Pharmacokinetics

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Pharmacokinetics

- The therapeutic effect of a drug is determined by the concentration of drug at the receptor site of action.
- Even though the concentration of drug that reaches the target receptor is dependent upon the dose of the drug, there are other factors that influence the delivery of the drug to the target site.
- These include:
  - absorption
  - distribution
  - metabolism
  - excretion.
Absorption

- Depends on patient compliance
- Depends on route of administration
- Small, non-ionized, lipid soluble drugs permeate plasma membranes most readily
  - The plasma membrane is impermeable to polar, water-soluble substances
# Routes of Administration

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Site of absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Mouth, GI tract</td>
</tr>
<tr>
<td>Sublingual</td>
<td>Under tongue</td>
</tr>
<tr>
<td>Buccal</td>
<td>Oral mucosa</td>
</tr>
<tr>
<td>Intra-ocular</td>
<td>Eyes</td>
</tr>
<tr>
<td>Topical</td>
<td>Skin</td>
</tr>
<tr>
<td>Rectal</td>
<td>Rectum</td>
</tr>
<tr>
<td>Vaginal</td>
<td>Vagina</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>Nasal passages or lungs</td>
</tr>
</tbody>
</table>
## Routes of Administration

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Site of absorption</th>
</tr>
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<tbody>
<tr>
<td>Intravenous</td>
<td>Directly into venous blood</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>Muscles</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Into blood from skin layers</td>
</tr>
<tr>
<td>Epidural</td>
<td>Epidural space</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>Directly into cerebro-spinal fluid</td>
</tr>
</tbody>
</table>
Factors affecting drug absorption

- Compliance
- Food
  - Enhance e.g. ketoconazole
  - Impair e.g. tetracyclines, penicillin V, etidronate
- Formulation
  - Enteric coated
  - Slow release
- Route of administration
  - IV = complete absorption (directly into blood stream)
  - Oral = partial absorption
- Lack of specific receptor needed for absorption
• Site of drug absorption
  • If drug is absorbed from stomach, could bypass absorption site e.g. E/C preparations, PEJ tubes

• Malabsorption syndromes  e.g. cystic fibrosis

• GI motility
  e.g. rapid GI transit – Crohn’s disease, pro-kinetic drugs

• Inactivation of drug in gut or liver
  e.g. insulin destroyed by proteolytic enzymes
  First pass effect

• Pre-existing medical conditions  e.g. Acute congestive heart failure

• Drug interactions
Bioavailability

• The fraction of the administered dose that reaches the systemic circulation of the patient

• Affected by:
  – Dosage form
  – Dissolution and absorption of drug
  – Route of administration
  – Stability of the drug in the GI tract (if oral route)
  – Extent of drug metabolism before reaching systemic circulation
  – Presence of food/drugs in GI tract
Bioavailability Factor (F)

- Estimates the EXTENT of absorption
- Does not consider the RATE of absorption

Amount of drug reaching systemic circulation = (F) x (dose)
Absorption

• I. Mechanisms for drug transport across membranes
  • A. Passive (simple) diffusion
    – 1. Rate of transfer of substances are directly proportional to the concentration gradient on both sides of the membrane
    – 2. Rapid for lipophilic, nonionic, small molecules
    – 3. No energy or carrier required
  • B. Aqueous channels
    – 1. Small hydrophilic drugs (<200 MW) diffuse along conc gradient by passing through pores (aqueous channels)
    – 2. No energy required
Absorption

• C. Specialized transport
  – 1. Facilitated diffusion – drugs bind to carrier noncovalently
    » No energy is required
  – 2. Active transport – identical to facilitated diffusion except that ATP (energy) powers drug transport against conc gradient

• D. Pinocytosis and phagocytosis
  – Engulfing of drug
  – Ex: Vaccines
Distribution

- Takes place after the drug has been absorbed into the blood stream
- Distribution of drugs through various body compartments (to various tissues) depends on:
  - Size of the organs (tissues)
  - Blood flow through tissues
  - Solubility of the drug in the tissues
  - Binding of the drug to macromolecules in blood or tissues
Distribution

