PharmSci III (PharmSci 464)
Pharmacokinetics and Biopharmaceutics

- Time: MWF
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### Absorption (Part 1) Outline

1. Pharmacokinetics and Pharmacodynamics
2. Absorption and Bioavailability
3. Drug Absorption Mechanisms
4. Four Primary Factors influence Drug Absorption

### 1. Pharmacokinetics and Pharmacodynamics

#### 1.1. Pharmacokinetics

- The study (or kinetics) of drug absorption, distribution, metabolism, and excretion (ADME) is known as Pharmacokinetics.
- The processes of drug distribution and elimination (metabolism and excretion) are also known as drug disposition.
- The processes of drug metabolism and excretion are called drug elimination.
- What the body does to the drug.

#### 1.2. Pharmacokinetics include ADMET

- **Intravenous injection**
- **Drug at site(s) of action**
- **Clinical effect**
- **DISTRIBUTION**
- **ABSORPTION**
- **ELIMINATION**
- **Metabolism**
- **Drug in tissues (including blood cells) and other fluids of distribution (e.g. lymph, interstitial fluid)**
- **Unchanged drug excreted**
- **Blood plasma**
- **Bound drug**
- **unbound drug**
1.2. Pharmacokinetics include ADMET (Con’t)

- **ADME**
  - Absorption (A): drug is absorbed from site of administration to systemic circulation.
  - Distribution (D): drug is distributed from circulation to other tissues.
  - Metabolism (M): drug is metabolized in liver or other tissues by metabolizing enzymes.
  - Excretion (E): drug is excreted from kidney or other organs.
- **ADMET**
  - T: Transporters

1.3. Methods to Study of Pharmacokinetics

- **Experimental approaches**:
  - biological sampling techniques
  - analytical methods for the measurement of drugs and metabolites in biological matrix
  - procedures that facilitate data collection and analysis
- **Theoretical approaches**:
  - development of pharmacokinetic models that predict drug absorption and disposition after administration

1.4. Application of Pharmacokinetics

1. Predict plasma, tissue, and urine drug levels with any dosage regimen
2. Calculate the optimum dosage regimen for each patient individually.
3. Estimate the possible accumulation of drugs and/or metabolites.
4. Correlate drug concentration with pharmacologic or toxicological activity.
5. Evaluate differences in the rate and extent of availability between different formulations
6. Describe how changes in physiology or disease affect absorption, distribution, or elimination.
7. Explain drug interactions.
1.5. Pharmacodynamics

- Pharmacodynamics is the study of the effects of the drug, their mechanism of action, and relationship between drug concentrations at the site of action (receptor) as well as the intensity of pharmacologic effect.
- What the drug does to the body.

1.5. Pharmacodynamics (Con’t)

- The relationship between dose and effect can be plotted and results in a hyperbolic curve with maximum effect at the plateau.

2. Absorption and Bioavailability

Absorption:
Drug entry into systemic circulation from site of administration

2.1. Drug absorption and Bioavailability

- $F_{abs} = 86$
- $F_{g} = 41$
- $F_{hep} = 24$
- $F = 8.5$
2.2. Mass Balance of a Drug

\[
\text{Dose} \rightarrow \text{Drug at absorption site} \rightarrow \text{Drug in body} \rightarrow \text{Drug excreted} \rightarrow \text{Metabolite in body} \rightarrow \text{Eliminated metabolite}
\]

\[
\text{Rate of change of drug in body} = \text{Rate of absorption} - \text{Rate of elimination}
\]

2.3. Bioavailability

\[ F = F_a \cdot F_g \cdot F_h \]

- \( F \): bioavailability
- \( F_a \): fraction of drug absorbed
- \( F_g \): fraction of drug escaped from gut wall metabolism
- \( F_h \): fraction of drug escaped from liver metabolism

- First pass effect
  - The drug loss as it passes, for the first time, through sites of elimination, such as in GI membranes and the liver

2.3. Bioavailability (Con’t)

CFR 21.320.1 (Definitions)

Bioavailability means “the rate and extent to which the active drug ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by the measurements intended to reflect the rate and extent to which active ingredient or active moiety becomes available at the site of action.”

3. Drug Absorption Mechanisms

Types of Intestinal Membrane Transport:
3. Drug Absorption Mechanisms (Con’t)

- 3.1. Passive diffusion
- 3.2. Carrier-mediated processes (active transporters)
- 3.3. Paracellular tight junction
- 3.4. Endocytosis

3.2. Membrane Transporters

A Few hundreds of transporters have been studied in human body

<table>
<thead>
<tr>
<th>Intestinal lumen</th>
<th>Apical membrane</th>
<th>Basal membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>rBAT</td>
<td>h^+AT</td>
<td>HLAT ?</td>
</tr>
<tr>
<td>h^+AT</td>
<td>TAUT</td>
<td>4F2hc</td>
</tr>
<tr>
<td>ATB</td>
<td>ATB0</td>
<td>h+ LAT ?</td>
</tr>
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<td>hPepT1</td>
<td>MCT1</td>
<td>OCT1</td>
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<tr>
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<td>MOAT</td>
<td>OCT3</td>
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<td>MDR</td>
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<td>GLUT5</td>
</tr>
<tr>
<td>ILBP</td>
<td></td>
<td>GLUT2</td>
</tr>
</tbody>
</table>

3.1. Passive Diffusion

- Different molecules have distinct membrane permeability across artificial lipid bilayer
3.3. Paracellular Tight Junctions

Functions:

• Prevent passage of molecules and ions between cells (MW <300-1000 pass through)

• Block the movement of integral membrane proteins
  – heregulin and erbB
  – bronchitis, asthma, and cystic fibrosis

• Cell-cell adhesion

3.4. Endocytosis

3.5. Which routes dominate (control) drug absorption?

• Drug absorption (or movement through membrane) include passive, active, paracellular, and endocytosis routes.

• Fastest process dominates (control) drug absorption (movement across membrane)
  – Lipophilic compounds (passive diffusion)
  – Carrier substrates (active transport)
  – Small polar molecules with MW < 300 (paracellular)
  – Nanoparticles (endocytosis/transcytosis)
4. Four Primary Factors influence drug absorption

4.1. Factors influence drug permeability

- Passive diffusion permeability (cm/s)
  - Partition coefficient (K)
  - Diffusion coefficient (D, cm²/s)
  - Membrane thickness (h, cm)

\[ P = \frac{DK}{h} \]

- Active transporter permeability
  - Substrate specificity (Km)
  - Concentration (C)
  - Drug flux (J)

- Paracellular permeability
  - Molecular size, 300-1000 Da
  - polarity

4.2A. Solubility
- Physiochemical properties of drug molecules

4.2B. Dissolution
- Dosage form variables

4.2C. Dose

Permeability Across Lipid Bilayer

- High permeability
  - Water (H₂O)
  - Urea
  - Glycerol
  - Tryptophan
  - Glucose

- Low permeability
  - Chloride (Cl⁻)
  - Sodium (Na⁺)
  - Potassium (K⁺)
  - Iodide (I⁻)
  - Nitrate (NO₃⁻)
4.2. Solubility, Dissolution, and Dose  

Governing Drug absorption

- Solid drug $\xrightarrow{K_1}$ Drug Solution $\xrightarrow{K_2 \text{, membrane}}$ Blood
  - Disintegration
  - Dissolution
  - Solubility---ionization
  - Aqueous transport
  - Membrane transport

4.2. Solubility, Dissolution, and Dose (Con't)

- 2A. Solubility
  - Extent of ionization (pH-partition hypothesis)
  - Oil / water partition coefficient ($K_{o/w}$)
- 2B. Dissolution (Extent and Rate)
  - Dosage forms
- 2C. Dose
  - Small dose: easy to be dissolved.
  - Large dose: Difficult to be dissolved.

Summary

- 1. Pharmacokinetics and Pharmacodynamics
  - PK (ADMET): What the body does to the drug
  - PD (Efficacy vs. dose): What the drug does to the body
- 2. Absorption and Bioavailability
  - $F = F_a, F_g, F_h$
- 3. Drug Absorption Mechanisms
  - Passive diffusion
  - Active transporters
  - Paracellular tight junction
  - Endocytosis
- 4. Four Primary Factors influence Drug Absorption
  - Permeability, solubility, dissolution, dose.
5. Secondary Factors Influence Drug Absorption

- Biological factors of gastric intestinal (GI) tract
  - Gastric emptying
  - Gastric and intestinal pH
  - GI content
  - Food effect
  - GI transit time and motility
  - GI surface area
  - Drug stability in GI tract
  - Blood flow
  - Age
- Dosage form factors
  - Excipients
  - Diluents
  - Surfactants
  - Dosage forms

5.1. Gastric Emptying

- Anything slowing down gastric emptying is likely to slow down the rate (not extent) of drug absorption, and thus affecting onset of the therapeutic response.

