20.201 Mechanisms of Drug Action

Lecture #18: Pharmacokinetics
October 31, 2005
Review

• Dose-response

• Protein binding, drug transport(ers)

• Metabolism

• NOW: PHARMACOKINETICS
Circulatory System and Drug Distribution

Image removed due to copyright restrictions.

Figure by MIT OCW.
Portal Circulation and Enterohepatic Circulation

• Unique circulation of blood from gut to liver: all venous blood from stomach and intestines proceeds via portal vein directly to liver.

• Poses problem for development of orally-active drugs: can achieve nearly complete removal of drug by metabolism in one pass through the liver.

Figure by MIT OCW.
Process by which drug leaves site of absorption and enters tissues

(1) Blood flow: rate varies widely as function of tissue structure/function:

<table>
<thead>
<tr>
<th>Organ/Tissue</th>
<th>Resting Blood Flow (ml/min)</th>
<th>ml/min/100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>1350 (27%)</td>
<td>95</td>
</tr>
<tr>
<td>Muscle</td>
<td>750 (15%)</td>
<td>4</td>
</tr>
<tr>
<td>Kidney</td>
<td>1100 (22%)</td>
<td>360</td>
</tr>
<tr>
<td>Heart</td>
<td>200 (4%)</td>
<td>70</td>
</tr>
<tr>
<td>Skin</td>
<td>300 (6%)</td>
<td>3</td>
</tr>
<tr>
<td>Brain</td>
<td>700 (14%)</td>
<td>50</td>
</tr>
<tr>
<td>Bronchi</td>
<td>100 (2%)</td>
<td>25</td>
</tr>
<tr>
<td>Other</td>
<td>500 (10%)</td>
<td></td>
</tr>
</tbody>
</table>

(2) Capillary structure:
- Most capillaries are “leaky” and do not impede diffusion of drugs
- Blood-brain barrier formed by high level of tight junctions between cells
- BBB is impermeable to most water-soluble drugs

(3) Plasma protein binding: Albumin!
# Blood Cells

<table>
<thead>
<tr>
<th>Classes</th>
<th>Cell Type</th>
<th>Products</th>
<th>Function</th>
<th>Size</th>
<th>Number</th>
<th>Lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes</td>
<td>Erythrocytes</td>
<td>Hemoglobin</td>
<td>O₂ transport</td>
<td>7.5x2.5 um</td>
<td>5x10⁶/ul (M) 4x10⁶/ul (F)</td>
<td>120 days</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>Neutrophils</td>
<td>Oxidative chemicals</td>
<td>Bacterial phagocytosis</td>
<td>15 um</td>
<td>5000/ul</td>
<td>6-7 hr blood</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>Eosinophils</td>
<td>Inflamm. modulating chemicals</td>
<td>Parasite defense, mod. of inflamm.</td>
<td>15 um</td>
<td>300/ul</td>
<td>1-4 d tissues</td>
</tr>
<tr>
<td></td>
<td>Basophils</td>
<td>Histamine, heparin</td>
<td>Allergic reactions</td>
<td>15 um</td>
<td>100/ul</td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>Monocytes</td>
<td>Lysosomal enzymes</td>
<td>Phagocytosis of viruses, protozoa, dead cells</td>
<td>20 um</td>
<td>500/ul</td>
<td>12-100 hr blood</td>
</tr>
<tr>
<td>Mononuclear</td>
<td>B-Lymphocyte</td>
<td>Antibodies (IgG, IgM, IgE)</td>
<td></td>
<td>6-18 um</td>
<td>2-3000/ul</td>
<td></td>
</tr>
<tr>
<td>Leukocytes</td>
<td>T-Lymphocyte</td>
<td>Cytokines, etc.</td>
<td></td>
<td>6-18 um</td>
<td>2-3000/ul</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Killer Cells</td>
<td></td>
<td></td>
<td>6-18 um</td>
<td>2-3000/ul</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>Platelets</td>
<td>Blood clotting elements</td>
<td>Clot formation</td>
<td>2-4 um</td>
<td>3x10⁵/ul</td>
<td>10 days</td>
</tr>
</tbody>
</table>
# Proteins in blood

