Group
  - Heart, Lungs, Liver, Kidney, Brain
  - 10% of Body Mass
  - 75% of Cardiac Output
- Peripheral Compartment
  - Muscle, Fat, Vessel Poor Group
  - 90% of Body Mass
  - 25% of Cardiac Output

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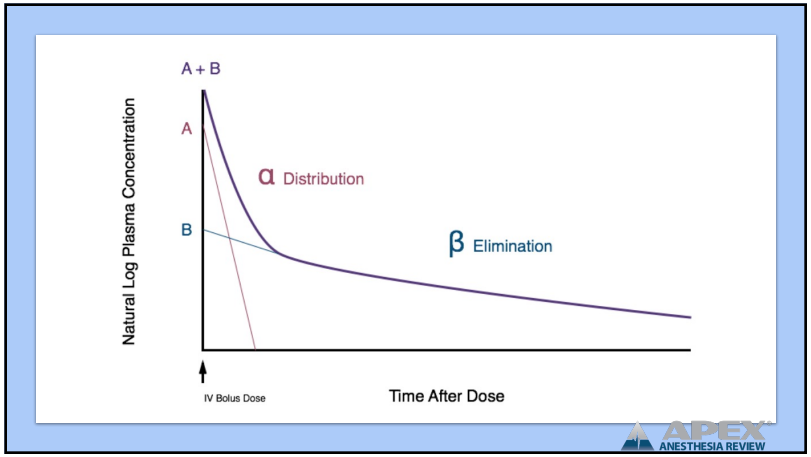

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Metabolism/Biotransformation

- Elimination of most drugs occurs via the kidney
  - Renal elimination requires drugs to be water soluble (polar or hydrophilic)
- Metabolism
  - Lipid soluble → water soluble
- Metabolism is not elimination
- Exception
  - Prodrugs-activated by biotransformation

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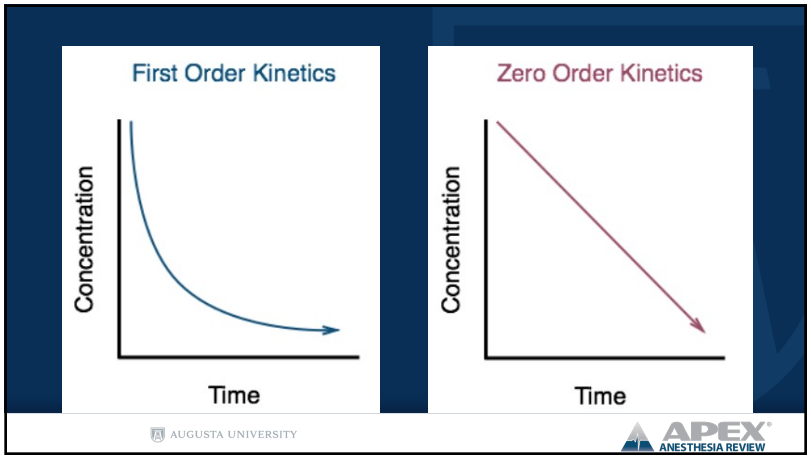

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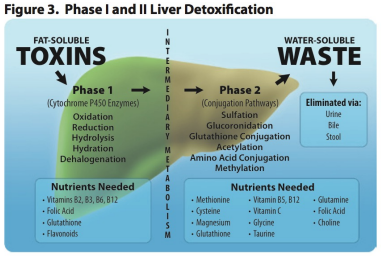
Metabolism Pathways

- Phase I
- Phase II

Figure 3. Phase I and II Liver Detoxification



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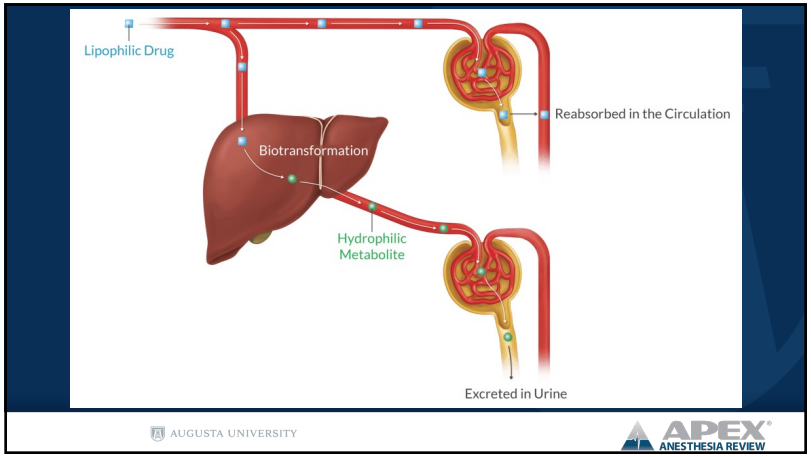