Gastric Emptying Rate at Fasted State

- Fasted emptying of low volume of non-caloric liquids (50 ml)
  - 0-2 hrs
- Fasted emptying of high volume non-caloric liquids (200 ml)
  - \( V = V_0 \exp(-kt) \), first order kinetics, rate is proportional to the volume remaining in the stomach.
  - \( T_{1/2} = 10 \text{ – } 20 \text{ min} \)
  - Increase absorption rate
Gastric Emptying Rate at Fed State

- **Fed state emptying liquid**
  - Proportional caloric density (cal/ml)
  - Zero order, e.g., glucose, 2-3 kcal/min
  - Slow down drug absorption rate

- **Fed state emptying solid**
  - Proportional to caloric density
  - Size
    - < 7-10 mm particle can be emptied to intestine
    - > 7-10 mm (Phase III contraction) takes long time for gastric emptying
  - Slow down drug absorption rate

Gastric emptying controlled absorption (con’t)

Example:

- Acetaminophen
  - mw: 151
  - Solubility: 100 mM
  - Log Kp = 0.2
  - It is very permeable

Gastric emptying change absorption rate of acetaminophen

- Co-administered with metoclopramide to hasten gastric emptying
- Co-administered with propantheline to slow down gastric emptying

5.2. Surface area of different regions of GI influences drug absorption

- **Stomach**
  - Surface area with folds: 1 m²
  - Blood flow: 150 ml/min
  - No villi and microvilli, small surface area for drug absorption
5.2. Surface area of different regions of GI influences drug absorption (Con’t)

- Small intestine
  - duodenum, jejunum, ileum
  - has largest effective surface area for absorption due to the presence of
    - Folds of mucosa; Villi; Microvilli
  - is the most important region for carrier-mediated drug absorption
    - Most transporters are expressed in small intestine
    - Surface areas: 200 m²
    - Blood flow: 1000 ml/min

- Large Intestine
  - No villi and microvilli, small surface area for drug absorption
  - Less transporter expression for carrier-mediated drug absorption
  - Receives 500-1500 ml per day

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**Small Intestinal Anatomy**

**Example 1: Regional dependent absorption Bidisomide**
Example 2: Regional dependent absorption

5.3. pH of Gastrointestinal Tract

- GI pH change may:
  - Change drug solubility
  - Change drug dissolution
  - Change absorption
    - Ionization
    - Then, dissolution controls absorption

GI pH and Drug Absorption

- Human
  - Gastric pH 1-3.5
    - Gastric pH 4-6 after meal
    - H-2 blocker (famotidine) increase gastric pH to 5
  - Intestinal pH
    - Duodenum (pH 5-6.5)
    - Jejunum (pH 6-7)
    - Ileum (pH 7-7.5)
    - Colon (pH 6.5-8)
- Dog
  - Gastric pH 1.2 - 8
  - Less fluctuation after meal
  - H2 blocker increase gastric pH 7-8

GI pH Changes Dissolution

- The rate of dissolution from a dosage form, particularly tablets and capsules, is dependent on pH
  - Acidic drugs dissolve most readily in alkaline media and will have a greater dissolution in the intestinal fluids than in gastric fluids
  - Basic drugs will dissolve most readily in acidic solutions, and thus the dissolution will be greater in gastric fluids than in intestinal fluids
Effect of Gastric pH on drug absorption:
Example (dog model)

Water Placebo capsule
Pentagastrin
Ranitidine

Effects of Gastric pH on absorption and bioavailability (con't)
Example: Dipyridamole

- Dipyridamole
  - Anti-platelet, anti-thrombosis
  - Weak base, pKa 6.4
- Solubility:
  - < 1.5 ug/ml at pH 6-8;
  - > 1-10 mg/ml at pH 1.2

Gastric pH on absorption and bioavailability (Con't)
Example: Dipyridamole tablet dissolution at different pH

Gastric pH on absorption and bioavailability (Con't)
Example: Dipyridamole in combination use of H2-antagonists

Plasma Conc. (ng/ml, ± SEM)
Clinical implication of pH dependent absorption

- Combination use of antacid with other drugs, especially weak basic drugs with pH-dependent solubility
  - Decrease bioavailability (more than 50-80%),
  - Many take antacid (H-2 blocker or other antacids)
  - Antacid is prescribed after surgery
    - e.g. some weak basic anti-thrombosis drugs should be avoided with combination use.

5.4. Food Effects on drug absorption

- Food (high fat) increase drug solubility and dissolution, increase bioavailability (BA) for certain drugs with low solubility
- Food (high fat) may stimulate bile salt secretion and increase drug solubility and dissolution, and increase BA for certain drugs with low solubility
- Food (high calories) decrease gastric emptying rate, delay the rate of absorption, and delay the onset of therapeutic drugs

5.4. Food Effects on drug absorption (Con’t)

- Food (high protein) may increase gastric pH---- decrease dissolution of weak base, decrease BA
- Food component may compete for drug absorption that mediated by transporter system
  - Grapefruit juice inhibit efflux pump (P-gp) and increase BA of P-gp substrates
- Food component form complex with drugs (complexation) and decrease drug absorption and bioavailability
  - Tetracycline with calcium (milk)

Food Effect Example: Grapefruit Juice Inhibit P-gp and Increase Bioavailability

![Graph showing the effect of grapefruit juice on bioavailability of a drug.](image)
5.6. Dosage Form Factors Influence Drug Absorption

- Drug has to be in solution for absorption
- Factors, which influence dissolution, may affect drug absorption
- Controlled drug releases formulation
  - Completely change absorption profiles, which is different from immediate release dosage forms.
  - The rate of drug release will control the rate of drug absorption

Summary

Factors Control Drug Absorption

- Permeability controlled drug absorption
  - If a drug has high water solubility and low membrane permeability (hydrophilic drugs), permeability usually limits (controls) absorption, unless it is carrier-mediated or paracellular absorption.
- Solubility (and dissolution) controlled drug absorption
  - If a drug has low solubility and high permeability (lipophilic drugs), solubility (and dissolution) usually limits (controls) absorption. Permeability does not limit absorption.
- Gastric emptying controlled drug absorption
  - If neither above two properties limits the absorption (for drugs with high solubility and high permeability), then gastric emptying rate limits (controls) the drug absorption

Summary

- Physiological factors influence drug absorption
  - Gastric emptying: change absorption rate
  - Surface: regional dependent absorption
  - pH effect: combination use of antacid may change bioavailability
  - Food effect: decrease or increase bioavailability

- Dosage form factor influence drug absorption
  - Changes in dissolution may change drug absorption
  - Controlled release formulations change absorption profiles compared to immediate release formulations
Distribution

An equilibrium distribution or reversible transfer of drug between circulation and tissues

Outline

• 1. Rate of Distribution
  – 1.1. Perfusion limited
  – 1.2. Diffusion limited
• 2. Extent of Distribution
  – 2.1. Volume of distribution
  – 2.2. Fraction of drug in the body
  – 2.3. 2.4. 2.5. Drug binding in blood, plasma, tissues
  – 2.6. Physiological volume and special case of tissue distribution

Drug Distribution

1. Rate of Distribution

• 1.1. Perfusion limited distribution
• 1.2. Diffusion limited distribution
1.1. Perfusion Limited Distribution (Flow Rate Limited)

- Direct correlation between tissue perfusion rate and the time required to distribute a drug to a tissue
  - Normally for high permeable drugs

- Perfusion rate (ml/min/ ml tissue) = blood flow (Q) / tissue volume (V_T)

Perfusion Rates In Different Tissue

- Highly perfused
  - Heart, lung, liver, kidney, gut

- Poorly perfused
  - Skim, muscle, fat

- Negligibly perfused
  - Bone, cartilage

Mass Balance of Perfusion Limited Distribution

Rate presentation to tissue (amount/time) = Q\cdot C_A

Rate of exit (amount/time) = Q\cdot C_V

Net rate uptake (amount/time) = Q\cdot (C_A - C_V)

Amount of drug in tissue = V_T\cdot C_T = V_T\cdot K_P\cdot C_V

Equilibrium distribution ratio: K_P = \frac{C_T}{C_V}
**Distribution Rate Constant $K_T$**

\[
K_T = \frac{Rate\cdot of\cdot exit}{Amount\cdot in\cdot tissue} = \frac{Q \cdot C_v}{V_T \cdot K_p \cdot C_v}
\]

\[
K_T = \frac{Q}{V_T} \cdot \frac{1}{K_p}
\]

- $k_T$: time$^{-1}$
- $Q$: Flow rate (ml/min)
- $V_T$: Tissue volume
- $C_A$: Artery drug concentration (mg/ml)
- $C_v$: venous drug concentration (mg/ml)
- $Q/V_T$: perfusion rate of the tissue (ml/min/ml tissue)
- $K_p$: Equilibrium distribution ratio

**Distribution Half-Life**

Half-life (T1/2) = \[
\frac{0.693}{K_T} = \frac{0.693 K_p}{Q/V_T}
\]

- Distribution equilibrium takes a long time: when drug has a high affinity for the tissue ($K_p$) and the tissue is poorly perfused (low $Q/V_T$).

**Tissue Drug Concentration**

Tissue concentration = $K_p \cdot C_A (1 - e^{K_T t})$

- Tissue drug concentration rises with time
- At equilibrium
  - Rate of uptake = 0
  - $C_T = C_A$

\[
C_{T_{eq}} = K_p \cdot C_A = K_p \cdot C_v
\]
Time to Reach Plateau

- Time to reach plateau of tissue drug concentration is determined only by tissue distribution half life
  - 1 half life: 50% plateau
  - 2 half lives: 75% plateau
  - 3.3 half lives: 90% plateau

Example (1)

- If distribution is perfusion rate-limited, please calculate the time to deliver 50% of equilibrium amount to tissues.

Fig A:

- The arterial concentration of drug A is (1 mg/L):
- \( K_p = 1 \) of drug A in kidney, brain, and fat tissues

Example (1)

- If distribution is perfusion rate-limited, please calculate the time to deliver 50% of equilibrium amount to tissues.