- The following factors influence drug distribution:
  
  • 1. **Protein binding**
    
    - Two factors determine degree of plasma protein binding:
      
      » 1. Affinity of drug for plasma protein
      » 2. # of binding sites available
    
    - Weak acid drugs bind to albumin (phenytoin, salicylates, and disopyramide are extensively bound)
    
    - Weak basic drugs bind to serum globulins → α-1 acid glycoprotein (lidocaine, propranolol)
Plasma Protein Binding

- Many drugs bound to circulating plasma proteins such as albumin
- Only free drug can act at receptor site
Effect of a change in plasma protein binding

Drug with low plasma protein binding

90mg unbound

10mg bound
Effect of a change in plasma protein binding

90mg + 5mg (unbound)
10mg - 5mg (bound)

If the plasma protein level drops:
Change in the unbound fraction is negligible
Effect of a change in plasma protein binding

Drug with high plasma protein binding

10mg unbound

90mg bound
Effect of a change in plasma protein binding

If plasma protein level drops:

10mg + 5mg unbound

90mg – 5mg bound

Change in the unbound fraction is significant
Highly Protein Bound Drugs

• > 95% bound
  – Thyroxine
  – Warfarin
  – Diazepam
  – Furosemide
  – Heparin

• > 90% but < 95% bound
  – Phenytoin
  – Propranolol
  – Sodium Valproate

Changes in plasma protein binding are significant for drugs which are greater than 90% bound to plasma proteins
Factors which can increase the fraction of unbound drug:

- Renal impairment due to rise in blood urea
- Low plasma albumin levels (<20-25g/L)
  - E.g. chronic liver disease, malnutrition
- Displacement from binding site by other drugs
  - e.g. aspirin, sodium valproate, sulphonamides,
- Saturability of plasma protein binding within therapeutic range
  - e.g. phenytoin
Distribution

2. Membrane permeability
   - For a drug to enter an organ (tissue), it must permeate all membranes that separate the organ from the site of drug administration

   • A. Blood brain barrier (BBB) – lipid membrane located between plasma and the extracellular space in the brain
     » The entry of drugs is restricted into the CNS and CSF (cerebrospinal fluid)
     » Lipid solubility and cerebral blood flow limit permeation of the CNS
     » Highly lipophilic drugs can pass the BBB (i.e. benzodiazepines)
     » It is difficult to tx the brain or CNS, however, the difficulty of passage into the brain can also serve as a protective barrier when treating other parts of the body
3. **Storage Depots**

- **Fat** – lipophilic drugs accumulate here and are released slowly (due to low blood flow)
  - Ex: thiopental (or other anesthetic) – causes ↑ sedation in obese patients

- **Bone** – Ca++ binding drugs accumulate here
  - Ex: tetracycline can deposit in bone and teeth → will cause mottling or discoloration of teeth

- **Liver** – many drugs accumulate in the liver due to an affinity for hepatic cells
  - Ex: quinacrine (antimalarial agent) – has higher conc (22,000 times) in the liver than in plasma due to long term administration
**Distribution**

- **Redistribution** – after a drug has accumulated in tissue, i.e. thiopental in fatty tissues, drug is gradually returned to the plasma
  - Equilibrium between tissue drug and plasma drug
Distribution

- Vd = total amt of drug in body concentration of drug in blood or plasma

- Drugs with very high volumes of distribution have much higher concentrations in extravascular tissue than in the vascular compartment (plasma membrane)

- When drugs are protein bound, it can make the apparent volume smaller
Distribution

- TBW = 0.6 L/Kg (42 l)
- ECF vol = 0.2 L/Kg (12 l)
- Plasma vol. = 0.05 L/Kg (3 l)
- Blood vol = 5.5 l

- Clinical prediction:
  - If Vd = 3L, you can assume drug is distributed in plasma only
  - If Vd = 18L, you can assume drug is distributed in plasma and tissues
  - If Vd > 46L, the drug is likely stored in a depot because the body only contains 40-46L of fluid
Distribution

– drugs with low Vd are often bound to plasma proteins

– drugs with high Vd are often bound to tissue components (proteins or fat)
Distribution