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Mol. Wt.</th>
<th>G/dL</th>
<th>μM</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>66,500</td>
<td>4.5</td>
<td>670</td>
<td>Chemical transport, plasma oncotic pressure</td>
</tr>
<tr>
<td>Globulins (α, β, γ) immunoglobulins (IgG, etc.)</td>
<td>150,000</td>
<td>1.5-2</td>
<td>130</td>
<td>Humoral Immunity</td>
</tr>
<tr>
<td>lipoproteins</td>
<td></td>
<td></td>
<td></td>
<td>Lipid and chemical transport</td>
</tr>
<tr>
<td>transferrin</td>
<td>79,000</td>
<td>0.2</td>
<td>17</td>
<td>Iron transport</td>
</tr>
<tr>
<td>ceruloplasmin</td>
<td>150,000</td>
<td>0.3</td>
<td>20</td>
<td>Copper transport</td>
</tr>
<tr>
<td>gluco/mucoprotein:haptoglobin</td>
<td>53,000</td>
<td>0.05</td>
<td>0.8</td>
<td>Binds to hemoglobin</td>
</tr>
<tr>
<td>coagulation factors (~10)</td>
<td></td>
<td></td>
<td></td>
<td>Clot formation</td>
</tr>
<tr>
<td>steroid-binding globulin</td>
<td></td>
<td></td>
<td></td>
<td>Transport of steroid hormones</td>
</tr>
<tr>
<td>thyroid hormone-binding globulin</td>
<td></td>
<td></td>
<td></td>
<td>Transport of thyroxine</td>
</tr>
<tr>
<td>macroglobulins</td>
<td>42,000</td>
<td>0.4-1</td>
<td>9</td>
<td>Acute phase reactant, chemical transport</td>
</tr>
<tr>
<td>α1-acid glycoprotein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>400,000</td>
<td>0.5</td>
<td>12</td>
<td>Clot formation</td>
</tr>
<tr>
<td>Complement proteins (~12)</td>
<td></td>
<td></td>
<td></td>
<td>Antibody-dependent responses and bacterial immunity</td>
</tr>
</tbody>
</table>
Pharmacokinetics and the Distribution of Chemicals in the Body

• Definition of Pharmacokinetics/Toxicokinetics: quantitative temporal analysis of the processes of absorption, distribution, metabolism and elimination of a chemical in the body

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

• Uses:
  ~ Pharmacology: need to determine how often to administer a drug to maintain therapeutic concentration in the blood
  ~ Toxicology: need to define the association between the concentration of a chemical in the blood or in a tissue and the progression of disease

• Approaches to pharmacokinetic analysis:
  ~ Simple compartment models
  ~ Physiologically-based pharmacokinetic models
Pharmacokinetics: Basic Concepts

Route of Administration

Absorption

Blood/Plasma

Distribution

Tissues

Route of Elimination

Routes of administration

(1) Enteral -
   • oral
   • sublingual
   • rectal

(2) Parenteral -
   • intravenous (iv)
   • intramuscular (im)
   • subcutaneous (sc)

(3) Other -
   • inhalation
   • topical
   • transdermal
Pharmacokinetics: Absorption

Quantitative aspects of absorption are important for GI, pulmonary and topical administration.

(1) Transport
   • passive
   • active

(2) pH effects

(3) Physical factors
   • blood flow:
   • surface area: lungs, 140 m²; GI tract, 300 m² (small intestine); skin, 1.5-2 m²
   • contact time
**Apparent Volume of Distribution**

Hypothetical volume into which the drug is dissolved or distributed. Limited physical interpretation but useful concept to understand water compartments.

