

Pharmacokinetics & Pharmacodynamics

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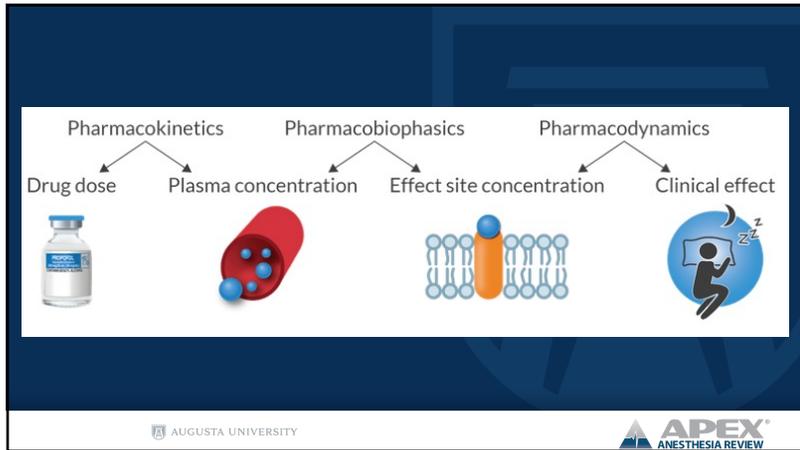
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Objectives

-  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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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

Nature Reviews | Drug Discovery

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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

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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:

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

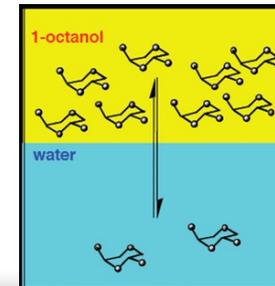
Fick's Law applies only to uncharged particles

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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

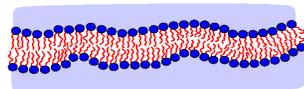


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Movement Across Membranes

- 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



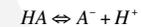
How do we know what state the drug will be in????

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Henderson-Hasselbalch Equation

Weak Acid
 $HA + H_2O \rightleftharpoons A^- + H_3O^+$
 Weak Base
 $HB^+ + H_2O \rightleftharpoons B + H_3O^+$



- Most drugs are weak acids or weak bases
- In solution these compounds dissociate 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

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

$HB^+ \rightleftharpoons B + H^+$

(Protonated is bound to hydrogen)

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

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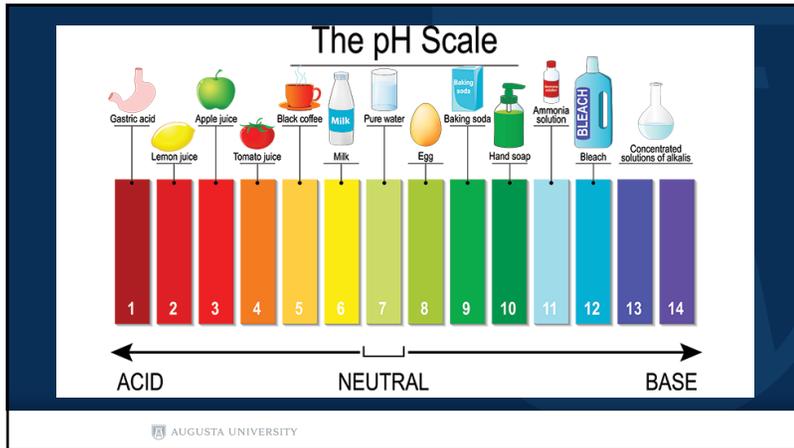
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Henderson-Hasselbalch Equation

- 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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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

pH scale

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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 <ul style="list-style-type: none"> • Hydrophilic • Lipophobic 	Lipid <ul style="list-style-type: none"> • 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	No	Yes
• GI tract	No	Yes
• Placenta	No	Yes

APEX ANESTHESIA REVIEW

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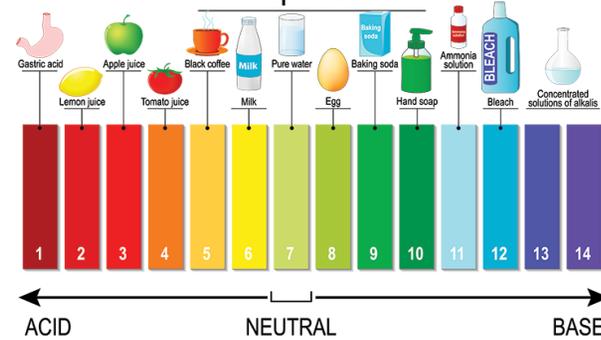
Example