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Phase I Pathways

- Modification
  - Oxidation
  - Reduction
  - Hydrolysis
- Primary purpose is to increase drug's polarity
  - Primary site of action is the hepatic smooth endoplasmic reticulum
  - Reaction catalyzed by Cytochrome P450 enzyme family

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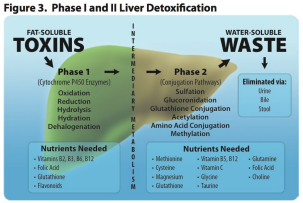
Phase II Pathway

- Conjugation
  - Takes polar product and bonds to macromolecules for easy filtration by the kidney

Figure 3. Phase I and II Liver Detoxification



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Plasma Metabolism

Pseudocholinesterase (Enzyme)	Nonspecific Esterases (Enzyme)	Alkaline Phosphatase (Enzyme)	Hofmann Elimination (pH & Temp)
Succinylcholine Mivacurium Ester local Anesthetics • Tetracaine • Procaine • Chloroprocaine • Cocaine (+ hepatic)	Remifentanil Remimazolam Esmolol (RBC esterases) Etomidate (+ hepatic) Atracurium (+ Hofmann) Clevidipine	Fospropofol *It's a prodrug that is converted to propofol (active metabolite) by alkaline phosphatase	Cisatracurium Atracurium (+ Nonspecific esterases)

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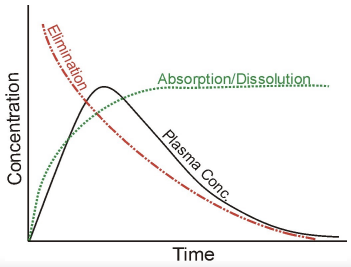
Elimination

- Clearance
  - Plasma volume cleared of a drug per unit time
- Kidney primary site of elimination
- The summation of organ and non-organ elimination



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CL Is Directly Proportional To:	CL Is Inversely Proportional To:
Blood flow to clearing organ Extraction ratio Drug dose	Half-life Drug concentration in the central compartment

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Elimination Half-Time/Half Life

- Half-Time
  - The time for the plasma conc. of a drug to decrease to 50% during the elimination (beta) phase
- Half-Life
  - The time for the body conc. of a drug to decrease 50% during the elimination (beta) phase

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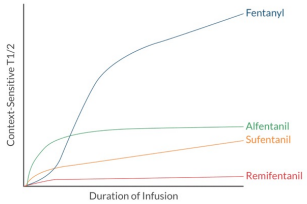
Context-Sensitive Half-time

- The time needed for drug in plasma to drop by 50% after stopping a continuous infusion
- Context refers to the duration of the infusion
- Influenced by
  - Vd
  - Lipid solubility
  - Clearance mechanisms



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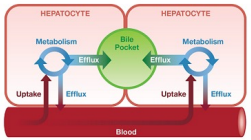
Hepatic Clearance

- Perfusion Dependent
  - High hepatic extraction ratio
  - Flow dependent, not enzyme dependent
- Capacity Dependent
  - Low hepatic extraction ratio
  - Flow independent, enzyme dependent
- Elimination via bile



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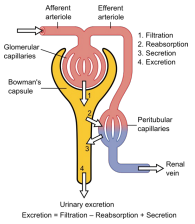
Renal Clearance

- Primary site of clearance
- Clearance is correlated with creatinine concentration - indicator of kidney function



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Pharmacodynamics

What the drug does to the body

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Drug Responses

- Tolerance
  - Gradual onset
  - Variety of causes
- Tachyphylaxis
  - Rapid onset
- Additive effect
- Synergistic effect

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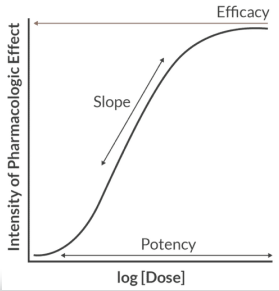
Dose-Response Curve

- Graphically represents the relationship between dose of a drug and the pharmacological response
- Dose is usually displayed on a logarithmic scale
- Resulting line is usually a sigmoidal plot



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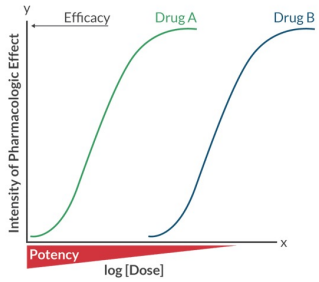
Potency



- Graphically depicted by the location of the dose-response curve along the dose axis
- Impacted by pharmacokinetic factors and receptor affinity

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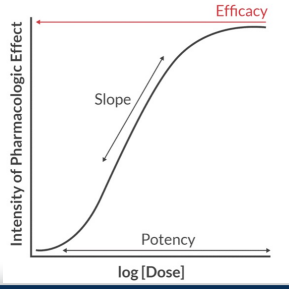
Efficacy