Fig A:

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Equil. Dist. Ratio (Kp)</th>
<th>Perfusion Rate (Q/V_T)</th>
<th>Time to deliver 50% of Equil. Amount to Tissue, ( 0.693 \times \frac{K_p}{Q/V_T} ) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>1</td>
<td>4</td>
<td>0.17 min</td>
</tr>
<tr>
<td>Brain</td>
<td>1</td>
<td>0.5</td>
<td>1.4 min</td>
</tr>
<tr>
<td>Fat</td>
<td>1</td>
<td>0.03</td>
<td>23 min</td>
</tr>
</tbody>
</table>
Example (2)

- If distribution is perfusion rate-limited, please calculate the time to deliver 50% of equilibrium amount to tissues.
- Fig B:
  - The arterial concentration of drug 1, 2, 3 is (1 mg/L):
    - \(K_p = 1\) of drug 1 in fat
    - \(K_p = 2\) of drug 2 in fat
    - \(K_p = 5\) of drug 3 in fat

**Fig B**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equil. Dist. Ratio ((K_p)) (Fat Tissue)</th>
<th>Perfusion Rate ((Q/V_t))</th>
<th>Time to deliver 50% of Equil. Amount to Tissue (0.693 \times \frac{K_p}{Q/V_t}) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0.03</td>
<td>23 min</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0.03</td>
<td>46 min</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>0.03</td>
<td>115 min</td>
</tr>
</tbody>
</table>

1.2. Diffusion (Permeability) Limited Distribution

- Permeability across the membrane controls drug distribution
- Many factors that govern drug across membrane (permeability) apply to diffusion limited distribution (in absorption lecture)
- Normally for low permeable drugs
2. Extent of distribution

2.1. Apparent Volume of Distribution (V):
- At equilibrium, extent of distribution is defined by “V”, a proportionality constant relating the concentration of drug in the plasma or blood to the total amount of drug in the body.
- It does not correspond to a real physiological space

\[ V = \frac{\text{Amount in body at equilibrium}}{\text{Plasma drug concentration}} = \frac{A}{C} \]

---

2.1. Volume of Distribution (V, or \( V_d \))

- Lipophilic drugs (like digoxin):
  - extensively distributed in the tissues
  - the concentration in the plasma is very low
  - it has a high V (500 - 600 L)

- Hydrophilic drugs (like ampicillin):
  - limited tissue distribution,
  - lower V (2 L)

---

2.1. Volume of Distribution (Compartmental Model)

\[
\text{Amount in body } A = V_p \cdot C + V_T \cdot K_p \cdot C
\]

- \( A = V \cdot C \)

- \( C \): plasma drug concentration

- Volume of distribution: \( V = V_p + V_T \cdot K_p \)
2.2. Fraction of Drug In The Body and Volume of Distribution

- Drug amount in plasma = $V_p \cdot C$
- Drug amount in body = $V \cdot C$
- Fraction of drug in body in plasma = $V_p / V$
- Fraction of drug in body outside plasma = $(V-V_p) / V$
- $C$: plasma drug concentration

2.3. Drug Binding in Blood and Volume of Distribution

- Concentration of drug in whole blood: $C_b$
- Concentration of drug in plasma: $C$
- Concentration of unbound drug in plasma: $C_u$
- Unbound volume of distribution: $V_u$
- Volume of distribution based on blood concentration: $V_b$

2.4. Plasma Protein Binding and Fraction of Unbound

- Drug + Protein $\rightleftharpoons$ Drug-Protein Complex
- $C$: plasma drug concentration
- $C_u$: Free drug concentration
- $F_u$: Fraction unbound

$$f_u = \frac{C_u}{C}$$

$V_b = \frac{\text{Amount in body at equilibrium}}{\text{Concentration in whole blood}} = \frac{A}{C_b}$

$$V \cdot C = V_u \cdot C_u = V_b \cdot C_b$$
2.4. Plasma Protein Binding and Fraction of Unbound

- Fraction of Unbound (Free fraction):
  - $C_u$ is more closely related to the activity of the drug than is the total plasma concentration.
  - Only unbound drug can pass through most cell membranes
  - Only unbound drug can be metabolized
  - $fu$ in plasma could be measured
  - If it is saturable binding, nonlinear kinetics occurs
  - Drug-drug interaction is occurred by displacement of protein binding

2.5. Tissue Binding

- Tissue binding of a drug cannot be measured directly.

2.6. Commonly Used Physiological Volume and Special Cases of Volume of Distribution

- Total body water = 42 L
  - 70 Kg adult, water is 60% body weight (42 L)
- Extracellular fluids (ECF) = 15 L
  - Plasma = 3 L
  - Interstitial fluid = 12 L
- Intracellular fluid = 27 L
  - Red blood cell volume = 2 L

2.6. Commonly Used Physiological Volume and Special Cases of Volume of Distribution

**Total Body Water (TBW)**

<table>
<thead>
<tr>
<th>Blood (5 L)</th>
<th>Plasma (3 L)</th>
<th>Red blood cell (RBC) (2 L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (7.5 L)</td>
<td>Albumin</td>
<td>Other intracellular fluid 25 L</td>
</tr>
<tr>
<td>Interstitial fluid 12 L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extracellular fluid = 12 + 3 = 15 L</td>
<td>Intracellular fluid = 25 + 2 = 27 L</td>
<td></td>
</tr>
</tbody>
</table>
2.6. Commonly Used Physiological Volume and Special Cases of Volume of Distribution

- For macromolecules
  - \( V = 3 \) L, if macromolecules do not bind to endothelial linings
  - Extravascular distribution is very slow to nonexistent
- For small molecules
  - If they are bound in neither tissues nor plasma,
    - \( V = 15-42 \) L
  - If they are bound in tissues or plasma, \( V \) value is variable
  - \( V \) rarely corresponds to a real volume

### Summary

- 1. Rate of Distribution
  - 1.1. Perfusion limited
    - Half life and distribution rate constant
  - 1.2. Diffusion limited
    - Factors influence diffusion
- 2. Extent of Distribution
  - 2.1. Volume of distribution
  - 2.2. Fraction of drug in the body and volume of distribution
  - 2.3. Drug binding in blood and volume of distribution
  - 2.4. Plasma binding and fraction of unbound
  - 2.5. Tissue binding
  - 2.6. Physiological volume and special case of tissue distribution
Elimination

Metabolism and Excretion

Outline

• Total Body Clearance
  – Concept
  – Mass balance
  – Additivity
• Hepatic Clearance
  – Hepatic clearance and extraction ratio
  – Factor influence hepatic clearance
  – Examples
  – Bioavailability and first pass effect
• Renal Clearance
  – Nephron Function and Renal Clearance
  – Components of renal clearance
  – Examples

1. Total Body Clearance

• Drug Elimination Organs
  – Metabolism
    • Primarily in liver
    • Also in GI, lung, kidney, skin, blood
      – Phase I metabolism:
        » oxidation, reduction, hydrolysis
      – Phase II metabolism
        » Conjugation
  – Excretion
    • Primarily in kidney
    • Also biliary, intestine, breath, sweat

1.1. Total Body Clearance Concept

• A parameter relating rate of drug elimination to the blood or plasma drug concentration.

\[ \text{Clearance}(CL) = \frac{\text{Rate of Elimination}}{C} \]
1.2. Mass Balance and Rate Extraction

Organ extraction rate
= rate of drug in - rate of drug out

1.3. Total Body Clearance

Clearance (CL) = \( \frac{Q(C_A - C_V)}{C_A} \)

Clearance (CL) = QE
1.4. Total Body Clearance Using Blood or Plasma Drug Concentration

- When estimate extraction ratio, total body clearance using blood drug concentration has to be used.
- But plasma drug concentration are often determined.
- Blood clearance: total body clearance using blood drug concentration
- Plasma clearance: total body clearance using plasma drug concentration
- Appendix G (Blood to plasma concentration ratio)

\[
\text{Plasma Clearance} = \frac{\text{Blood Conc}(C_B)}{\text{Plasma Conc}(C_p)} \quad \text{CL}_p = \frac{C_B}{C_p}
\]

1.4. Total Body Clearance Using Blood Drug Concentration (Blood Clearance)

- Maximum Blood Clearance Value
  - Maximum \( E = 1 \)
  - Maximum \( \text{CL}_B = Q \)
    - \( Q_{\text{liver}} = 1.35 \text{ L/min} \)
    - \( Q_{\text{kidney}} = 1.1 \text{ L/min} \)

1.5. CL and V based on drug concentration in blood, plasma, and unbound

- Rate of elimination
  \[ = \text{CL}. \ C = \text{CL}_b \cdot C_b = \text{CL}_u \cdot C_u \]
- Amount in the body
  \[ = V. \ C = V_b \cdot C_b = V_u \cdot C_u \]
1.6. Additivity of Total Body Clearance

• Total clearance is the sum of the clearances by each of the eliminating organs.
• For a drug eliminated by both renal excretion and hepatic metabolism, then

\[
\text{Rate of elimination} = \frac{\text{Rate of renal excretion}}{C} + \frac{\text{Rate of hepatic metabolism}}{C}
\]

2. Hepatic Clearance

• Factors in this fig
  - Perfusion rate
  - Drug Binding
    - Drug to RBC
    - Drug Binding to plasma protein
  - Drug metabolism by hepatocytes
    - Drug secretion to bile

2.1. Hepatic Clearance (CL) and Extraction Ratio (E)

Example: Extraction Ratio (High and Low)

<table>
<thead>
<tr>
<th>(C_A)</th>
<th>(C_v)</th>
<th>Extraction ratio (E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>50</td>
<td>0.5</td>
</tr>
<tr>
<td>100</td>
<td>99</td>
<td>0.01</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
<td>0.99</td>
</tr>
</tbody>
</table>
2.2. Factors Influence Hepatic Clearance

- Hepatic Blood Clearance \( (CL_b) = Q_H \cdot E_H \)
  - All terms are in blood, not in plasma
- Depends on:
  - Blood Perfusion
  - Protein binding
  - Enzyme activity

\[
CL_b = Q_H \cdot f_{ub} \cdot CL_{int} \\
E_H = \frac{f_{ub} \cdot CL_{int}}{Q_H} \\
CL_b = Q_H \cdot E_H
\]

- \( Q_H \): hepatic blood flow
- \( f_{ub} \): fraction unbound in BLOOD.
- \( CL_{int} \): intrinsic clearance, which relates to metabolism to unbound drug

2.2.1. Perfusion and Hepatic Clearance

- High extraction ratio \( (E > 0.7 -1) \):
  - \( CL \) is determined by \( Q \)
  - \( E \) will not change with blood flow \( (E \approx 1) \)
- Intermediate \( (E = 0.3 - 0.7) \)
  - See equation
- Low \( E \) \( (E<0.3) \)
  - Concentration in artery and vein is similar
  - \( Q \) change will not alter tissue drug concentration
  - \( Q \) change will not alter rate of elimination
  - \( Q \) change will not alter \( CL \)
  - \( E \) will change with \( Q \) (when \( CL \) is constant)
2.2.1. Perfusion and Hepatic Clearance

**Sensitivity of CL to changes in blood flow**

<table>
<thead>
<tr>
<th>Drug with</th>
<th>Blood flow</th>
<th>Extraction ratio</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>High extraction ratio $E_h = 1$</td>
<td>↑</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>Low extraction ratio</td>
<td>↑</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td>↑</td>
<td>↔</td>
</tr>
</tbody>
</table>

Symbols: ↑ increase, ↓ decrease, ↔ little or no change.