- Propofol
 - pKa of 11

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The pH Scale



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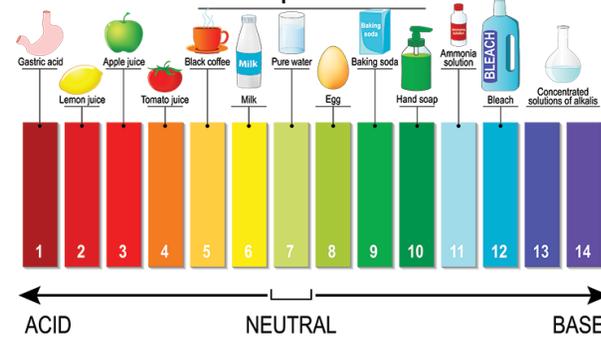
Locals

- 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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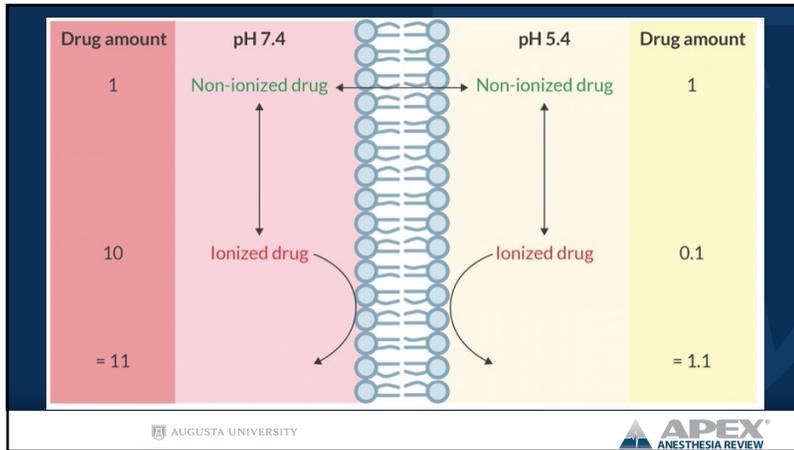
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The pH Scale



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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

The schematic shows drug molecules (red spheres) binding to protein molecules (blue structures). It labels 'Pharmacologic effect and clearance' for unbound drugs and 'Protein-bound drug' for bound drugs. A note states: 'Protein-bound molecules are not available to exert pharmacologic effects.'

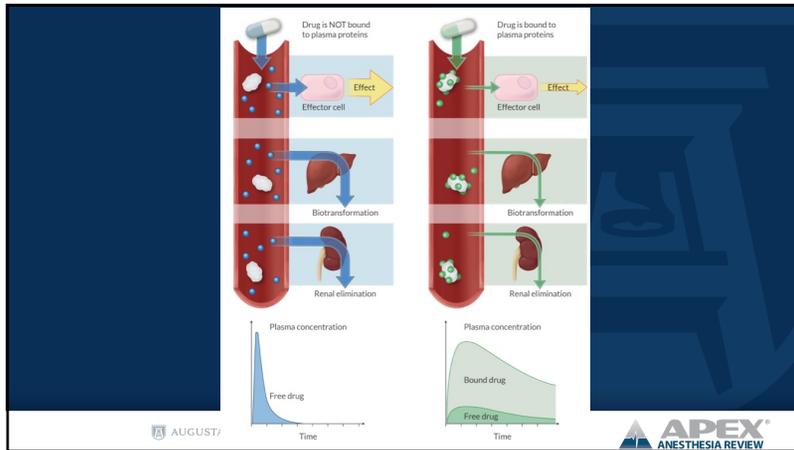
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	Key Facts	Cp Increased By:	Cp Decreased By:
Albumin	Most plentiful plasma protein Primary determinant of plasma oncotic pressure T1/2 = 3 weeks Carries a negative charge Primarily binds with acidic drugs Also binds with neutral and basic drugs	n/a	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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Volume of Distribution (Vd)