Variances:

• Increased adipose tissue leads to increased depot stores of a drug with large Vd
  – Which then leads to greater stores for eventual redistribution

• Patients with edema, ascites, or pleural effusion offer a larger volume of distribution to hydrophilic drugs than is predicted by their smaller, ideal Vd
Distribution

- **Variances**
  - Pediatrics
    - Body Composition
      » \( \uparrow \) total body water & extracellular fluid
      » \( \downarrow \) adipose tissue & skeletal muscle
    - Protein Binding
      » albumin, bilirubin, \( \alpha_1 \)-acid glycoprotein
    - Tissue Binding
      » compositional changes
Imagine the body was a bucket:

- Dose In
- Overflow into tissues
- Tissues
- Blood stream
- Excretion
Distribution

- **Uses of Vd**
  - If a drug is highly distributed to the tissues the first few doses disappear immediately from the blood stream
  - Loading doses are required to fill up the tissues and the plasma
  - Important if the site of drug action is in the tissues
Uses of Volume of Distribution

Imagine a bucket with a leak

You give a loading dose to fill up the bucket in the first place

After that you only need to give enough to replace the amount leaking out. This is the maintenance dose.
Volume of distribution can help calculate the dose needed to achieve a critical plasma concentration.

\[
\text{Loading Dose (LD)} = (V_d) \times (C_p)
\]
Metabolism

- Process of making a drug more polar and water soluble to be excreted out of the body (lead to termination)

- Drug metabolism often results in detoxification or inactivation of drugs where the metabolites are less active or inactive compared to the parent drug

- Some metabolites may be equally or even more active than the parent drug. Prodrug – inactive drug that is activated by metabolism (ex: enalapril)
Metabolism

– Some drugs have more than one metabolite

– Every tissue has some ability to metabolize drugs (i.e. GI tract, lungs, skin, kidneys)
  • however, the liver is the principal organ for drug metabolism

– First-pass effect – some drugs go straight from the GI tract to the portal system where they undergo extensive metabolism in the liver (ex: morphine) before entering the systemic circulation
Metabolism

- **First-pass effect**
  - This can limit the bioavailability of certain drugs
  - It can be greatly reduced by giving drug by other route of administration

- **Extraction ratio** – an expression of the effect of first-pass hepatic elimination on bioavailability.
  - Basically, how much drug is removed

\[ \text{Hepatic Clearance} = \text{Hepatic blood flow} \times \text{hepatic extraction ratio} \]
**Metabolism**

- Drugs with high extraction ratios: clearance depends on hepatic blood flow
  - Morphine

- Drugs with low extraction ratios: clearance depends on metabolic capacity of liver
  - Diazepam
  - Phenytoin
Metabolism

- **General pathways of drug metabolism**
  - **Phase I reaction** – (oxidation, reduction, hydrolysis)
    - Generally, the parent drug is oxidized or reduced to a more polar metabolite by introducing or unmasking a functional group (-OH, -NH₂, -SH)
    - The more polar the drug, the more likely excretion will occur
    - This reaction takes place in the smooth endoplasmic reticulum in hepatocytes
Metabolism

- **Phase I reaction**
  - The smooth microsomes are relatively rich in enzymes responsible for oxidative drug metabolism
  - Important class of enzymes – mixed function oxidases (MFOs)
    - The activity of these enzymes requires a reducing agent, NADPH and molecular oxygen \((O_2)\)
    - Two microsomal enzymes play a key role:
      » 1. NADPH-cytochrome P450 reductase, a flavoprotein
      » 2. Cytochrome P450, a hemoprotein, the terminal oxidase
Metabolism

- **Phase I reaction**
  - Cytochrome P450
    - Is a family of isoenzymes
    - Drugs bind to this enzyme and are oxidized or reduced
    - Can be found in the GI epithelium, lung and kidney
    - Cyp3A4 alone is responsible for more than 60% of the clinically prescribed drugs metabolized by the liver
Metabolism