**Total Body Water ~60% of body weight**
(calculations based on 70 kg male)

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>~8% (5-6 l)</td>
</tr>
<tr>
<td>Plasma</td>
<td>~5% (3-4 l)</td>
</tr>
<tr>
<td>Cells</td>
<td>~3%</td>
</tr>
<tr>
<td>Interstitial fluid</td>
<td>~15% (10-11 l)</td>
</tr>
<tr>
<td>Intracellular fluid</td>
<td>~40% (20-25 l)</td>
</tr>
</tbody>
</table>

- Definition: \( V_d = \text{(total amount of drug)}/(\text{plasma concentration}) \)
- Lipid soluble drugs have a high apparent volume of distribution
Amoxicillin

$V_d \sim 20 \text{ L}$

Chloroquine

$V_d \sim >10^4 \text{L}$

Figure removed due to copyright restrictions.
Basic Kinetics

- Use the example of chemical kinetics to develop concepts of pharmacokinetics

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

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

- Zero-order kinetics: \( n = 0 \)

  \( -\frac{dA}{dt} = k \cdot [A]^n \) becomes \( -\frac{dA}{dt} = k \cdot 1 \)

  - Rearrange and integrate rate equation:

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

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

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

  - 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: Zero Order

- Processes subject to zero order kinetics:
  ~ “Saturable” process: ligand molecules completely occupy available binding sites
  ~ Metabolic enzymes
  ~ Transport proteins

- Metabolic enzymes
  ~ Michaelis-Menten rate equation considerations:

\[
V = \frac{dP}{dt} = \frac{V_{\text{max}} \cdot [S]}{(K_m + [S])}
\]

~ When \([S] >> K_m\), all substrate binding sites occupied and enzyme operates at \(V_{\text{max}}\)

\[
V = \frac{dP}{dt} = \frac{V_{\text{max}} \cdot [S]}{[S]}
\]

- Examples of substrate/enzyme pairs frequently subject to zero-order kinetics in humans
  ~ Aspirin - glycine conjugation and phenolic glucuronidation
  ~ Ethanol - alcohol/aldehyde dehydrogenase
  ~ Phenytoin - CYP2C9; \(K_m \sim 5\) mg/L; therapeutic range 10-20 mg/L

- Transport proteins are just enzymes, the product of which is movement of the substrate
  ~ Glucose transporter in renal tubule cells (exceed filtered load of 320 ng/min)
  ~ Acid transporters that handle salicylates
Basic Kinetics: First Order

• First-order kinetics: \( n = 1 \)
  \( \sim -dA/dt = k \cdot [A]^n \) becomes \( -dA/dt = k \cdot [A] \)

  \( \sim \) Rearrange and integrate rate equation:
  \[
  \int -\frac{dA}{[A]_t} = k \cdot dt
  \]
  \[
  \ln([A]_t) = -k \cdot t + C \quad t = 0 \Rightarrow C = \ln([A]_0) \\
  \ln([A]_t) = -k \cdot t + \ln([A]_0)
  \]
  \[
  \ln\left(\frac{[A]_t}{[A]_0}\right) = -k \cdot t
  \]
  \[
  [A]_t = [A]_0 e^{-kt}
  \]

  \( \sim \) Rate of the reaction is dependent on substrate concentration
  \( \sim \) Rate constant \( k \) has units of reciprocal time
  \( \sim \) \( \ln(\text{Concentration}) \) versus time plot is linear

  \( \sim \) Half-life - time to decrease concentration by one-half
  \[
  \ln\left(\frac{[A]_t}{[A]_0}\right) = \ln\left(\frac{1}{2}\right) = -0.693 = -k \cdot t \\
  t_{1/2} = \frac{-0.693}{k}
  \]
First-Order Processes in the Body

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

• Absorption: 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

\[ \frac{d\text{Product}}{dt} = V = \frac{V_{\text{max}}}{K_m} \cdot [S] = k_{\text{met}} \cdot [S] \]
Pharmacokinetic Behavior

• Build an understanding of PK'S with simple models

• More complicated physiologically-based models combine many simple models

• Generally always consider elimination from blood with simple models

• Contributions to “elimination”