2.2.2. Binding Within Blood and Hepatic Clearance

- **High E drug**
  - Liver will remove all drugs regardless binding to RBC or protein
  - Binding will not change E
  - Binding will not change CL

2.2.3. Enzymatic Activity and Hepatic Clearance

- **High E**
  - Perfusion rate limited
  - Hepatic enzymatic activity is high
  - Change of enzyme activity cause little change in CL

- **Low E**
  - Enzyme activity limited
  - Clearance correlate to enzymatic activity
  - Inhibition or induction of enzyme will change clearance

- Low E drug
  - Plasma protein binding will change CL
    - Only unbound across membrane for elimination
  - Rate of elimination = $CL_u \cdot C_u$
    - $CL_u$: clearance based on unbound concentration
    - $C_u$: unbound concentration
  - Divided by $C$, then
  - Hepatic clearance (CL) = $CL_u \cdot fu$
2.2.3. Enzymatic Activity and Hepatic Clearance

- **Km**: the Michaelis-Menten constant, affinity for the enzyme,

- **Vmax (Vm)**: Maximum rate of metabolism,

- When \( Cu = Km \),
  - Rate of metabolism = 50% of Vm,
  - this is a convenient way of defining Km.

\[
\text{rate of metabolism} = \frac{V_m \cdot C_u}{K_m + C_u}
\]

\[
\text{unbound · metabolic · clearance} = \frac{V_m}{K_m + C_u}
\]
2.2.4. Example 3

• **EX 1:** Drug A has a plasma clearance of 1350 ml/min (100% liver metabolism) and a blood/plasma conc ratio of 0.92. Is the drug's elimination rate limited by protein binding or by hepatic blood flow? (Assuming a hepatic blood flow of 1500 ml/min)

2.2.4. Example 3

\[
\frac{CL_p}{CL_B} = \frac{C_B}{C_p}
\]

• \(CL_B = CL_p \times (C_p/C_B) = \) _____________?
• \(E = CL_B/Q = \) ________________?
• Elimination rate is determined by ?

2.2.4. Example 4.

• Predict the effect of liver blood flow increase on the CL of the 2 drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability</th>
<th>V (L)</th>
<th>Clearance (L/hr)</th>
<th>Fraction Excreted</th>
<th>Extraction ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unchanged</td>
<td>Hepatic</td>
</tr>
<tr>
<td>1</td>
<td>0.97</td>
<td>26</td>
<td>6</td>
<td>0.60</td>
<td>0.03</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>430</td>
<td>77</td>
<td>0.05</td>
<td>0.95</td>
</tr>
</tbody>
</table>

2.3. Bioavailability and First-Pass Effect

• Maximum oral bioavailability \((F) = 1 - E_H\)
  \(F = Fa \times Fg \times Fh\)
  \(Fa = 100\% \text{ (assume complete absorption)}\)
  \(Fg = 100\% \text{ (assume no gut metabolism)}\)

\[
F_H = 1 - E_H = 1 - \frac{fu_b \cdot CL_{int}}{Q_H + fu_b \cdot CL_{int}}
\]

\[
F_H = \frac{Q_H}{Q_H + fu_b \cdot CL_{int}}
\]
2.4. Biliary excretion and enterohepatic cycling

- Biliary clearance
  \[ \text{Biliary clearance} = \frac{\text{bile flow} \times \text{concentration in bile}}{\text{concentration in plasma}} \]
- Bile flow = 0.5 - 0.8 ml/min
- Enterohepatic circulation

**Hepatic Clearance Summary**

- **Total Body Clearance**
  - Concept:
  \[ \text{Clearance (CL)} = \frac{Q(C_t - C_e)}{C_t} \]
  - Mass balance
  - Blood and plasma clearance
  - Additivity
- **Hepatic Clearance**
  - Hepatic clearance and extraction ratio
    - High E and Low E
    - Factor influence hepatic clearance
      - Perfusion (High E and Low E)
      - Binding (High E and Low E)
      - Enzymatic activity (High E and Low E)
  - Bioavailability and first pass effect

**3. Renal Clearance**

- **Rate of excretion** = CL\(_R\) \cdot C
- **CL\(_R\)** = rate of excretion / plasma C
- **Factors influence CL\(_R\)**
  - Plasma C
  - Plasma protein binding
  - Urine flow
  - Urine pH
3.1. Nephron Function and Renal Clearance

3.2. Components of Renal clearance

- Glomerular filtration
  - (unbound drug blood → urine)
- Active secretion
  - (blood → urine, transporters)
- Reabsorption
  - (active vs. passive) (urine → blood)

3.1. Nephron Function and Renal Clearance

3.2. Components of Renal clearance

- Rate of Excretion
  = Rate of filtration + Rate of Active secretion – Rate of Reabsorption

\[
CL_R = \frac{fuGFR + Active\text{Secretion Rate}}{C} - \frac{Re\text{absorption Rate}}{C}
\]
3.2.1. Glomerular Filtration

- Renal blood flow \( (Q) = 1.1 \text{ L/ml} \) (20% cardiac output 5L/min)
  - 10% filtered at glomerulus
- Molecular weight cut off for glomerular filtration
  - 6000 - 20,000 Da: > 70% filtered
  - 32,000 Da: 33% filtered
  - cut off: 35,000 Da
  - Albumin (69,000 Da): 0.1% filtered
  - Only unbound drug (Cu) can be filtered

3.2.1. Glomerular Filtration

- Rate of filtration = GFR . Cu = fu. GFR. C
  - GFR: glomerular filtration rate (120 ml/min)
- \( CL_{\text{filtration}} = \text{rate of filtration} / C = \text{fu. GFR} \)

Renal Extraction Ratio by GFR

- Extraction ratio
  = rate of extraction / rate of presentation
  = GFR. Cu / (renal \( Q_R \) . \( C_b \))
- If small molecule not bound to protein (fu = 1)
  - Cu = \( C_b \)
  - Extraction ratio = GFR / \( Q_R \) = 120 (ml/min) /1100 (ml/min) = 0.11

Marker of GFR

- Creatinine
  - Mw: 113
  - Endogenous GFR marker
  - Muscle breakdown product
  - Not bound to protein
  - Distributed in TBW (V = 42 L)
  - Only renal elimination by glomerular filtration
  - CL = 120 ml/min
- Inulin
  - Mw: 5000
  - Exogenous GFR marker
  - Not bound to protein
  - Distributed in extracellular water (V = 15 L)
  - Only eliminated by glomerular filtration
  - CL = 120 ml/min
3.2.2. Active Secretion

- Active transport process applies
  - Saturation
  - Substrate specificity
  - Inhibition and competition
- Renal excretion rate = CL_R . C
- Renal filtration rate = fu. GFR. C
- If CL_R . C > fu. GFR. C or CL_R > fu. GFR
  - then it suggests active secretion occurs

3.2.3. Reabsorption

- If CL_R < fu . GFR, it suggests reabsorption
  - Secretion may still occurs, but less than reabsorption
- Reabsorption process
  - All principles and factors govern drug movement across membrane apply
    - Active transport
    - Passive diffusion
    - Paracellular
    - Endocytosis

3.3. Renal Clearance: Example 1 - reabsorption

- Methamphetamine
  - Weak base, pKa = 10
  - When urine pH is not controlled (pH 4.5–7.5), 16% dose is excreted
  - When urine pH is alkalized by sodium bicarbonate, 1-2% of dose excreted
  - When urine pH is acidified by ammonium chloride, 70-80% dose is excreted
  - Why?
Clinical application—overdose of Meth?
• Treat symptom
  – Sudden increase in blood pressure; Increased body temperature; Tremor; Muscle twitching; Confusion; Rapid breathing; Hallucinations; Panic; Muscle pain; Muscle weakness; Aggressive behavior; Tiredness; Nausea; Vomiting; Abdominal pain; Diarrhea; Irregular heart rhythm; Light-headedness; Fainting; Sweating; Seeing spots in vision; Convulsions
• Other method?

3.3. Renal Clearance: Example 2. - reabsorption
• Salicylic acid
  – Weak acid, pKa 3
  – High urine pH increase renal clearance
  – Why?

3.3. Renal Clearance: Example 3 Crystalluria
• Drug precipitate as function of pH
• Sulfonamide:
  – Weak acid,
  – Precipitate under low pH
  – Drink high volume of water
  – Alkalinize urine
• HIV protease inhibitor (Indinavir)
  – Weak base
  – Acidify urine

3.4. Detoxifying overdose by forced diuresis and urine pH control—Clinical application
• Renal excretion must be a major elimination route (fₑ > 0.5)
• Compounds must be extensively reabsorbed from renal tubule
• Reabsorption is pH sensitive
  – weak acid pKa 3-7.5
  – Weak base pKa 3-6
Renal Clearance Summary

- Nephron Function and Renal Clearance
  - Components of renal clearance
    - Glomerular filtration
    - Active secretion
    - Reabsorption
- Detoxifying overdose by forced diuresis and urine pH control---Clinical application
Intravenous Bolus Dose

Outline

• Different compartmental models for Pharmacokinetic analysis
• IV bolus administration
  – Volume of distribution
  – Drug concentration and drug amount changes over time
  – Elimination rate constant and half life
  – Fraction of drug remaining in the body
  – Total clearance
  – Better ways to calculate clearance and volume of distribution

Intravascular Administration

• Bolus injection
• IV infusion
  – More in practice
• Intra-arterial administration
  – Directly inject to target
  – Less used

1. Different Compartmental Models
1.1. One Compartmental Model

- Assume distribution is rapid

\[ D_{IV} \rightarrow \text{C, } V \xrightarrow{k} \text{Elimination} \]

\[ C = C(0) \cdot e^{-kt} \]

