20.201 Mechanisms of Drug Action

Uptake and Distribution

Pharmacokinetics

October 9, 2013
Review and Agenda

• Covered significant portions of ADMET
  A ~ Uptake = absorption
  D ~ Distribution
  M ~ Metabolism - Tannenbaum
  E ~ Elimination
  T ~ Toxicology - Wright, Tannenbaum

{ Transporters - Hoffmaster

• Pharmacokinetics was defined as 1/2 of pharmacology:
  ~ “Pharmacokinetics” - getting to the target
  ~ “Pharmacodynamics” - action at the target

• Now look at pharmacokinetics in a more practical, quantitative sense
Things to learn today

• Volume of distribution
• Portal circulation/Hepatic extraction
• Fluid compartments
• Protein binding concepts and constants
• Drug-drug interactions due to protein binding
• Routes of administration
• Bioavailability/bioequivalence
• Area under the plasma concentration-time curve
• Zero-, first-, second-order kinetics
• Plasma half-life
• Clearance
• Pharmacokinetic models – one-, two-, multi-compartment
• Dosing calculations
Once absorbed, a drug molecule is subject to distribution throughout body by the circulatory system.

- Major concepts of drug distribution
  - portal circulation
  - plasma protein binding
  - fluid compartments
  - Volume of Distribution ($V_d$)
Drug Distribution

• Unique circulatory system for intestines and liver: portal circulation

• Venous outflow from GI tract (lower stomach, small intestine, upper colon) enters portal vein

• Portal vein enters liver and branches as capillaries to deliver blood to hepatocytes

• 80% of blood entering liver from portal vein; 20% from hepatic artery

• Net result: orally administered drugs must pass through the liver before entering circulation

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Drug Distribution

- **Hepatic extraction**: degree to which drug is removed from blood on each pass through the liver
  
  - Example: 63% of *rosuvastatin* is "captured" by liver on each pass

- **First-pass metabolism**: degree to which a drug is metabolized on first pass through liver in portal circulation
  
  - Example: *nitroglycerin* for angina

- >90% first-pass metabolism demands alternate route for administration

- Sublingual and rectal routes: venous absorption leads to systemic circulation and bypasses liver

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**Nitroglycerin ADME**

- $V_d \sim 200$ L
- $t_{1/2} \sim 1-4$ min
- Metabolism: 1,3- & 1,2-dinitroglycerol (active, $t_{1/2}$ 3-4 hr); 2 inactive mets.
  
  - 60% protein bound
  - Renal excretion of parent, metabolites
**Apparent Volume of Distribution (V<sub>d</sub>)**

- *Hypothetical volume into which the drug is dissolved or distributed*
  
  \[ V_d = \frac{\text{total amount of drug}}{\text{plasma concentration}} = \frac{\text{Dose}}{C_{p0}} \]

- Limited physical interpretation but useful concept to understand water compartments and gross physicochemical properties of drug

- Affected by: plasma protein binding, binding in tissues, lipid solubility, etc.

- *Lipid soluble drugs have a high apparent volume of distribution*

- Concept of V<sub>d</sub> reflects fluid compartments
  - Total body water is ~ 60% of mass
  - Three fluid compartments:
    - blood
    - interstitial
    - intracellular
  - Epithelial barriers

- V<sub>d</sub>'s often reflect real fluid compartments

---

**Blood** ~8% (5-6 l)  
**plasma** ~5% (3-4 l)  
**cells** ~3%

**Interstitial water** ~15% (10-11 l)  
**Intracellular water** ~40% (20-25 l)
Blood ~8% (5-6 l)
Plasma ~5% (3-4 l)
Cells ~3%

Interstitial water ~15% (10-11 l)

Extracellular / non-marking return ~20% (13-15 l)

Intracellular water ~40% (20-25 l)

(calculation based on 70 kg male)
**Amoxicillin**  
$V_d \sim 20 \text{ L}$  
*Partition Coefficient*  
$(\text{Octanol}/\text{H}_2\text{O}) = 0.03$