- **Phase II reaction**
  - This involves coupling the drug or its polar metabolite with an endogenous substrate (glucuronic acid, sulfate, glycine, or amino acids)
  - The endogenous substrates originate in the diet, so nutrition plays a critical role in the regulation of drug conjugation
  - Drugs undergoing phase II conjugation reactions (glucuronidation, acetylation, methylation, and glutathione, glycine, and sulfate conjugation) may have already undergone phase I transformation
  - Some parent drugs may already possess a functional group that may form a conjugate directly
Metabolism

- Enterohepatic recirculation – some drugs, or their metabolites, which are concentrated in the bile then excreted into the intestines, can be reabsorbed into the bloodstream from the lower GI tract
Variations in drug metabolism:

- Generally, men metabolize faster than women (ex: alcohol)
- Diseases can affect drug metabolism
  - hepatitis,
  - cardiac (↓ blood flow to the liver)
- Biotransformation in the neonate
  - liver and metabolizing enzymes are under-developed
  - also have poorly developed blood brain barrier
- Genetic differences
  - Ex: Slow acetylators (autosomal recessive trait mostly found in Europeans living in the high northern latitudes and in 50% of blacks and whites in the US)
Excretion

- Elimination of unchanged drug or metabolite from the body – terminating its activity

- Drugs may be eliminated by several different routes:
  - exhaled air
  - Sweat
  - Saliva
  - Tears
  - Feces
  - Urine

- Urine is the principle route of excretion
- Three mechanisms for renal excretion:
  - 1. Glomerular filtration – passive diffusion
     - Small nonionic drugs pass more readily. Drugs bound to plasma proteins do not
     - Clearance by filtration = $f_u \times GFR$
  - 2. Tubular secretion - drugs which specifically bind to carriers are transported (ex: penicillin)
  - 3. Tubular reabsorption – Small nonionic drugs pass more readily (ex: diuretics)
Excretion

- filtration: free drug only, not protein bound
- reabsorption: passive, lipid soluble form only (pH)
- secretion: active, acids and bases, saturable

Plasma pH is constant; urine pH varies from 5.0-8.0
Excretion

• Elimination by the kidneys depends on
  – Renal blood flow
  – GFR
  – Urine flow rate and pH, which influence
    • Passive reabsorption
    • Active secretion
Excretion

- Glomerular filtration matures in relation to age, adult values reached by 3 yrs of age
- Neonate = decreased renal blood flow, glomerular filtration, & tubular function yields prolonged elimination of medications
Adding it up
Enzyme processes obey Michaelis-Menton kinetics

\[ V = \frac{V_{\text{max}} \cdot \text{[Substrate]}}{K_m + \text{[Substrate]}} \]

\( V_{\text{max}} \) is the maximum rate of the process
\( K_m \) is the michaelis-menton constant, the concentration at which the rate is \( \frac{1}{2} \) of the maximum rate, \( V_{\text{max}} \).
Enzyme processes obey Michaelis-Menton kinetics

$$V = \frac{V_{\text{max}} [\text{Substrate}]}{K_m + [\text{Substrate}]}$$

Drugs used at concentrations at or below their $K_m$ are in the “Linear” region.
Enzyme processes obey Michaelis-Menton kinetics

\[ V = \frac{V_{\text{max}} \cdot [\text{Substrate}]}{K_m + [\text{Substrate}]} \]

Drugs used at concentrations at or below their \( K_m \) are in the “Linear” region.

Drugs used at concentrations several times their \( K_m \) are in the “Saturated” region.
Zero-order Kinetics

- For a drug whose concentration is above the “Saturated” value
  - At this point, \([\text{Drug}] >> \text{Km}\), so the equation:
    \[
    V = \frac{V_{\text{max}} [\text{Drug}]}{\text{Km} + [\text{Drug}]}
    \]
    Simplifies to
    \[
    V = \frac{V_{\text{max}} [\text{Drug}]}{[\text{Drug}]}
    \]
    A Constant Amount of drug is eliminated/metabolized per unit time
  - Increased \([\text{Drug}]\) DOES NOT result in an increase in metabolism or excretion (as appropriate)
  - Referred to as “Zero-Order Kinetics”
Zero-order Kinetics