1.2. Two Compartmental Model

- Distribution faster than elimination
- Need two exponential terms

\[ C = C_1 \cdot e^{-k_1t} + C_2 \cdot e^{-k_2t} \]
Disposition From Plasma

- Concentration (C) vs. time curve
  - Dose: IV 500 mg, theophyline
  - fast early exponential decline
    - From 29 to 18 mg/ml, takes 30 min
  - Slower exponential decline
    - From 19 to 8 mg/ml, takes 4 hrs

- Log concentration (Log C) vs. time curve
  - Rapid fall to 16 mg/ml, within 1 hr
  - Then slow linear decline

Distribution Phase

- Dose = 500 mg
- Within 5 min
  - \( C = 33 \) mg/L
  - \( Vp = 3 \) L
  - Amount in plasma (A) = 3 x 33 = 99 mg
- Other 401 mg
  - Must be in other tissues---- distribution

Elimination Phase

- The time for plasma concentration (C) or amount of drug in the body (A) to fall by 50%
  - Theophyline, from 16 to 8 mg/ml, it takes 5 hrs
  - From 12 to 6 mg/ml, it takes 5 hrs
  - \( T_{1/2} \) is independent of amount of drug in the body

1.3. Three Compartmental Model

- Input
- \( k, \) elimination
- Peripheral compartment
- Central compartment
- Peripheral compartment
- Slow Distribution
- Fast Distribution
Three Compartmental Model

- Central compartment
  - Assume elimination from central compartment
- Fast distribution compartment
- Slow distribution compartment
- Need three exponential terms to define $C$

1.4. Physiologically Based Pharmacokinetic Model (PBPK)

2. IV Bolus Administration

One Compartment Model as An Example

Ln $C$ vs $T$ (hrs)
2.1. Volume of Distribution (V, V_d)

- One compartment model as an example
  - Hypothetical body distribution volume
  - Distribution equilibrium has to be reached before first data for V calculation
  - No drug has been eliminated yet at time 0
    * A: Dose of injection
    * Plasma concentration C(0) at time 0

\[
V = \frac{A}{C}
\]

<table>
<thead>
<tr>
<th>Volume of distribution</th>
<th>Amount in body</th>
<th>Plasma drug concentration</th>
</tr>
</thead>
</table>

2.2. Amount of Drug in the Body

- A = V \cdot C(t),
  * at any given time t
  * V is volume of distribution (or other related volumes)
  * C is after distribution equilibrium
Example

- Theophyline Dose = 500 mg
- C(0) = 18 mg/L
- V = 500 / 18 = 28 L
- How much drug in the body when plasma C is 5 mg/L?
  - $A = VC = 28 \times 5 = 140$ mg
- How much drug in the plasma when plasma C is 5 mg/L
  - $A = VC = 3 \times 5 \text{ mg/L} = 15$ mg

2.3. Plasma Drug Concentration Changes with Time

$$LnC = LnC(0) - kt$$

$$C = C(0) \cdot e^{-kt}$$

Multiply each side by V

$$A = Dose \cdot e^{-kt}$$

These two equations can estimate drug concentration and amount of drug in the body at any given time.

2.4. Amount of Drug in the Body Changing with Time

$$A = Dose \cdot e^{-kt}$$

$$\frac{dA}{dt} = -k \cdot Dose \cdot e^{-kt}$$

$$\frac{dA}{dt} = -k \cdot A \quad LnA = LnA(0) - k \cdot t$$

- First order elimination process
- K: first order rate constant

First order vs. Zero Order Kinetics

$$\frac{dA}{dt} = -k \cdot A \quad \frac{dA}{dt} = -k \cdot A^0$$

Divide both side by V

$$\frac{dC}{dt} = -k \cdot C \quad \frac{dC}{dt} = -k \cdot C^0$$

First order \hspace{1cm} Zero order
2.5. Elimination Rate Constant

\[ k = -\frac{dA}{dt/A} \]

- \( k \) = rate of elimination / amount in body

2.6. Half Life (\( t_{1/2} \))

- At one half life, \( C = \frac{1}{2} C(0) \)

\[ C = C(0) \cdot e^{-kt} \]

\[ e^{kt_{1/2}} = 2 \]

\[ kt_{1/2} = \ln 2 = 0.693 \quad t_{1/2} = \frac{0.693}{k} \]

Calculation of Half Life (\( t_{1/2} \))

Example-Theophyline IV (500mg)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Cp (mg/ml)</th>
<th>Ln Cp</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>16</td>
<td>2.77</td>
</tr>
<tr>
<td>3</td>
<td>13.9</td>
<td>2.63</td>
</tr>
<tr>
<td>4</td>
<td>12.2</td>
<td>2.5</td>
</tr>
<tr>
<td>5</td>
<td>10.6</td>
<td>2.36</td>
</tr>
<tr>
<td>6</td>
<td>9.2</td>
<td>2.22</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>2.08</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>1.94</td>
</tr>
</tbody>
</table>

C ~ T, and Ln C ~ T
Calculation of Half Life ($t_{1/2}$)

- Elimination rate constant $K = \text{slope of Ln C- t curve}$
  - $K = 0.1386 \text{ hr}^{-1}$
  - $t_{1/2} = 0.693 / K = 0.693 / 0.1386 = 5 \text{ hrs}$

2.8. Fraction of Dose Remaining in the Body

- Fraction of dose remaining at any give time
  
  $A = Dose \cdot e^{-kt}$
  
  $\text{Fraction of dose remaining} = \frac{A}{Dose} = e^{-kt}$

- Define $n$ is number of half lives

  $n = \frac{t}{t_{1/2}}$  \hspace{1cm}  $k = \frac{0.693}{t_{1/2}}$

2.8. Fraction of Dose Remaining in the Body

- Then

  $\text{Fraction of dose remaining} = e^{-kt} = e^{-0.693n}$

  $e^{-0.693} = \frac{1}{2}$

  $\text{Fraction of dose remaining} = \left(\frac{1}{2}\right)^n$

<table>
<thead>
<tr>
<th>Number of half lives $n$</th>
<th>Fraction of dose remaining $e^{kt}$</th>
<th>Fraction of dose loss $1-e^{-kt}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>0.75</td>
</tr>
<tr>
<td>3</td>
<td>0.125</td>
<td>0.875</td>
</tr>
<tr>
<td>4</td>
<td>0.0625</td>
<td>0.9375</td>
</tr>
<tr>
<td>5</td>
<td>0.03</td>
<td>0.97</td>
</tr>
</tbody>
</table>
2.9. Total Clearance

- Rate of elimination = CL. C
  \[
  \frac{dA}{dt} = -k \cdot A = -k \cdot V \cdot C
  \]
- A = V. C
- Clearance \( CL = k \cdot V \)

Relationship among CL, V, k, and \( t_{1/2} \)

\[
CL = k \cdot V
\]
\[
k = \frac{0.693}{t_{1/2}}
\]
\[
t_{1/2} = \frac{0.693 \cdot V}{CL}
\]
- Two independent parameters (V, CL) controls \( t_{1/2} \)

Examples

- Creatinine
  - MW 113
  - CL = 7.2 L/hr
  - V = 42 L (total body water)
  - \( T_{1/2} = ? \)
- Inulin
  - MW 5000
  - CL = 7.2 L/hr
  - V = 15 L
  - \( T_{1/2} = ? \)

2.10. Calculate CL using AUC and Dose

- Rate of elimination = CL. C
  \[
  \frac{dA}{dt} = CL \cdot C
  \]
  \[
dA = CL \cdot C \cdot dt
  \]
- Amount eliminated in interval dt, \( dA = CL \cdot C \cdot dt \)
  - C. dt: small area under C-time curve within time interval dt
  - Amount of drug eliminated from time 0 to infinity = adding up or integrating amount eliminated in each interval = Dose
  - AUC: adding up or integrating small area in each time interval

\[
Dose = CL \cdot AUC
\]
\[
CL = \frac{Dose}{AUC}
\]
Advantage to Use AUC for Calculation of CL

\[ Dose = CL \cdot AUC \]

- No need to know \( t_{1/2} \)
- No need to know \( V \)
- Independent of shape of C-t curve
- Appendix A

- Amount eliminated up to time \( t \),
  \[ A_t = CL \cdot AUC(0, t) \]
- Fraction of drug eliminated up to time \( t \),
  \[ F_t = AUC(0, t) / AUC(0, \infty) \]
- Fraction of drug remaining up to time \( t \),
  \[ A_{remaining} = 1 - AUC(0, t) / AUC(0, \infty) \]

Example

- Theophyline
  - Dose 500 mg
  - At 3.6 hrs, AUC (0, 3.6) = 40% of total AUC
  - At 3.6 hrs, 40% dose has been eliminated (200 mg)
  - At 3.6 hrs, 300 mg dose remains in the body

Fraction of Does Remaining using AUC

![Graph](image)

2.11. Better Method to Calculate V

- Extrapolation
  - \( V = \text{Dose} / C(0) \)
  - It is not suitable when extensive elimination during distribution phase

- Using CL and \( K \)
  - No need \( C(0) \)
  - Can be used in both IV and infusion

\[ V = \frac{CL}{K} = \frac{Dose}{AUC \cdot K} \]
**Summary**

- Different compartmental models
- IV bolus (one compartmental model)
  - Volume distribution calculation using Dose and C(0)
  - Concentration and amount of drug change with time
  - Elimination rate constant and half life
  - Fraction of dose remaining in the body
  - Clearance and relationship among CL, V, K
  - Calculate CL using AUC and dose
  - Better method to calculate V