*Blood and interstitial fluids*

<table>
<thead>
<tr>
<th>Drug</th>
<th>$V$ (L/Kg)</th>
<th>$V$ (L, 70 Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfisoxazole</td>
<td>0.16</td>
<td>11</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0.3</td>
<td>20</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0.55</td>
<td>38</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0.63</td>
<td>44</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2.4</td>
<td>168</td>
</tr>
<tr>
<td>Digoxin</td>
<td>7</td>
<td>490</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>$&gt;100$</td>
<td>$&gt;10^4$</td>
</tr>
</tbody>
</table>

**Digoxin**  
$V_d \sim 490 \text{ L}$  
*Partition Coefficient*  
$(\text{Octanol}/\text{H}_2\text{O}) = 18.4$  

**Chloroquine**  
$V_d \sim >10^4 \text{ L}$  
*Partition Coefficient*  
$(\text{Octanol}/\text{H}_2\text{O}) = 52,000$  
*Fat depot!*
Concepts of distribution: Protein binding

• Binding of drugs to proteins in blood is a major determinant of PKs and a source of toxic drug-drug interaction

• Binding generally depends on charge and water solubility: hydrophobic drugs bind to hydrophobic pockets in serum proteins

• Importance of protein binding:
  ~ "active" drug = unbound drug = can bind to target
  ~ binding affects concentration of "active" drug at the site of action
  ~ wide variation in serum protein concentrations in different diseases
  ~ drug-drug interactions can involve competition for protein binding
  ~ "bumping" a drug off of protein increases its unbound concentration
Concepts of distribution: Protein binding

- Focus on two critical serum proteins:
  - ~ albumin
  - ~ α1-acid glycoprotein
- Fundamental binding isotherm quantifies binding affinity

<table>
<thead>
<tr>
<th>Proteins in serum</th>
<th>Molecule</th>
<th>KDa</th>
<th>G/dL</th>
<th>μM</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Albumin</td>
<td>66.5</td>
<td>4.5</td>
<td>670</td>
<td>Chemic. trans., oncotic press.</td>
</tr>
<tr>
<td>Globulins</td>
<td>Immunoglobulins (IgG)</td>
<td>150</td>
<td>1.5-2</td>
<td>130</td>
<td>Humoral immunity</td>
</tr>
<tr>
<td></td>
<td>Lipoprotein</td>
<td></td>
<td></td>
<td></td>
<td>Lipid and chemical transport</td>
</tr>
<tr>
<td></td>
<td>Transferrin</td>
<td>79</td>
<td>0.2</td>
<td>17</td>
<td>Iron transport</td>
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<tr>
<td></td>
<td>Ceruloplasmin</td>
<td>150</td>
<td>0.3</td>
<td>20</td>
<td>Copper transport</td>
</tr>
<tr>
<td></td>
<td>Haptoglobin</td>
<td></td>
<td></td>
<td></td>
<td>Binds to hemoglobin</td>
</tr>
<tr>
<td></td>
<td>Steroid-binding globul.</td>
<td>53</td>
<td>0.05</td>
<td>0.8</td>
<td>Transport of steroid hormones</td>
</tr>
<tr>
<td></td>
<td>Thyroid-binding globul.</td>
<td></td>
<td></td>
<td></td>
<td>Transport of thyroxin</td>
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<tr>
<td></td>
<td>Macroglobulins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>α1-Acid glycoprotein</td>
<td>42</td>
<td>0.4-1</td>
<td>9</td>
<td>Acute phase reactant, chem. trans.</td>
</tr>
<tr>
<td></td>
<td>Fibrinogen</td>
<td>400</td>
<td>0.5</td>
<td>12</td>
<td>Clot formation</td>
</tr>
<tr>
<td></td>
<td>Complement proteins</td>
<td></td>
<td></td>
<td></td>
<td>Immune function</td>
</tr>
</tbody>
</table>

