

First-Pass Effect

- I. Drug metabolized by liver, GI mucosal enzymes, gut bacteria, luminal enzymes prior to reaching systemic circulation

Bioavailability

- I. Amount of drug administered that is available to the body
- II. IV = 100%

Routes of Administration

Oral

- I. Common, inexpensive, easy
- II. Must pass through stomach
- III. Subject to First-Pass Effect
- IV. Extended-Release Formulation
- V. Enteric Coating

Sublingual or Buccal

- I. Dissolves in mouth and absorbed by capillaries into circulation
- II. Bypasses first-pass metabolism
- III. Useful in nausea/vomiting

Parenteral (IV, IM, SQ)

- I. Increased control of quantity and timing of administration
- II. No exposure to enteral environment
- III. Avoid first-pass metabolism

Intravenous (IV)

- I. Bolus – Rapid administration
- II. Infusion – Constant administration

Intramuscular (IM)

- I. Absorbed by diffusion rapidly
- II. Depot formulations/effects prolong release
- III. Useful when IV access/oral admin not available

Subcutaneous (SQ)

- I. Absorbed by diffusion
- II. Allows ~constant and slow drug effects

Inhalation

- I. Drug inhaled and delivered to respiratory mucosa

II. Fast absorption

III. Delivery to site of action

Intrathecal or Intraventricular

- I. Direct delivery to CNS
- II. Bypasses blood-brain barrier

Topical

- I. Delivery to site of action
- II. Limited systemic effects

Transdermal

- I. Absorption through skin/dermis to systemic circulation
- II. Sustained drug levels

Rectal

- I. Bypasses first-pass metabolism
- II. Useful when oral route not available

Mechanisms of Absorption

Passive Diffusion

- I. Drug flows down concentration gradient

Facilitated Diffusion

- I. Drug flows through channels or pores down concentration gradient

Active Transport

- I. Selective, requires energy (ATP)
- II. May go against concentration gradient
- III. Mediated by transmembrane proteins
- IV. MDR1 (P-glycoprotein)
 - a. Efflux pump
 - b. Found in various organs/cancer cells/drug resistant organisms

Biochemical Factors of Absorption

- I. Absorption surface area
- II. Contact time with surface area
- III. Molecule size
- IV. Lipid solubility – lipids diffuse more readily across membranes
- V. pKa/pH: pH of environment will determine ionized: non-ionized ratio for a given substance.

Drug Distribution

I. Blood Flow

II. Capillary Permeability

- a. Basement membrane – level of coverage by endothelial cells determines permeability, gaps are called fenestrations
- b. Blood-brain barrier
 - i. No fenestrations
 - ii. Tight junctions – present in capillaries of the CNS

III. Protein Binding

- a. Drugs bound to albumin released as concentration in plasma decreases
- b. Increasing drug stores may lead to toxicity

IV. Lipophilia – lipophilic drugs diffuse across membranes readily

Volume of Distribution

$$I. V_d = \frac{\text{Amount of Drug in Body}}{\text{Amount of Drug in Plasma}}$$

- II. Drugs distribute to functional compartments over time

III. Functional Compartments

- a. Intravascular
- b. Interstitial
- c. Intracellular

IV. More compartments = $\uparrow V_d$

- V. Small, lipophilic drugs have large V_d and access intracellular space readily

VI. Large, hydrophilic, protein bound drugs more limited to intravascular space

VII. $\uparrow V_d$ correlates with longer half-life

Drug-Receptor Interactions

I. G-protein coupled receptors

- a. 7 transmembrane protein receptor coupled with G-protein
- b. Activation of receptor results in downstream effects based on G-protein type
 - i. $G_{\alpha_s} > \uparrow cAMP > \uparrow PKA$ (protein kinase A)
 - ii. $G_{\alpha_i} > \downarrow cAMP > \downarrow PKA$ (protein kinase A)
 - iii. $G_q \text{ \& } G_{11} > \uparrow PLC$ (phospholipase 3) $> IP_3$ ($\uparrow Ca^{2+}$ from SR) & PKC

II. Enzyme Linked Receptors (Tyrosine Kinase Receptors)

- a. Receptors dimerize or form multiunit complexes when activated by ligand, which results in activation of cytoplasmic enzymes

III. Ligand Activated Ion Channels: Activation changes conformation of channel, allowing ions to flow down gradient

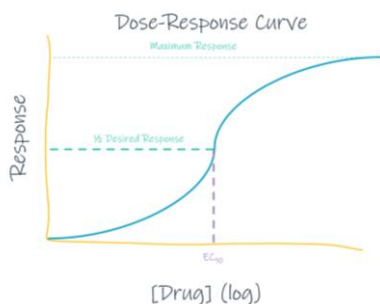
IV. Intracellular/Intranuclear Receptors

- a. Primarily activate transcription factors
- b. Lipid soluble drug/hormone passes through membrane and interacts with receptors, which release/activate bound proteins allowing for mobilization of effects (i.e., translocating to nucleus with other transcription factors to increase transcription of certain genes)

V. Antimetabolites: Drugs that are similar to naturally occurring compounds that insert into and disrupt metabolic function

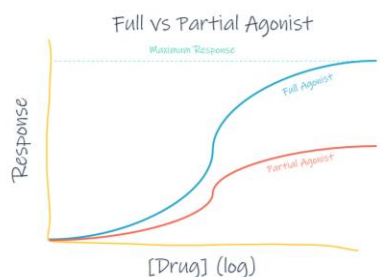
Dose-Response Relationship

- I. Physiologic response increases as drug dose increases until saturation of enzymes/receptors occurs:



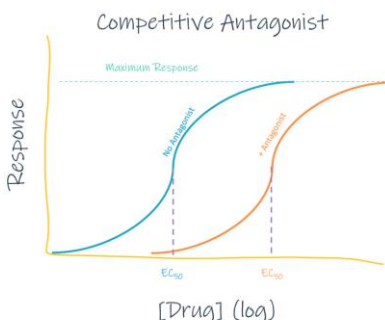
II. Full Agonist/Partial Agonist

- a. Full agonist: full response when engaged
- b. Partial agonist: partial response when engaged



III. Competitive Antagonist

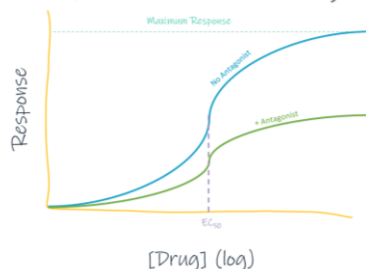
- a. Blocks receptor site: does not allow natural substances to stimulate/activate site:



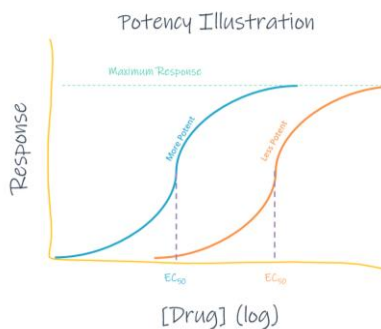
IV. Irreversible and Non-competitive antagonist

- a. Irreversible: binds covalently to site making it permanently unavailable
- b. Non-competitive: binds remotely from receptor site and changes conformation of receptor site making it unavailable
- c. Both types result in reduced maximum effect

Noncompetitive & Irreversible Antagonists



- I. Potency: ↑Potency, requires less drug for same effect



ED₅₀: median dose producing desired effect in 1/2 population

TD₅₀: median dose producing toxic effect in 1/2 population

Efficacy: Ability of drug to produce desired effect

Therapeutic Index: Ratio of ED₅₀ and TD₅₀, larger is better, indicates large window of dosing to produce desired effect without causing toxicity

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

Bioequivalence: Performs in same manner as the compared drug

Pharmaceutical Equivalence:

- I. Same active ingredient(s)
- II. Same dosage form
- III. Same route of administration
- IV. Same strength

Therapeutic Equivalence = Bioequivalence + Pharmaceutically Equivalence

Pharmacokinetics and Dosing

First-Order Kinetics

- I. Most drugs follow first-order kinetics
- II. Rate of metabolism is proportional to the concentration of drug:

$$v = \frac{V_{max} [Drug\ Concentration]}{K_m}$$

- III. Constant half-life (Constant proportion of drug eliminated over time)

Zero-Order Kinetics

- I. Drug Concentration >>>> K_m, results in equation:

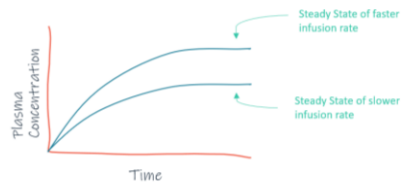
$$v = V_{max}$$

- II. Constant amount of drug eliminated over fixed period without correlation to concentration of the drug.

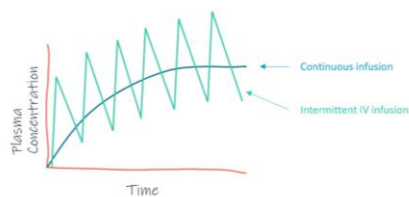
Dosing Regimens

- I. Drug metabolism begins immediately upon administration
- II. IV Infusion: drug is constantly administered, steady-state concentration depends on rate

of infusion (time to steady-state concentration does not vary)



III. Intermittent IV Infusion: Plasma concentration follows a saw-tooth pattern as drug is administered and eliminated



Loading Dose: An initial larger dose is used to decrease the time to reach steady-state, useful for long-acting medications

Dosing Adjustments: Use of plasma drug levels or surrogate laboratory values to make dosing adjustments specific to each patient

Drug Elimination

Metabolism

- I. Primarily performed in liver
- II. Allows lipophilic drugs to be eliminated renally

Phase I

- I. Adds a polar functional group
- II. Examples: Alcohol dehydrogenase, amine oxidation
- III. Cytochrome P450 system
 - a. Group of metabolic enzymes in liver and GI tract
 - b. Enzymes have various forms and specialize in metabolizing certain compounds
 - c. Polymorphisms -> variable patient responses to drugs
 - d. CYP450 can be induced & inhibited

Phase II

- I. Drugs requiring additional polarization
- II. Example: Glucuronidation

Renal Elimination

- I. Most drugs eliminated via kidneys
- II. Impaired renal function can lead to toxicity
- III. 2 Paths:
 - a. Path 1: Filter through Bowman's capsule
 - b. Path 2: Active excretion (weak acids/bases)
- IV. Reabsorption: Occurs in distal tubules
- V. Ion-trapping: Drugs become ionized after excretion & cannot passively be reabsorbed
 - a. Alkalinization/acidification of urine can be used therapeutically to assist in detoxifying certain compounds in overdose