**Example**

- A 45 year male hospitalized and has concurrently developed an infection in urine and blood (resistant to penicillin). Doctor has decided to use vancomycin.
- The patient was loaded with vancomycin (1 gram) IV on 9/14 at 12 noon. Drug levels in plasma are determined below.
  - Vancomycin 9/16: 08:00am: 22 ug/mL
  - Vancomycin 9/17: 08:00am: 20 ug/mL
- If pharmacokinetic of vancomycin follows one compartment model, and if the desired effective vancomycin concentration is 15 ug/mL (assume that the second dose has to be given when vancomycin concentration is below 15 ug/ml):
  - When should the vancomycin be re-dosed?
  - What is the volume of distribution and clearance of vancomycin? (MD may not be interested in these numbers, but you may need them for dose calculations)
  - What dose regimen (time and dose) do you recommend? (you may not be able to do the second question yet)

**Summary**

- Pharmacokinetic parameter calculation after IV bolus (one compartmental model)
  - \( t_{1/2} = \frac{0.693}{k} \)
  - \( CL = \frac{Dose}{AUC} \)
  - \( V = \frac{CL}{K} = \frac{Dose}{AUC \cdot K} \)

- C ~ V curve (Ln C ~ T curve)
- Calculate K, then calculate T1/2
- Calculate AUC
- Calculate CL using dose and AUC
- Calculate V
- Other method to calculate V
  - \( V = \frac{Dose}{C(0)} \)
IV Infusion

Outline
- Infusion plasma C vs. T
- The plateau value
- Approaching plateau
- Time to reach plateau
- Post infusion
- Change infusion rate
- Bolus and infusion
- Calculate PK parameters from infusion data
  - During infusion
  - Post infusion
  - Post infusion before Css has been reached

Constant-Rate Regimens
- IV infusion
  - Maintain constant plasma or tissue concentration
  - Infusion pump or drip
  - Mainly in hospital setting
- Controlled release device achieve the same purpose
- Transdermal delivery
- Implants

IV Infusion

\[ \text{Constant infusion} \rightarrow \text{C, V} \rightarrow \text{Elimination} \]

\[ R_0 = \frac{\text{amount}}{\text{time}} \]
1. Infusion Plasma C – T Relationship

- Time 0: amount of drug in the body is zero, no elimination
- Time 0-t: amount of drug in the body increase
- Plateau:
  - rate of infusion = rate of elimination
  - Plasma C reaches steady state (plateau)
  - Rate of change is zero

2. The Plateau Value

- Rate change in the body = rate of infusion – rate of elimination
  - Ro: constant rate of infusion
  - K.A: rate of elimination

\[
\frac{dA}{dt} = R_o - k \cdot A
\]

\[
V \cdot \frac{dC}{dt} = R_o - CL \cdot C
\]

1. Infusion Plasma Concentration C vs. T

2. The Plateau Value

- At steady state, Rate of change is zero

\[
0 = R_o - k \cdot A_{ss} \quad 0 = R_o - CL \cdot C_{ss}
\]

\[
A_{ss} = \frac{R_0}{k} \quad C_{ss} = \frac{R_0}{CL}
\]
2. The Plateau Value

- Amount of drug in the body at steady state is determined by
  - Infusion rate
  - Elimination constant
- Steady state plasma concentration is determined by
  - Infusion rate
  - Clearance
- All drug infused at the same rate and have the same CL reach the same plateau concentration
  - The amount of drugs in the body vary with volume of distribution.
- All drugs infused with same rate and having the same half life accumulate same amount of drugs at the plateau

2. The Plateau Value: Example

- Theophylline
  - CL = 4 L/h
  - Infusion rate = 60 mg/h
  - K = 0.14 hr⁻¹
  - V = 29 L
  - Desired Plasma Css = 15 mg/L
- How much drug in the body at steady state
  - Ass = Ro/k = 60/0.14 = 428 mg
  - Ass = Css . V = 15 x 29 = 435 mg
- If you find plasma C (15 mg/L) is too high, you need to decrease the desired plasma C to 10 mg/L in another patient (assume the drug’s PK is the same). What infusion rate you need to adjust?

3. Approaching Plateau

\[
\frac{dA}{dt} = R_o - k \cdot A
\]

Integrate both sides

\[
A = \frac{R_0}{k} (1 - e^{-kt}) = A_{ss} (1 - e^{-kt})
\]

Divided both sides by V

\[
C = C_{ss} (1 - e^{-kt})
\]
3. Approaching Plateau: Loading dose analogy

- To reach certain desired plasma levelCss
  - Loading dose by IV bolus \( D = \text{Ass} = \frac{R_0}{k} \)
- The plasma levelCss can be maintained by infusion \( R_0 \) thereafter.
- The amount of drug eliminated from IV bolus dose at any given time

\[
A_{\text{remaining from bolus dose}} = A_{ss} \cdot e^{-kt}
\]

3. Approaching Plateau: Loading dose analogy

- The drug loss from IV bolus will be exactly matched from IV infusion to maintain the plateau (\( \text{Ass} \))

\[
A_{\text{inf}} = A_{ss} - A_{ss} \cdot e^{-kt}
\]

Divide both side by \( V \)

\[
C_{\text{inf}} = C_{ss} (1 - e^{-kt})
\]

4. Time to Reach Plateau

<table>
<thead>
<tr>
<th>Time (in half lives)</th>
<th>Percent of plateau (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>87.5</td>
</tr>
<tr>
<td>3.3</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>93.75</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
</tr>
</tbody>
</table>

4. Time to Reach Plateau
4. Time to Reach Plateau

- Half life is the only factor to control the time to reach plateau
  - The shorter of half life, the sooner is the plateau reached
- The time is independent of infusion rate and plateau concentration
  - Although infusion rate and the plateau concentration will be different

Example

- The recombinant tissue-type plasminogen activator (t-PA): a drug with a short t½ (5 min) would reach a plateau after a short infusion (~17.5 minutes)
  - A drug with a long t½, like phenobarbital (t½ =100 hr) would not reach steady-state for a really long time (~15 days).
  - This becomes important to clinicians when they try to attain therapeutic results over a long period of time and avoid toxicity

5. Infusion Rate and Infusion Time

- Infusion rate (dose) is based on CL and desired Css
  - Css is determined by infusion rate and clearance
- Infusion time is based on T\(\frac{1}{2}\)
  - Time to reach Css is only determined by T\(\frac{1}{2}\)

6. Post-Infusion

- Postinfusion after steady state
  - Amount of drug in the body Ass
  - Steady state concentration Css
  - The decline of A or C follow the IV bolus kinetics from Ass or Css
- Postinfusion before steady state
  - Amount of drug in the body A\(_{\inf}\)
  - Steady state concentration C\(_{\inf}\)
  - The decline of A or C follow the IV bolus kinetics from A\(_{\inf}\) or C\(_{\inf}\)
7. Changing Infusion Rate

If first infusion reaches plateau ($C_{ss1}$), new infusion rate needs to be adjusted to reach ($C_{ss2}$),
- Since $C_{ss} = \frac{R_0}{CL}$
  - To double $C_{ss}$, double $R_0$
  - To halve $C_{ss}$, halve $R_0$
- The time to reach new $C_{ss2}$ from $C_{ss1}$ is solely depends on the $T_{1/2}$

7. Changing Infusion Rate

If first infusion has not reach plateau ($C_{inf}$), new infusion rate needs to be adjusted to reach new plateau ($C_{ss2}$)
- The time to reach new $C_{ss2}$ from $C_{inf}$ is solely depends on the $T_{1/2}$

7. Changing Infusion Rate: Example 1

- Theophylline
  - Original infusion rate = ($C_{ss1}$ x CL) = 30 mg/min
  - $C_{ss1} = 7.5$ mg/L
  - New target conc $C_{ss2} = 15$ mg/L
  - New infusion rate = $C_{ss2}$ x CL = 60 mg/min
  - Time to reach new plateau is dependent on $T_{1/2}$
7. Changing Infusion Rate: Example 2

- **T-PA**
  - IV bolus 10 mg
  - **C** = 350 IU/ml
  - IV infusion rate = 1.6 mg/min for 60 min
  - **C**\text{ss1} = 550 IU/min
  - IV infusion rate drop to 0.3 mg/min
  - **C**\text{ss2} = "103 IU/ml
  - Time to reach is dependent on \( T_{1/2} \) (but since there was a first infusion, the time to reach plateau may be longer than that of only one infusion)

---

8. Bolus and Infusion

- **Loading dose**
  - IV bolus
  - **C**\text{ss} can reach rapidly due to clinical demand
  - Dose = \( V \cdot \text{Css} \)
  - \( \text{Ass} = R_0/K \)
    - When Dose = Ass, maintain **Css** at time 0
    - When Dose > Ass, \( C \) will gradually decrease to **Css**
    - When Dose < Ass, \( C \) will gradually increase to **Css**

- **Maintenance dose**
  - Infusion to maintain **Css**
  - Infusion dose
    - Infusion rate \( R_0 = \text{Css} \cdot \text{CL} \)

---

8. Bolus and Infusion: Example

\[ C = C(0) \cdot e^{-kt} \quad C(0) = \frac{D}{V} \]

IV infusion
\[ C_{\text{inf}} = C_{\text{ss}} (1 - e^{-kt}) \]

IV bolus and infusion
\[ C = C(0) \cdot e^{-kt} + C_{\text{ss}} (1 - e^{-kt}) \]

- **Drug X**
  - IV bolus, Initial \( C(0) = 500 \text{ ug/L} \)
  - IV infusion, \( \text{Css} = 100 \text{ ug/L} \)
  - Desired \( C = 110 \text{ ug/L} \)
  - How long the desired \( C \) (110 \text{ ug/L}) can be reached?
8. Bolus and Infusion: Example

\[ C = C(0) \cdot e^{-kt} + C_{ss} (1 - e^{-kt}) \]

\[ C = C(0) \cdot e^{-kt} + C_{ss} - C_{ss} \cdot e^{-kt} \]

\[ (C_{ss} - C(0)) \cdot e^{-kt} = C_{ss} - C \]

\[ e^{-kt} = \frac{C_{ss} - C}{C_{ss} - C(0)} \]

9. Calculate PK Parameters From IV Infusion Plasma Data (Example)

- Drug Y
- Infusion rate = 40 mg/hr
- \( C_{ss} = 9.5 \) mg/L
- Calculate
  - CL
  - V
  - \( T_{1/2} \)