![Graph of binding isotherm]

\[ r = \frac{[XR]}{[XR] + [R]_{free}} = \frac{nK_a[X]_{free}}{1 + K_a[X]_{free}} \]

\[ r = 0.5 \Rightarrow [R]_{free} = [RX] \]

\[ r = 0.5 \Rightarrow K_a = \frac{1}{[X]_{free}} \]
Serum albumin as a drug transport protein

• Most abundant protein in plasma, most important protein for drug

• Member of a protein family
  ~ α-fetoprotein, vit. D binding protein
  ~ 3 heart-shaped domains
  ~ most drugs bind subdomains IIA, IIIA
  ~ IIA and IIIA have hydrophobic pocket
  ~ I lacks hydrophobic pocket

• Endogenous ligands: fatty acids, bilirubin, steroids, NO, metals

• Drug binding
  ~ Most drugs bound less tightly than endogenous chemicals:
  ~ 1-4 primary/high-affinity binding sites; many weaker/nonspecific binding sites

<table>
<thead>
<tr>
<th>Chemical</th>
<th>$K_a$, M$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>bilirubin</td>
<td>$10^8$</td>
</tr>
<tr>
<td>oleate</td>
<td>$10^8$</td>
</tr>
<tr>
<td>Ca$^{+2}$</td>
<td>$10^2$</td>
</tr>
<tr>
<td>drugs</td>
<td>$10^4$-$10^6$</td>
</tr>
</tbody>
</table>

Concepts of distribution: Protein binding

- **Bound drugs can be displaced by competition**
- Competition by endogenous ligands or other drugs
- Net result: increase in the unbound/free concentration of a drug
- Danger for drugs with narrow TI!
  - ~ Digitoxin (compare to digoxin)
  - ~ Warfarin

**Drug**

- Digitoxin  ~95% bound
- Digoxin  ~20% bound
- Atenolol, Lithium
- Amoxicillin
- Digoxin
- Gentamicin
- Penicillin G
- Theophylline
- Phenobarbital
- Carbamazepine
- Quinidine
- Verapamil
- Phenytoin
- Tolbutamide, Diazoxide
- Propranolol, Furosemide
- Nifedipine
- Digitoxin
- Oxazepam
- Ketoprofen
- Diazepam
- Warfarin
- Phenylbutazone
- Naproxen
- Dicumarol

**Unbound** ($f_u \times 100$)

0.1

0.2

0.5

1

2

5

10

20

50

100

- **Danger!**
Consequences of altered protein binding in disease

• **Propranolol**: β-adrenergic receptor antagonist used to treat hypertension, tachyarrythmias, migraine

• Bound extensively to α-acid glycoprotein: cationic charge

• What happens to the level of drug binding when the protein level is altered by disease?

\[
K_a = \frac{[X]_b}{[X]_f \cdot [P]_f}
\]

**Binding of drug X to protein P**

\[
f_u = \frac{[X]_f}{[X]_f + [X]_b} = \frac{[X]_f}{[X]_t}
\]

\[
(1 - f_u) \cdot [X]_t = [X]_b
\]

\[
f_u = \text{Fraction of drug unbound}
\]

\[
f_p = \frac{[P]_f}{[P]_t}
\]

\[
f_p = \text{Fraction of protein unoccupied}
\]

**Free concentration of drug depends on binding constant, concentration of unoccupied binding sites on protein, and protein concentration**

• In general, \( f_p \approx 1 \): most sites are unoccupied

**Thus, concentration of free drug depends on protein concentration and is relatively constant at different drug concentrations (steep part of binding isotherm)**

Consequences of altered protein binding in disease

- **Propranolol**: β-adrenergic receptor antagonist used to treat hypertension, tachyarrhythmias, migraine

- Bound extensively to α-acid glycoprotein: cationic charge

- The level of α-acid glycoprotein changes as a function of inflammation and disease (*acute phase reactant*)

- A reduction in the level of the protein leads to an increase in the proportion of unbound drug

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• Two drugs bind to albumin with the following dissociation constants:

\[
\begin{align*}
\text{Drug A} & \\
K_d & \sim 1 \text{ pM} \\
\text{Drug B} & \\
K_d & \sim 1 \mu\text{M}
\end{align*}
\]

• Which drug has a higher affinity for albumin?