Amount of drug

Plasma Concentration (C_p)

Volume of distribution

$V_d = \frac{\text{Amount of Drug}}{\text{Desired Plasma Concentration}}$

- Relationship between administered dose and plasma concentration that results
- Assumes
 - Drug distribution is spontaneous
 - Drug 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

Two compartment model

Before Administration

Immediately after Administration

After distribution equilibrium

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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

Amount of Drug

Volume of distribution

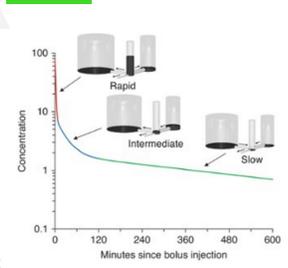
Plasma concentration (C_p)

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Two (Three) Compartment Model

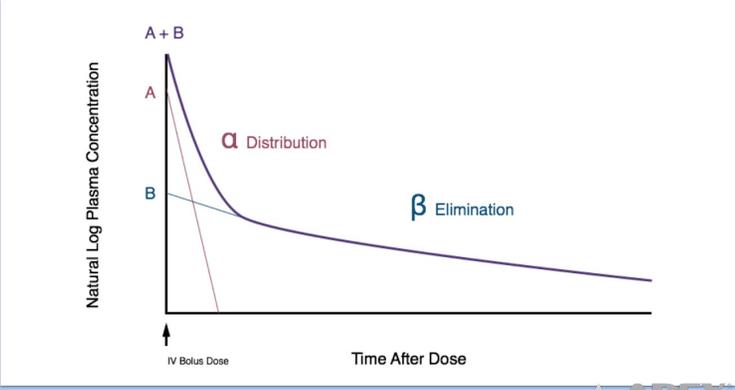


The graph shows concentration on a logarithmic y-axis (0.1 to 100) and minutes since bolus injection on the x-axis (0 to 600). Three phases are labeled: Rapid (0-120 min), Intermediate (120-360 min), and Slow (360-600 min). Each phase is associated with a schematic of drug distribution in the body.

- 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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The graph plots Natural Log Plasma Concentration against Time After Dose. It shows a biphasic decay curve. The initial steep decline is labeled α Distribution, and the terminal linear decline is labeled β Elimination. The peak concentration is labeled A + B, and the concentration at the end of the distribution phase is labeled B. An arrow indicates the IV Bolus Dose at time zero.

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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 \rightarrow water soluble
- Metabolism is not elimination
- Exception
 - Prodrugs-activated by biotransformation

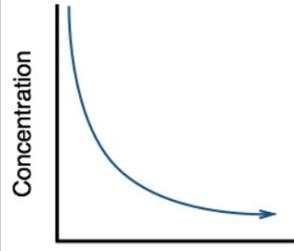


A semi-circular gauge with a needle pointing towards the right, labeled METABOLISM.

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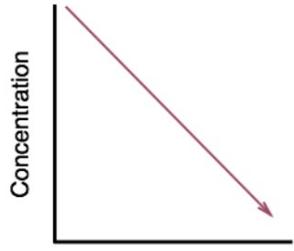
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First Order Kinetics



Concentration vs. Time

Zero Order Kinetics



Concentration vs. Time

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Metabolism Pathways

- Phase I
- Phase II

Figure 3. Phase I and II Liver Detoxification

Phase 1 (Cytochrome P450 Enzymes)	Phase 2 (Conjugation Pathways)
<ul style="list-style-type: none"> Oxidation Reduction Hydrolysis Hydration Dehalogenation 	<ul style="list-style-type: none"> Sulfation Glucuronidation Glutathione Conjugation Acetylation Amino Acid Conjugation Methylation
Nutrients Needed <ul style="list-style-type: none"> Vitamins B2, B3, B6, B12 Folic Acid Glutathione Flavonoids 	Nutrients Needed <ul style="list-style-type: none"> Methionine Cysteine Magnesium Glutathione Vitamin B5, B12 Vitamin C Glycine Taurine Glutamine Folic Acid Choline

Eliminated via: Urine, Bile, Stool

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Lipophilic Drug

Biotransformation

Hydrophilic Metabolite

Reabsorbed in the Circulation

Excreted in Urine

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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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Eliminated via: Urine, Bile, Stool

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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)	Remifentanyl 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

The graph plots Context-Sensitive T_{1/2} on the y-axis against Duration of Infusion on the x-axis. Fentanyl (blue line) shows a steep, exponential increase in T_{1/2} as infusion duration increases. Alfentanil (green line) shows a moderate, linear increase. Sufentanil (orange line) shows a slight increase. Remifentanil (red line) shows a constant, low T_{1/2} that is independent of infusion duration.