9.1. Plasma C vs. T During and After IV Infusion

\[
\begin{array}{cccc}
\text{Time, hr} & \text{C, mg/L} & \text{C}_{ss} - C & \ln(C_{ss} - C) \\
\hline
\text{During Infusion} & & & \\
1 & 1 & 3.3 & 6.2 & 1.02 \\
2 & 2 & 5.4 & 4.1 & 1.41 \\
4 & 4 & 7.6 & 1.9 & 0.64 \\
6 & 6 & 8.7 & 0.8 & -0.22 \\
8 & 8 & 9.3 & & \\
10 & 10 & 9.6 & & \\
12 & 12 & 9.5 & & \\
\hline
\text{Post Infusion} & & \ln(C) & \ln(C) \\
14 & 9.5 & & 2.25 \\
16 & 4.1 & & 1.41 \\
18 & 1.8 & & 0.59 \\
6 & 0.76 & & -0.27 \\
8 & 0.33 & & -1.11 \\
10 & 0.14 & & -1.97 \\
\end{array}
\]
9.1. Plasma C vs. T During and After IV Infusion

9.2. Calculate CL

- $CL = \frac{R_0}{C_{ss}} = \frac{40 \text{ mg/hr}}{9.5 \text{ mg/L}} = 4.2 \text{ L/hr}$
  - Best way to calculate CL

9.3. Calculate K (or T1/2) (Method 1: During Infusion)

- $C_{inf} = C_{ss} (1 - e^{-kt})$
- $C_{ss} - C_{inf} = C_{ss} \cdot e^{-kt}$
- $Ln(C_{ss} - C_{inf}) = LnC_{ss} - kt$

- Plot $Ln(C_{ss} - C_{inf})$ vs. t
  - Slope = $k$
  - $T_{1/2} = \frac{0.693}{k} = 1.7 \text{ hr}$
- $V = \frac{CL}{k} = \frac{CL \cdot T_{1/2}}{0.693} = 10 \text{ L}$

\[\text{Plasma Drug Concentration (mg/L)}\]

\[\text{0} \quad \text{4} \quad \text{8} \quad \text{12} \quad \text{16} \quad \text{20} \quad \text{10} \quad \text{8} \quad \text{6} \quad \text{4} \quad \text{2} \quad \text{0} \quad \text{40 mg/hr} \quad C_{ss}\]
9.4. Calculate K (or T1/2)
Method 2: based on postinfusion data after Css has been reached

<table>
<thead>
<tr>
<th>Time, hr Post-infusion</th>
<th>C, mg/L</th>
<th>ln(C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9.5</td>
<td>2.25</td>
</tr>
<tr>
<td>2</td>
<td>4.1</td>
<td>1.41</td>
</tr>
<tr>
<td>4</td>
<td>1.8</td>
<td>0.59</td>
</tr>
<tr>
<td>6</td>
<td>0.76</td>
<td>-0.27</td>
</tr>
<tr>
<td>8</td>
<td>0.33</td>
<td>-1.11</td>
</tr>
<tr>
<td>10</td>
<td>0.14</td>
<td>-1.97</td>
</tr>
</tbody>
</table>

\[ C = C_{ss} \cdot e^{-kt} \]
- Identical to IV bolus
  - When dose = Ass
  - C(0) = Css = 9.5 mg/L
- Slope = K
- \( T_{1/2} = 0.693/K \)
- What is the concentration two hour post-infusion (afterCss) (mg/L)

\[ C = 9.5 \cdot e^{-2k} \]

9.5. Post Infusion Before Css Has Been Achieved: Example

- A drug is administered by constant-rate intravenous infusion at a rate of 40 mg/hr for 6 hrs. Plasma levels are collected during and post the infusion and listed below.
- Estimate \( t_{1/2} \), Css, and drug concentration at 5 hr post-infusion.

\[ C_1 = C_{ss} (1 - e^{-kt_1}) \]
\[ C_2 = C_1 \cdot e^{-kt_2} \]
### Plasma C vs. t during and post infusion before Css has been reached

<table>
<thead>
<tr>
<th>Time, hr</th>
<th>C, mg/L</th>
<th>ln(C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>During infusion</strong> (t1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3.3</td>
<td>1.17</td>
</tr>
<tr>
<td>2</td>
<td>5.4</td>
<td>1.67</td>
</tr>
<tr>
<td>3</td>
<td>6.7</td>
<td>1.99</td>
</tr>
<tr>
<td>4</td>
<td>7.6</td>
<td>2.04</td>
</tr>
<tr>
<td>6</td>
<td>8.7</td>
<td>2.16</td>
</tr>
<tr>
<td><strong>Post infusion</strong> (t2)</td>
<td>ln(C)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>5.5</td>
<td>1.71</td>
</tr>
<tr>
<td>8</td>
<td>3.5</td>
<td>1.26</td>
</tr>
<tr>
<td>10</td>
<td>1.4</td>
<td>0.36</td>
</tr>
<tr>
<td>12</td>
<td>0.58</td>
<td>-0.54</td>
</tr>
<tr>
<td>14</td>
<td>0.24</td>
<td>-1.44</td>
</tr>
</tbody>
</table>

![Graph showing plasma C vs. t during and post infusion before Css has been reached](image)
Extravascular Dose

Outline
• Absorption kinetics
• Bioavailability
• Absorption and elimination phase
• Changes of absorption kinetics
• Changes of disposition kinetics
• Calculation of bioavailability
• PO plasma concentration vs. time
• Calculation of PK parameters
• Linear and nonlinear pharmacokinetics
• $T_{lag}$ and $T_{max}$

1. Extravascular Dose
   Oral Administration (per os, P.O.)

   - Zero order
   - First order
   - Absorption rate constant ($K_a$) and Absorption half life ($T_{1/2}$) depend on the drug amount (or concentration) at the absorption site
     - Oral administration (p.o.)
     - Subcutaneous administration (s.c.)
     - Intramuscular administration (i.m.)

2. Absorption Kinetics
2. Absorption Kinetics

- 2.2. Zero order kinetics
  - Absorption rate is constant: rate constant ($K_a$) is independent of drug amount (or concentration) at the absorption site
    - Controlled drug release
    - Transdermal delivery
    - Implants (such as stents)
    - Carrier mediated saturation limited absorption

3. Plasma C vs. T for PO and IV Dose

4. Bioavailability (F)

- Both rate and extent of drug input into the systemic circulation
  - Rate:
    - How fast drug absorbed--- useful for therapeutic onset
  - Extent:
    - fraction or percent of dose absorbed intact
    - Mainly focus extent in this chapter

Bioavailability (F), Clearance (CL), and AUC

- Total amount eliminated = CL · AUC
- Total amount eliminated = total amount absorbed
- Total amount absorbed = F · Dose
- To calculate F from dose, CL, and AUC

$$F \cdot Dose = CL \cdot AUC$$
5. Absorption Phase and Elimination Phase After PO Dose

- Absorption phase
  - Absorption rate > elimination phase
- Elimination phase
  - Absorption phase < elimination phase
- When absorption rate = elimination phase
  - C = Cmax
  - Cmax (po) < Cmax (iv)
  - T = Tmax
- The plot may be misleading to identify absorption and elimination phase

6. Changes of Absorption Kinetics

6.1. Disposition Rate-liming Kinetics (case A and B)

- Assume the following parameters remain unchanged for a drug
  - F, CL, V, T1/2
- Case A
  - Ka >> K (absorption T1/2 < elimination T1/2)
  - Elimination half life is determined by decline phase
  - AUC remain the same (compared to case B)
- Case B
  - Ka > K (absorption T1/2 < elimination T1/2)
  - Elimination half life is determined by decline phase
  - But Tmax is longer than that in case A
  - But Cmax is lower than that in case A
  - AUC remain the same compared to case B

6.2. Absorption Rate Liming Kinetics (case C)

- Assume the following parameters remain unchanged for a drug
  - F, CL, V, T1/2
- Case C
  - Ka < K (absorption T1/2 > elimination T1/2)
  - Tmax is longer than that in case A and B
  - Cmax is lower than that in case A and B
  - Decline phase corresponds to absorption T1/2
  - AUC remains the same compared to case A and B
6. Changing Absorption Kinetics
6.3. Examples – How to distinguish Ka or K-limiting kinetics

- Use different routes of administration
  - IV vs. PO
- Use different formulations in the same route of administration
- Use different oral fluid volume
- Compare fast vs. fed state
- Ka-limiting may occur with oral controlled release formulation
- Ka-limiting may occur with poorly soluble drugs

6. Changes of Absorption Kinetics
6.3. Example 1: Theophylline --- Ka or k-limiting? Why?

- Tablets, each containing 130 mg theophylline, were taken by 6 healthy volunteers under various conditions:
  - Taking the tablets that were dissolved in 500 mL of water and on an empty stomach (□).
  - Taking the tablets with 20 mL of water immediately following a standardized high carbohydrate meal (●).
  - Taking tablet on an empty stomach (○)
- The terminal half-life was 6.3 hours in all three conditions

6. Changes of Absorption Kinetics
6.3. Example 2: Penicillin G--- ka or k-limiting? Why?

- Penicillin G (3 mg/kg) was administered to the same person on different occasions
  - IM aqueous Penicillin G solution (I.M.)
  - IM procaine penicillin in oil (P-I.M.)
  - IM aluminum monostearate in oil (AP-I.M.)
- Different decline phase?
6. Changes of Absorption Kinetics
6.3. Example 2: Penicillin G--- k<sub>a</sub> or k-limiting? Why?