• Which drug would be displaced by bilirubin, which has a \(K_d \sim 10 \text{ nM}\)
Pharmacokinetics and the Fate of Drugs in the Body

- **Definition of Pharmacokinetics/Toxicokinetics**: quantitative temporal analysis of the processes of ADME; how much of and how fast the drug reaches its target

- **Compare to pharmacodynamics**: mechanism by which a chemical or agent exerts its effects (e.g., binding to receptor, interfering with cell wall formation)

- **Applications in pharmacology**: determine how often to administer a drug to maintain therapeutic concentration

- **Applications in toxicology**: define the association between exposure and the progression of disease

- **Approaches to pharmacokinetic analysis**:
  - Simple compartment models
  - Physiologically-based pharmacokinetic models (PBPK)
Paradigm for Pharmacokinetics Concepts

Route of Administration

Absorption $k_{abs}$

Blood/Plasma

$K_{elim}$

Route of Elimination

Metabolism $k_{met}$

Distribution $k_{dist}$

Liver

Tissues

Target

Bile
Routes of administration and absorption

• Already looked at mechanisms of absorption

• Now look at quantifying the kinetics of absorption

• Rates of absorption dictated by route of administration:
  ~ Enteral vs parenteral
  ~ Vascular vs extravascular

• **Enteral routes**
  ~ Oral - portal!
  ~ Sublingual - bypass portal
  ~ Rectal - bypass portal

• **Parenteral routes**
  ~ Intravenous (iv)
  ~ Intramuscular (im)
  ~ Subcutaneous (sc)
  ~ Topical/transdermal
  ~ Inhalation/nasal
  ~ Ocular
Factors affecting absorption from site of administration

• Quantitative aspects of absorption are important for GI, lung and topical routes

• Transport
  ~ diffusion - not saturable
  ~ active, facilitated; saturable

• pH effects
  ~ charge affects transport/diffusion
  ~ pH stomach ~ 2; tissue pH ~6.5-8

• Physical factors at the site of absorption
  ~ blood flow
  ~ surface area
    - lungs 140 m²
    - skin 1.5-2 m²
    - GI tract 300 m² (small intestine)
  ~ contact time
Quantifying absorption: Bioavailability

• Concept of **AUC**:
  ~ area under plasma concentration vs time curve
  ~ measure of the total quantity of drug entering the general circulation

• **Bioavailability**
  ~ defined as fraction \( F \) of administered drug entering general circulation
  ~ calculate as plasma \( \text{AUC}_{\text{oral}} / \text{AUC}_{\text{IV}} \)

• Determinants of bioavailability
  ~ Formulation (salt form, particle size, excipients) affects rate of dissolution
  ~ Chemical stability - E.g. penicillin unstable at acid pH of stomach
  ~ Hepatic extraction - E.g. nitroglycerin has >90% 1st pass metabolism

• **Bioequivalence** - relative bioavailability of two drugs

\[
F = \frac{\text{AUC}_{\text{ev}}}{\text{AUC}_{\text{iv}}}
\]

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- 500 mg of a drug administered IM and orally to same subject
- Quantify [drug] in plasma vs time

<table>
<thead>
<tr>
<th>Route</th>
<th>AUC ((\text{mg} \cdot \text{hr}/\text{L}))</th>
<th>(t_{1/2}) decay phase ((\text{min}))</th>
<th>Cumul. Excret. ((\text{mg}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>7.6</td>
<td>190</td>
<td>152</td>
</tr>
<tr>
<td>IM</td>
<td>7.4</td>
<td>185</td>
<td>147</td>
</tr>
<tr>
<td>Oral</td>
<td>3.5</td>
<td>193</td>
<td>70</td>
</tr>
</tbody>
</table>