- Referred to as “Zero-Order Kinetics”
- Rate of elimination of [Drug] is Independent of [Drug]

\[
\frac{dC}{dt} = \text{Constant}
\]
Zero-order Kinetics

• Only 2 common drugs:
  – Acetylsalicylic Acid (ASA)
  – Alcohol

• Example:

  Enzyme 94% saturated at 0.1% Blood Ethanol

  At saturation metabolizes ~ 10ml Ethanol / hour (~ 1 standard drink)
First-order Kinetics

• For a drug at a concentration in the “Linear” region

Rate of elimination is Proportional to concentration = First-Order Kinetics

Most Drug Elimination obeys First-Order Kinetics
First-order Kinetics

- For a drug whose concentration is in the “linear” region
  - At this point, [Drug] << Km, so the equation:

\[
V = \frac{V_{\text{max}} [\text{Drug}]}{K_m + [\text{Drug}]}
\]

Simplifies to

\[
V = \frac{V_{\text{max}} [\text{Drug}]}{K_m}
\]

Rate of Elimination is **Proportional** to concentration - First-Order Kinetics

- Where Vmax/Km equals the First-Order rate constant, \( k_e \)
First-order Kinetics

First-Order Kinetics – A constant Proportion eliminated per unit time

\[
\frac{dC}{dt} = -10\% \ C \ / \ \text{Unit Time}
\]

\[
= -0.1 \ C \ / \ \text{Unit Time}
\]

Note: A curve, not a straight line
Half-Life

- Ke values are difficult to conceptualize
- Solution: Concept of Half-Life (\(t_{1/2}\))

\[ t_{1/2} = \text{time required for [Drug] to decline by 1/2} \]
Relationship between $k_e$ and $t_{1/2}$

$t_{1/2} = 0.693/k_e$
Some purposeful examples
Pediatrics

• Differences in Distribution
  – Less protein binding in infants
    • Lower total protein and albumin than adults
    • Leads to higher free plasma levels
      – More free drug, greater pharmacologic effect
        » Phenytoin, salicylate, barbituates and diazepam
        » Also greater potential for toxicity
Volume of Distribution

- Infants have a greater proportion of bodyweight in the form of water
  - Water soluble meds thus need higher initial loading dose
    » Digoxin, succinylcholine and gentamicin
- Smaller proportion of weight as fat and muscle mass
  - Drugs that redistribute to muscle and fat have higher peak level and more sustained blood level
    » Barbiturates and narcotics
    » Small muscle mass also means lower serum levels of muscle relaxants are required for effect
– Hepatic Excretion

• Hepatic drug metabolism less active in neonates
  – Phase I and II reactions reach adult activity by 6 to 18 months of age
• Lower proportion of blood flow to liver in younger children
• Diazepam, thiopental and phenobarbital have much increased serum half lives in infants
– Renal Excretion

• Renal function less efficient in infants than adults relative to body weight
  – Fully mature GFR by 2 years of age
  – Drugs excreted by filtration have longer half lives
    » Aminoglycosides and cephalosporins
Propofol

- Highly lipophilic with rapid distribution to organs
  - High Vd
- Termination of action secondary to redistribution and rapid hepatic and extrahepatic clearance
  - Redistribution accounts for rapid onset and offset
- Children require lower induction doses than adults secondary to lower redistribution to fat stores
Morphine

• Half life markedly prolonged in infants
  – Secondary to decreased capacity of liver glucuronidation activity
    • Adult activity reached by one month of age
• Immaturity of blood brain barrier accounts for increased sensitivity to morphine
Fentanyl

- Longer half life in infants and neonates
  - Lower hepatic blood flow
  - Lower hepatic function
  - Lower Vd secondary to lower fat mass
- Low dose fentanyl – termination of action is by redistribution to fat and muscle
- High dose – termination is secondary to metabolism
- EXTREMELY lipid soluable – quickly passes through BBB
Vecuronium

- Infants less than 1yo more sensitive, with a longer duration of action
- Plasma conc required for given effect lower
  - Less neuromuscular junctions secondary to less muscle mass
  - Larger Vd, combined with lower necessary plasma level, leads to a slower decrease in plasma concentration