7. Changes of Disposition Kinetics

• 7.1. If F, CL remain the same, V is increased
  – K is decreased, T<sub>1/2</sub> longer
  – AUC remains the same
  – Tmax is prolonged
  – C<sub>max</sub> is decreased

• 7.2. If CL is reduced
  – T<sub>1/2</sub> is longer (K is decreased)
  – V has no change
  – AUC is increased
  – Tmax is prolonged
  – C<sub>max</sub> is increased
  – F is increased
7. Changes of Disposition Kinetics

\[ CL = V \cdot k \]

If \( CL \downarrow \),
Then
\( k \downarrow \)
\( T_{max} \uparrow \)
\( AUC \uparrow \)
\( C_{max} \uparrow \)
\( V \leftrightarrow, \)
\( F \uparrow \)

8. Predicting Changes For Cmax and Tmax

• The faster the absorption process, the greater of the slope of absorption line (\( K_a \) is larger)
  – If \( K_a \) is increased, peak amount is increased
  – If \( K_a \) is increased, \( T_{max} \) is earlier
  – If \( K_a \) is increased, \( C_{max} \) is increased (if \( V \) has no changes)

8. Predicting Changes For Cmax and Tmax

• The faster the elimination process, the steeper is the decline of the elimination line (\( K \) is larger)
  – If \( K \) is increased, peak amount is decreased
  – If \( K \) is increased, \( T_{max} \) is earlier
  – If \( K \) is increased, \( C_{max} \) is decreased (if \( V \) has no changes)
9. Calculation of Bioavailability

- 500 mg dose
- Solid circle: IM
- Open circle: PO

Example: Data obtained after administration of 500 mg of drug in solution

<table>
<thead>
<tr>
<th>Route</th>
<th>Plasma</th>
<th>Urine data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC (mg.hr/L)</td>
<td>Half life (min)</td>
</tr>
<tr>
<td>IV</td>
<td>7.6</td>
<td>190</td>
</tr>
<tr>
<td>IM</td>
<td>7.4</td>
<td>185</td>
</tr>
<tr>
<td>PO</td>
<td>3.5</td>
<td>193</td>
</tr>
</tbody>
</table>

9. Calculation of Bioavailability

- Absolute Bioavailability

\[ Dose_{iv} = clearance \cdot AUC_{iv} \]

\[ F_{ev} \cdot Dose_{ev} = clearance \cdot AUC_{ev} \]

- Assume clearance is the same in both IV and PO

\[ F_{ev} = \frac{AUC_{ev}}{AUC_{iv}} \cdot \frac{Dose_{iv}}{Dose_{ev}} \]

9. Calculation of Bioavailability

\[ F_{im} = \frac{AUC_{im}}{AUC_{iv}} \cdot \frac{Dose_{iv}}{Dose_{im}} = \frac{7.4}{7.6} = 97\% \]

\[ F_{po} = \frac{AUC_{po}}{AUC_{iv}} \cdot \frac{Dose_{iv}}{Dose_{po}} = \frac{3.5}{7.6} = 46\% \]
9. Calculation of Bioavailability

- Relative bioavailability
  - Two different formulation
  - Two different routes of administration
  - Two different conditions (food, disease)

\[
F_A \cdot \text{Dose}_A = \text{clearance}_A \cdot \text{AUC}_A
\]
\[
F_B \cdot \text{Dose}_B = \text{clearance}_B \cdot \text{AUC}_B
\]

Relative bioavailability = \[
\frac{F_A}{F_B} = \left(\frac{\text{AUC}_A}{\text{AUC}_B}\right) \cdot \left(\frac{\text{Dose}_B}{\text{Dose}_A}\right)
\]

10. Model for Extravascular Dose

- F: Bioavailability (%)
- D: Dose (mg)
- Aa: amount of drug in the gut lumen (mg)
- Ab: amount of drug in the body (mg)
- Ae: amount of drug metabolites (mg)
- Ka: absorption rate constant (hr\(^{-1}\))
- K: elimination rate constant (hr\(^{-1}\))

11. PO Plasma C vs. T

- Integration equation 2

\[
\int dA_a = k_a \int A_a \, dt - k \int A_b \, dt
\]
\[
A_a = FD \cdot e^{-k_e t}
\]
\[
A_b = \frac{FDk_a}{(k_a - k)} (e^{kt} - e^{-k_e t})
\]
\[
C = \frac{FDk_a}{V(k_a - k)} (e^{kt} - e^{-k_e t})
\]
12. Estimate PK Parameters From PO Plasma Data Example

- 500 mg dose
- Solid circle: IM
- Open circle: PO

<table>
<thead>
<tr>
<th>Route</th>
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<td>185</td>
</tr>
<tr>
<td>PO</td>
<td>3.5</td>
<td>193</td>
</tr>
</tbody>
</table>

12.1. From oral dose only
- AUC, can be calculated
- CL, unknown
- F, unknown
- $T_{1/2}$: can be calculated without knowing absorption or elimination rate limiting
- $V = CL/K$
  - Without knowing $K$, $V$ can not be calculated
- Need additional study to distinguish absorption and elimination phase

12.2. From both po and im dose (im similar to iv)
- If use im data
  - Elimination phase is decline phase (why?)
  - AUC, can be calculated
  - $F = 1$ (im similar to iv)
  - $CL_{im} = F \cdot Dose / AUC = 500 \text{ mg} / 7.4 \text{ mg.h/L} = 1.1 \text{ L/min}$
  - $T_{1/2} = 185 \text{ min}$ ($T_{1/2} = 0.693/K$, $K$ is slope)
  - $V = CL/K = CL \cdot T_{1/2} / 0.693 = 1.1 \times 185 / 0.693 = 300 \text{ L}$
12. Estimate PK Parameters From PO Plasma Data

Example

- 12.2. From both po and im dose (im similar to iv)
  - If use PO data
    - $F = 0.46$
    - $CL_{po} =$ ?
    - $T_{1/2} =$ ?
    - $V =$ ?

12.3. Estimate Absorption Rate Constant (Ka)

- Method of residuals
- Assumption
  - First order absorption kinetics
  - One compartment disposition kinetics

$$C = \left(\frac{F \cdot \text{Dose} \cdot Ka}{V \cdot (K_a - K)}\right)(e^{-kt} - e^{-k_a t})$$

12.3. Estimate Absorption Rate Constant (Ka)

- Ka > K
- Ka.t > k.t
- At later time point after Cmax
  $$e^{kat} = 0$$
  $$\bar{C} = \left(\frac{F \cdot \text{Dose} \cdot Ka}{V \cdot (K_a - K)}\right)e^{-kt}$$
  $$C = \left(\frac{F \cdot \text{Dose} \cdot Ka}{V \cdot (K_a - K)}\right)(e^{-kt} - e^{-k_a t})$$
  $$\bar{C} - C = \left(\frac{F \cdot \text{Dose} \cdot Ka}{V \cdot (K_a - K)}\right)e^{-k_a t}$$

$$\ln(\bar{C} - C) = \ln\left(\frac{F \cdot \text{Dose} \cdot Ka}{V \cdot (K_a - K)}\right) - K_a t$$
12.3. Estimate Absorption Rate Constant (Ka) Example

<table>
<thead>
<tr>
<th>Observation</th>
<th>Plasma Concentration (C) (mg/L)</th>
<th>Extrapolated Concentration (C) (mg/L)</th>
<th>Difference in Concentration (C - C) (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.38</td>
<td>1.90</td>
<td>1.52</td>
</tr>
<tr>
<td>2</td>
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<td>0.92</td>
</tr>
<tr>
<td>3</td>
<td>0.91</td>
<td>1.40</td>
<td>0.49</td>
</tr>
<tr>
<td>4</td>
<td>0.77</td>
<td>1.23</td>
<td>0.46</td>
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<tr>
<td>5</td>
<td>0.97</td>
<td>1.07</td>
<td>0.10</td>
</tr>
<tr>
<td>6</td>
<td>0.92</td>
<td>0.95</td>
<td>0.03</td>
</tr>
<tr>
<td>8</td>
<td>0.71</td>
<td>0.71</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
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<td>0.53</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>0.40</td>
<td>0.30</td>
<td>-</td>
</tr>
</tbody>
</table>

12.3. Estimate Absorption Rate Constant (Ka) Example

- Dose = 100 mg
- $T_{1/2} = 5$ hr
- Ln Residual vs. time plot
- $Ka = \text{slope} = 0.53 \text{ hr}^{-1}$
- $T_{a1/2} = 1.3$ hr

$$k_a = \frac{\ln (\bar{C}_1 - C_1) - \ln (\bar{C}_2 - C_2)}{\Delta t}$$
13. Two Different Scenarios
Elimination or Absorption Rate-Limiting

- **Case A** (the standard model, $ka >> k$):
  - The IV line is parallel to the terminal slope of the PO curve.
  - Elimination is rate limiting (the terminal slope for the PO curve = $k$)
  - Slope of residual plot is $Ka$

- **Case B** (flip-flop model, $k >> ka$):
  - The IV line is parallel to the residual slope.
  - Absorption is rate limiting (the terminal slope for the PO curve = $ka$)
  - Slope of residual plot is $k$

14. Linear and Nonlinear Pharmacokinetics with Dose Change

- **14.1. If linear pharmacokinetics**
  - Increasing dose produce proportionally increase of plasma C, Cmax, and AUC
  - $Tmax$ remain the same
14. Linear and Nonlinear Pharmacokinetics with Dose Change

• 14.2. If nonlinear pharmacokinetics
  – Dose changing may unproportionally change C, Cmax, and AUC
    – Increase dose with unproportional decrease of C, Cmax, AUC, F
      • Saturate carrier system
      • Dose exceeds solubility
      • Enzyme induction
    – Increase dose with unproportional increase of C, Cmax, AUC, F
      • Saturate first-pass elimination
      • Saturate exporter system

15. Lag Time After PO Dose

• The time between administration and start of absorption
• Change drug onset
• Calculate lag time. Appendix 1-C
• Examples for lag time
  – enteric coating formulation
    • Slow gastric emptying
    • Slow dissolution

16. $T_{\text{max}}$ After PO Dose

• At $T_{\text{max}}$
  – Absorption rate = elimination rate
    – $\frac{dc}{dt} = 0$
  – Rate of absorption and rate of elimination influence $T_{\text{max}}$
• If there is $T_{\text{lag}}$
  – $C_{\text{max}}$ occurs at $T_{\text{lag}} + T_{\text{max}}$