- Measure of ability for a drug to cause an effect
- The heigh represents efficacy
  - Higher plateau → greater effect
  - Once plateau is reached, no further effect
  - Additional drug increases toxicity risk



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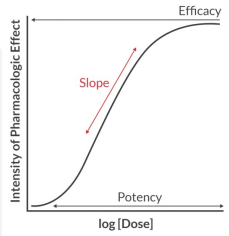
Slope



- Shows how many receptors need to be occupied to elicit effect
  - Steep → most must be occupied
  - NMB and volatile anesthetics have steep slopes

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Receptor Theory

- Most drugs create their effect by interacting with a receptor on the cell
- Receptors have evolved to bind with endogenous substances (ligands) in the cell
- The effect of most drugs occur because the drug mimics or inhibits the interaction of the endogenous ligand and the receptor

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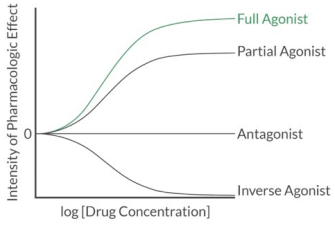
Full Agonist

- Binds to a receptor and turns on cellular response
  - Mimics endogenous ligand
- Instructs receptor to produce its maximal response
- Examples
  - Norepinephrine, dopamine, propofol, alfentanil



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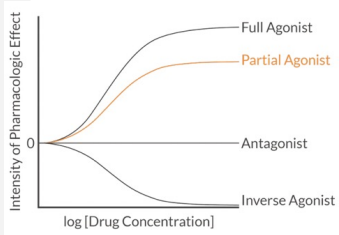
Partial Agonist



- Binds to receptor but only partial cellular response
- Also can be called agonist-antagonist
  - Blocks agonist by competing for site
- Examples
  - Nalbuphine (Nubain)

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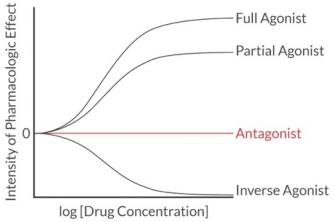
Antagonist

- Binds to receptor and prevents agonist from binding
  - Does not tell the cell to do anything
  - Has no efficacy
- Competitive antagonist
  - Rocuronium, atropine
- Noncompetitive antagonist
  - ASA



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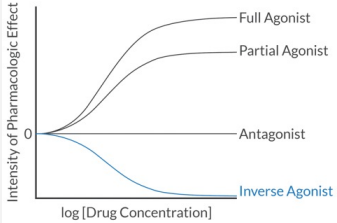
Inverse Agonist



- Binds to receptor and causes opposite effect of an agonist
- Negative efficacy
- Drugs previously thought to be antagonists are really inverse agonists
- Example
  - Propanolol

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ED50, LD50, Therapeutic Index

$$TI = \frac{LD_{50}}{ED_{50}}$$

- ED_{50} – median effective dose
- LD_{50} – median lethal dose
- Therapeutic Index – the measure of the margin of safety associated with the use of a drug
- TI – Bigger is better
- TI=1 = BAD

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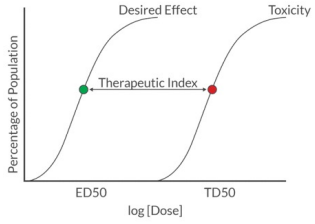
Drug Dosing

- Therapeutic Window
  - The range of drug concentration at the site of action between which the therapeutic effect begins and adverse effects starts



$$\text{Therapeutic Index} = \frac{\text{Toxic Dose 50}}{\text{Effective Dose 50}}$$

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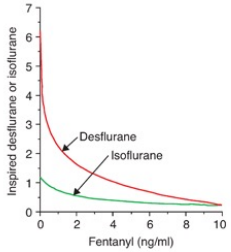
Drug Interactions

- Opioids reduce the minimum alveolar concentration (MAC) of inhaled anesthetics
- Modest opioid use greatly reduces inhalational anesthetic requirement to prevent movement
- Even with huge doses of opioids, some hypnotic component must be added to the anesthetic to prevent movement



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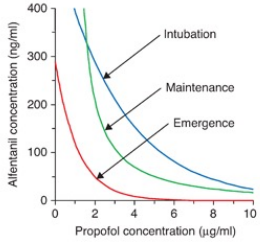
Drug Interactions

- Hypnotics and opioids work synergistically as well
- Modest amounts of alfentanil greatly decreases the amount of propofol



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Summary

- Pharmacokinetics
  - What the body does to the drug
    - Absorption
    - Distribution
    - Metabolism
    - Elimination
- Pharmacodynamics
  - What the drug does to the body
    - Potency
    - Efficacy
    - Dose response curve
    - Receptor/ligands

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