EXERCISE
Basic Kinetics

• Use elements of chemical kinetics to develop pharmacokinetic concepts

• Basic rate law for a reaction in which molecule A is converted to molecule B:

\[ A \rightarrow B \quad -\frac{dA}{dt} = \frac{dB}{dt} = k \cdot [A]^n \]

**Zero-order kinetics: n = 0**

~ \(-dA/dt = k\cdot [A]^n\) becomes \(-dA/dt = k\cdot 1\)

~ Rearrange and integrate rate equation:

\[
\int -dA = k \cdot dt
\]

\[
[A]_t = -k \cdot t + C \\
 t = 0 \Rightarrow C = [A]_0
\]

\[
[A]_t = -k \cdot t + [A]_0
\]

~ Rate of the reaction is independent of substrate concentration

~ Rate constant k has units of concentration per unit time

~ Concentration versus time plot is linear
**Basic Kinetics**

- **First-order kinetics: n = 1**

  \(-\frac{dA}{dt} = k \cdot [A]^n\) becomes \(-\frac{dA}{dt} = k \cdot [A]\)

  \(\int -\frac{dA}{[A]_t} = k \cdot dt\)

  \(\ln([A]_t) = -k \cdot t + C\)  \(t = 0 \Rightarrow C = \ln([A]_0)\)

  \(\ln([A]_t) = -k \cdot t + \ln([A]_0)\)

  \(\ln\left(\frac{[A]_t}{[A]_0}\right) = -k \cdot t\)

  \([A]_t = [A]_0 e^{-kt}\)

- Rate of the reaction is **dependent on substrate concentration**

- Rate constant \(k\) has **units of reciprocal time**

- \(\ln[A]\) vs. time plot is **linear**
**Basic Kinetics**

- **Half-life** - fundamental pharmacokinetic concept and parameter
  - Definition: time to decrease concentration by one-half
  - Define mathematically by setting $[A]_t = [A]_0/2$

\[
\ln\left(\frac{[A]_t}{[A]_0}\right) = \ln(0.5) = -0.693 = -k \cdot t
\]

\[
t_{1/2} = \frac{0.693}{k}
\]
Basic Kinetics: Processes subject to zero-order kinetics

• “Saturable” processes: ligand molecules completely occupy available binding sites

• Metabolic enzymes
  ~ *Aspirin* - glycine conjugation and phenolic glucuronidation
  ~ *Ethanol* - alcohol/aldehyde dehydrogenase
  ~ *Phenytoin* - CYP2C9; \( K_m \approx 5 \text{ mg/L} \); therapeutic range 10-20 mg/L

• Transporters: *glucose transporter* in renal tubule
  (filtered [glucose] > 320 ng/min)

• Mathematical basis for zero-order kinetics

  ~ Michaelis-Menten rate equation considerations:

\[
V = \frac{dP}{dt} = \frac{V_{max} \cdot [S]}{K_m + [S]} \quad V = \frac{dP}{dt} = \frac{V_{max} \cdot [S]}{K_m + [S]} \approx \frac{V_{max} \cdot [S]}{[S]} = V_{max}
\]

~ When \([S] \gg K_m\), all substrate binding sites occupied and enzyme operates at \(V_{max}\)
Basic Kinetics: Processes subject to first-order kinetics

• Definition of a first-order process: a reaction or activity, the rate of which depends on the concentration of reactants or the chemical of interest

• Most processes of absorption, distribution, metabolism, elimination are first-order

• Diffusion: Rate of diffusion depends on the concentration gradient (i.e., the concentration of the "reactant")

\[- \frac{dQ}{dt} = P \cdot A \cdot \Delta C\]

