Drug Distribution

Objectives

- to understand the processes by which drugs distribute throughout the body
- to understand the effect of protein binding on drug distribution
- to understand the methods used to measure protein binding

Drug Distribution

- transfer of drug between regions of the body
- distribution between blood/plasma, tissues, organ, body fluids
- drug characteristics, tissue properties and blood flow determine distribution
Distribution Patterns

- drug stays within vascular system
- drug distributes throughout body water
- drug concentrates in specific tissues
- drug distributes throughout body and tissue

Drug Stays in Vascular System

- Large molecular weight or tightly bound to plasma protein
  - e.g. plasma substitutes

Drug Distributes in Body Water

- Low molecular weight molecules
  - e.g. ethanol, water (D₂O)
Drug Concentrates in Specific Tissues

- Chloroquine in liver
  - concentration 1000 times plasma concentration
- Tetracycline to bone, teeth
- Radiopharmaceuticals
- Iodine in thyroid glands
- PCBs, highly lipid soluble compounds in fat tissue

Normal Bone Scan with $^{99m}\text{Tc}$-MDP

Injection Site

Saha, G.B. 1984 Fundamentals of Nuclear Pharmacy, 2nd ed. P239 Fig 12-26
PCBs, highly lipid soluble compounds in fat tissue

- PCBs = polychlorinated biphenyls
  - Pesticide extenders ... industrial uses
  - Study in growing pigs
  - Excreted only in milk
  - http://www.epa.gov/toxteam/trtpcb1.htm

- DDT = dicophane
  - Banned in several countries

- Silent Spring by Rachel Carson, 1962

Drug Distributes throughout Tissues and Body Fluids

- Distribution determined by ability to pass through membranes, and lipid/water partition
- A common distribution pattern
- Highest concentration often in organs of elimination
  - kidney, liver, intestine
Body Water in Various Organs

Distribution Patterns

Specific Organ or Tissue, e.g. thyroid, bone, fat

General Organs, e.g. muscle, liver

Blood

Apparent Volume of Distribution

<table>
<thead>
<tr>
<th>Drug</th>
<th>Liter/Kg</th>
<th>Liter/70 Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>94 – 250</td>
<td>6600 – 17500</td>
</tr>
<tr>
<td>Nor triptyline</td>
<td>21</td>
<td>1500</td>
</tr>
<tr>
<td>Digoxin</td>
<td>7</td>
<td>500</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1.7</td>
<td>120</td>
</tr>
<tr>
<td>Theophylline</td>
<td>0.5</td>
<td>35</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>0.11</td>
<td>8</td>
</tr>
</tbody>
</table>

Apparent Volume

- Pattern 1 > 3-5 L
- Pattern 2 > 30 - 50 L (total body water)
- Pattern 3 > Very large V
  - Chloroquine 17,000 L
- Pattern 4 > 10 - 200 L
  - Lidocaine 120 L
### Test Values

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Volume (L)</th>
<th>Test Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracellular Fluid</td>
<td>13 – 16</td>
<td>Insulin, Na(^+), Br(^-), I(^-)</td>
</tr>
<tr>
<td>Plasma</td>
<td>3 – 4</td>
<td>Evans Blue, D(^+)</td>
</tr>
<tr>
<td>Intestinal Fluid</td>
<td>10 – 13</td>
<td>Albumin, Dextran</td>
</tr>
<tr>
<td>Intracellular Fluid</td>
<td>25 – 28</td>
<td>--</td>
</tr>
<tr>
<td>Total Body Water</td>
<td>40 – 46</td>
<td>Antipyrine, D(^+), Ethanol</td>
</tr>
</tbody>
</table>

### Factors Affecting Drug Distribution

- **Rate of Distribution**
  - Membrane Permeability
  - Blood Perfusion
- **Extent of Distribution**
  - Lipid Solubility
  - pH - pKa
  - Plasma Protein Binding
  - Intracellular Binding

### Membrane Permeability

The walls of capillaries are very thin, consisting of only a single layer of endothelial cells, making them highly permeable.
Capillary Walls

- quite permeable
- lipid material passes through quickly
- water soluble material more slowly
- pH and pKa influence transfer
  - renal capillaries and hepatic sinusoids allow extensive transfer
  - ‘blood-brain’ barrier restrict transfer to lipid soluble drugs