• Single compartment with I.V. injection

  ~ Considers the body as a single box
  ~ Rapid injection and presumed rapid (“instantaneous”) distribution
  ~ Sample compartment (blood) and quantify drug as a function of time

  ~ Zero-order - strongly linear region of concentration vs time plot
  ~ First-order - linear plot of ln(concentration) vs time
  ~ The rate constant, k, is now the elimination rate constant, $k_{el}$
  ~ Half-life = $\frac{0.693}{k_{el}}$

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

• Single compartment with absorption from gut

  ~ Factor in kinetics of absorption from gut with kinetics of elimination from blood
  ~ Distribution no longer instantaneous
  ~ Assume first-order absorption from gut (why?)
  ~ How to prove both first-order absorption and elimination?

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

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

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

- Two compartments with I.V. injection
  ~ Injected drug distributes in blood “instantaneously”
  ~ Drug moves out of blood into tissue compartment: first-order (why?)
  ~ As blood concentration falls, higher tissue concentration drives return to blood (why?)
  ~ Examine plasma concentration versus time plot in this model

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

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

\[
\alpha + \beta = k_{12} + k_{21} + k_{el} \quad A = [D]_{p0}\left(\frac{\alpha - k_{21}}{\alpha - \beta}\right)
\]

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

• Correlate single- and multi-compartment models

  ~ Graph of $[D]_{tissue}$ versus time from two compartment model is identical to graph of single compartment model with 1° absorption and 1° elimination

  ~ Thus, string together single compartment models for each entry and exit component

  ~ Don’t hassle with the complexity of ≥ 2 compartment models
Clearance

• Important concept in toxicoco- and pharmacokinetics

• Clearance represents the rate of removal of a chemical from blood, tissue, compartment or entire body

• Physical interpretation: volume of blood/tissue from which the chemical is removed in a set time period. Example: Cl = 100 ml/min means that the chemical is completely removed from 100 ml of blood every minute.

• Parameter is independent of the mechanism of removal (i.e., excretion, equilibrium binding in tissue, metabolism, etc.)

• Definitions:

\[ CL = k_{el} \cdot V_d \] where \( k_{el} \) 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.

\[ CL = \frac{\text{Dose}}{\text{AUC}_{\infty}} \] where AUC is the area under the blood/tissue concentration versus time curve over the time period \( t = 0 \) to \( t = \infty \).

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

(1) Defined as the percentage (fraction) of administered drug entering the blood.
   • AUC: area under the plasma concentration versus time curve
   • Ratio of oral (or other route) AUC to intravenous AUC

\[
CL_{\text{organ}} = Q \left( \frac{C_A - C_V}{C_A} \right) = Q \cdot E
\]

\[
F_{\text{max}} = 1 - E_H
\]

where \( F_{\text{max}} \) is the maximum oral bioavailability for a drug given by mouth, and \( E_H \) is the hepatic extraction ratio

(2) Influences
   • First pass metabolism
   • solubility - hydrophilic implies poor diffusion; hydrophobic implies insoluble in aqueous media
   • chemical stability - penicillin and acid pH
   • drug formulation - salt form, particle size, "excipients" all affect rate of dissolution

(3) Bioequivalence - relative bioavailability of two drugs
How to administer a drug

• 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 between dose rate (how many times a day), rate of absorption from gut and rate of elimination blood
  ~ eventually reach a state in which drug concentration fluctuates within a narrow window (akin to chemical kinetics with formation balancing degradation)

• Achieve $C_{ss}$ at ~4 half-lives: quantify average $[D]_p$ at $t > 4 \times t_{1/2}$

• Solve equation below for $T$

$$C_{ss} = \frac{F \cdot dose}{CL \cdot T}$$

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

$[D]_p$ Fluctuations about $C_{ss}$
• proportional to $T$ and $t_{1/2}$
• amplitude dampened by slow absorption

$C_{ss}$ usually attained at ~4 $t_{1/2}$