• Metabolism and transport proteins: Enzyme kinetics generally first-order, except under conditions of substrate saturation:

\[\frac{d[\text{Product}]}{dt} = V = \frac{V_{\text{max}} \cdot [S]}{K_m + [S]}\]

when \(K_m \gg [S]\), then
\[\frac{d[\text{Product}]}{dt} = V = \frac{V_{\text{max}} \cdot [S]}{K_m} = k_{\text{met}} \cdot [S]\]
**Concept of clearance**

- **Clearance (Cl):** rate of removal of a chemical from any compartment (blood, tissue, entire body) by any process (metabolism, excretion, distribution to another tissue, etc.)

- Whole body or systemic Cl is sum of other Cl's: \( \text{Cl}_s = \text{Cl}_{\text{hepatic}} + \text{Cl}_{\text{renal}} + \text{Cl}_{\text{other}} \)

- Physical interpretation: volume of blood/tissue "cleared" of chemical per min
  Example: \( \text{Cl} = 100 \text{ ml/min} \) \( \Rightarrow \) chemical removed from 100 ml of blood/min

- Mathematical definitions:
  \[
  \text{CL} = k_{\text{el}} \cdot V_d
  \]
  where \( k_{\text{el}} \) is the first-order rate constant for elimination of a chemical from the blood or tissue; \( V_d \) is the apparent volume of distribution of the chemical

  \[
  \text{CL} = \frac{\text{Dose}}{\text{AUC}_0^\infty}
  \]
  where AUC over the time period \( t = 0 \) to \( t = \infty \)

  \[
  \text{CL}_{\text{organ}} = Q \left( \frac{C_A - C_V}{C_A} \right) = Q \cdot E
  \]
  where \( Q \) is blood flow to the organ, \( C_A \) is the arterial blood concentration, \( C_V \) is the venous blood conc. and \( E \) is the extraction ratio

- **Intrinsic clearance (Clint):** the contribution of metabolism to the overall clearance associated with an organ; \( \text{CL}_{\text{int}} \) is independent of blood flow
Pharmacokinetic Models

• Build an understanding of PK’S with simple models

• More complicated physiologically-based models combine many simple models

• **Single compartment with I.V. injection and first-order elimination**

  ~ Consider the body as a "box" with blood as the **sampling compartment**
  ~ Rapid injection and presumed rapid (“instantaneous”) distribution
  ~ Obtain blood sample and quantify drug as a function of time
  ~ **First-order** - linear plot of ln(plasma concentration) vs time
  ~ The rate constant, k, is now the **elimination rate constant**, $k_{el}$
  ~ Plasma half-life = $0.693/k_{el}$

• Loss of drug from plasma due to metabolism, excretion, distribution to tissue…

\[
\ln([D]_p) = -k_{el} \cdot t + \ln([D]_{p \mid t=0})
\]

*Already wrote and solved the mass balance differential equation!*
Pharmacokinetic Models

- Single compartment with absorption from gut and first-order elimination

  - Factor in kinetics of absorption with kinetics of elimination from blood
  - Distribution is no longer instantaneous
  - Assume first-order absorption from gut (why?)
  - Write rate equation that accounts for 1° absorption and 1° elimination

\[
\frac{d[D]_p}{dt} = k_{abs} [D]_{gut} - k_{el} [D]_p
\]

\[
\frac{d[D]_p}{dt} = k_{abs} [D]_{gut} - k_{el} [D]_p = k_{abs} \left( [D]_{gut0} e^{-k_{abs}t} \right) - k_{el} [D]_p
\]

Integrate ⇒ \([D]_p(t) = [D]_{gut0} \left( \frac{k_{abs}}{k_{abs} - k_{el}} \right) \left( e^{-k_{el}t} - e^{-k_{abs}t} \right)\)