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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

The diagram illustrates two hepatocytes. The left hepatocyte shows 'Metabolism' and 'Efflux' processes. The right hepatocyte shows 'Metabolism' and 'Efflux' processes. A central 'Bile Pocket' is shown between the two cells, with 'Uptake' and 'Efflux' arrows indicating the movement of substances between the hepatocytes and the bile. The entire system is connected to 'Blood' at the bottom.

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Renal Clearance

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

The diagram shows a nephron with the following components and processes:

- Afferent arteriole**: Enters the glomerulus.
- Efferent arteriole**: Exits the glomerulus.
- Glomerular capillaries**: Site of **1. Filtration**.
- Bowman's capsule**: Surrounds the glomerulus.
- Peritubular capillaries**: Site of **2. Reabsorption** and **3. Secretion**.
- Renal vein**: Carries blood away from the kidney.
- Urinary excretion**: **Excretion = Filtration - Reabsorption + Secretion**.

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Pharmacodynamics

What the drug does to the body

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Drug Responses

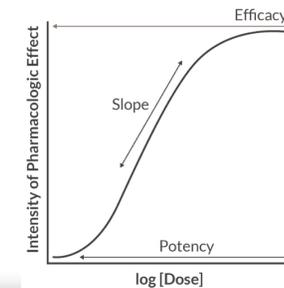
- Tolerance
 - Gradual onset
 - Variety of causes
- Tachyphylaxis
 - Rapid onset
- Additive effect
- Synergistic effect

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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

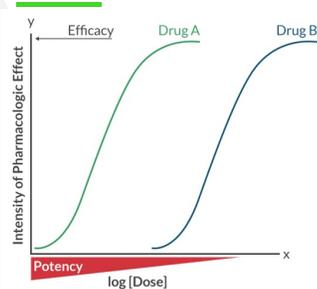


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Potency



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

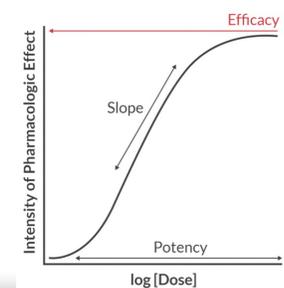
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Efficacy

- Measure of ability for a drug to cause an effect
- The height 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

The graph plots the intensity of pharmacologic effect against the logarithm of drug concentration. The y-axis is labeled 'Intensity of Pharmacologic Effect' and has a zero line. The x-axis is labeled 'log [Drug Concentration]'. Four curves are shown: a red curve for 'Antagonist' that remains at zero; a black curve for 'Full Agonist' that rises to a high plateau; a grey curve for 'Partial Agonist' that rises to a lower plateau; and a blue curve for 'Inverse Agonist' that falls below the zero line.

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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
 - Propranolol

The graph plots the intensity of pharmacologic effect against the logarithm of drug concentration. The y-axis is labeled 'Intensity of Pharmacologic Effect' and has a zero line. The x-axis is labeled 'log [Drug Concentration]'. Four curves are shown: a black curve for 'Full Agonist' that rises to a high plateau; a grey curve for 'Partial Agonist' that rises to a lower plateau; a red curve for 'Antagonist' that remains at zero; and a blue curve for 'Inverse Agonist' that falls below the zero line.

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ED50, LD50, Therapeutic Index

- ED₅₀ – median effective dose
- LD₅₀ – 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

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

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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

The graph plots the percentage of the population against the logarithm of dose. The y-axis is labeled 'Percentage of Population'. The x-axis is labeled 'log [Dose]'. Two sigmoidal curves are shown: 'Desired Effect' on the left and 'Toxicity' on the right. A horizontal line labeled 'Therapeutic Index' spans the distance between the ED50 (median effective dose) on the left curve and the TD50 (median toxic dose) on the right curve.

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

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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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