- As drug absorbed from gut, \(e^{-k_{abs}t}\) goes to zero and \([D]_p\) dominated by \(k_{el}\)
**Pharmacokinetic Models**

- **Two compartments with I.V. injection and first-order elimination**
  - Rate equation now has 3 terms
  - Injected drug distributes in blood compartment “instantaneously”
  - Observe two "phases"
  - Rapid movement of drug out of blood into tissue compartment
  - Slower phase: as plasma concentration falls below tissue concentration, drug moves into blood

\[
d \frac{[D]_p}{dt} = k_{21}[D]_{tis} - k_{12}[D]_p - k_{el}[D]_p
\]

Integrate \( \Rightarrow [D]_{p,t} = Ae^{-\alpha t} + Be^{-\beta t} \)

\[
\alpha + \beta = k_{12} + k_{21} + k_{el}
\]

\[
\alpha \cdot \beta = k_{21} \cdot k_{el}
\]

\[
A = [D]_{p0} \left( \frac{\alpha - k_{21}}{\alpha - \beta} \right)
\]

\[
B = [D]_{p0} \left( \frac{k_{21} - \beta}{\alpha - \beta} \right)
\]
Pharmacokinetic Models

• Correlate single- and multi-compartment models

  ~ Graph of $[D]_t$ vs. time for the tissue compartment of a 2-compartment model is identical to graph of 1 compartment model with 1° absorption and 1° elimination

  ~ $k_{\text{abs}} = k_{12}$ and $k_{\text{el}} = k_{21}$

  ~ Easy: string together single compartment models for each entry and exit component, solve ordinary differential equations (Physiologically-based PK models; PBPK)

  ~ Don’t hassle with the complexity of $\geq 2$ compartment models
Pharmacokinetics of Multiple Doses

- Need to determine how frequently to give a drug so that we maintain blood concentration in the therapeutic range and below the toxic range

- Define the concept of steady-state concentration of drug in blood ($C_{ss}$):
  ~ balance of rates: dosing, absorption, elimination
  ~ reach a state in which drug concentration fluctuates within a narrow window

- Achieve $C_{ss}$ after ~4 half-lives

- First example with constant infusion:

$$C_t = \left(\frac{k_{inf}}{Cl}\right)\left(1 - e^{-k_{el} \cdot t}\right)$$

$$C_{ss} = \frac{C_t}{\frac{1 - (0.5)^{\left(t / t_{1/2}\right)}}{}} = \frac{k_{inf}}{k_{el} \cdot V_d}$$

- $k_{inf}$ = rate of infusion
- $k_{el}$ = elimination rate constant
- $C_{ss}$ = steady-state concentration (mg/mL)
- $C_t$ = concentration at time = t
- $t$ = time
- $t_{1/2}$ = half-life

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Pharmacokinetics of Multiple Doses

- Consider the case of multiple daily doses
- Now see saw-tooth drug concentration profile due to peak and trough fluctuation
- Simply string together 1° abs/1° elim graphs
- Achieve $C_{ss}$ after ~4 half-lives: quantify average $[D]_p$ at $t > 4 \times t_{1/2}$

$C_{ss}$ usually attained at $\sim 4 \times t_{1/2}$

$C_{ss} = \frac{F \cdot \text{dose}}{CL \cdot T} = \frac{F \cdot \text{dose}}{k_{el} \cdot V_d \cdot T}$

$C_{ss} =$ steady-state concentration (mg/mL)
$F =$ fractional bioavailability
$CL =$ blood clearance (mL/min)
$T =$ dosage interval (min)
Dose in mg
Pharmacokinetics Web Sites

• Excellent web site for pharmacokinetics: [http://www.boomer.org/c/p1/index.html](http://www.boomer.org/c/p1/index.html)

• JAVA calculator for plotting blood concentrations approaching steady-state: [http://www.boomer.org/c/p1/Ch15/Fig57/Fig57.html](http://www.boomer.org/c/p1/Ch15/Fig57/Fig57.html)