Blood Perfusion Rate

<table>
<thead>
<tr>
<th>Organ</th>
<th>Perfusion Rate (ml/min/ml)</th>
<th>% of Cardiac Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>0.02</td>
<td>5</td>
</tr>
<tr>
<td>Brain</td>
<td>0.5</td>
<td>14</td>
</tr>
<tr>
<td>Fat</td>
<td>0.03</td>
<td>4</td>
</tr>
<tr>
<td>Heart</td>
<td>0.6</td>
<td>4</td>
</tr>
<tr>
<td>Kidney</td>
<td>4.0</td>
<td>22</td>
</tr>
<tr>
<td>Liver</td>
<td>0.8</td>
<td>27</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.025</td>
<td>15</td>
</tr>
<tr>
<td>Skin</td>
<td>0.024</td>
<td>6</td>
</tr>
</tbody>
</table>

Blood Perfusion...

- % of C.O. highest for brain, kidney, liver, muscle
- Perfusion rate highest for brain, kidney, liver, heart
- Concentration should change rapidly in these organs
  - other organs: adrenals (1.2/0.2%) and thyroid (2.4/1%)
Relative Perfusion…

- thiopental gets into brain faster than into muscle
  - thiopental gets across brain or muscle quickly: perfusion limited - brain has higher perfusion [perfusion limited]
- penicillin gets into muscle more quickly than into brain
  - penicillin more polar, only slowly perfused into brain [transfer limited]

Relative Perfusion

![Diagram showing relative perfusion rates between brain and muscle]

- Brain
  - 0.5 ml/min/ml tissue

- Muscle
  - 0.025 ml/min/ml tissue

Extent of Distribution

- Plasma protein binding
  - proteins involved
  - forces involved
  - protein binding determination
  - protein binding equilibria
- Tissue localization
Plasma Protein Binding

- Proteins involved
  - Albumin
  - α<sub>1</sub>-acid glycoprotein
  - lipoprotein
  - globulins

Drugs
- Bilirubin, Bile acids, Fatty Acids, Vitamin C, Salicylates, Sulfonamides, Barbiturates, Phenytoin, Tetracyclines, Probenecid
- Adenosine, Quinacrine, Quinine, Streptomycin, Chloramphenicol, Digoxin, Ouabain, Coumarin

Binding Sites

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Binding Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin, Bile acids, Fatty Acids, Vitamin C, Salicylates, Sulfonamides, Barbiturates, Phenytoin, Tetracyclines, Probenecid</td>
<td>Acidic Agents</td>
</tr>
<tr>
<td>Adenosine, Quinacrine, Quinine, Streptomycin, Chloramphenicol, Digoxin, Ouabain, Coumarin</td>
<td>Basic Agents</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
</tr>
<tr>
<td></td>
<td>Globulins, α&lt;sub&gt;1&lt;/sub&gt;, β&lt;sub&gt;1&lt;/sub&gt;, β&lt;sub&gt;2&lt;/sub&gt;, γ</td>
</tr>
</tbody>
</table>

Forces Involved

- Electrostatic Interactions
  - -NH<sub>3</sub> of lysine and N-terminal amino acids
  - -NH<sub>2</sub> of histidine and -S- of cysteine
  - -COO- of aspartic and glutamic acid
- van der Waal’s forces
  - dipole - dipole, dipole - induced, induced dipole
- hydrogen bonding
Binding Forces

- short range forces distorted by altered protein configuration
- binding may be competitive resulting in displacement

Percent Unbound

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent Unbound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>90</td>
</tr>
<tr>
<td>Digoxin</td>
<td>77</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>50</td>
</tr>
<tr>
<td>Theophylline</td>
<td>85</td>
</tr>
<tr>
<td>Phenytine</td>
<td>14</td>
</tr>
<tr>
<td>Diazepam</td>
<td>4</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.8</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>5</td>
</tr>
<tr>
<td>Dicumarol</td>
<td>3</td>
</tr>
</tbody>
</table>

Changes in Binding

- Slight changes in binding of tightly bound drugs can be significant
  - 99 to 98% leads to double the free concentrations
  - increased activity
  - increased elimination
- e.g. phenylbutazone displacing tolbutamide
Protein Binding Determination

• Spectral changes
• Gel filtration
• Equilibrium dialysis
• Ultrafiltration

Spectral Changes

• Drug have distinct UV or visible spectra
  – absorbance versus wavelength
• Free and bound drug may have different spectra
• Fraction bound can be quantitated
• Fluorescence spectra could be used - warfarin

Spectral Changes
Gel Filtration

- Porous gel acts as a molecular sieve
- Components separated on the basis of molecular size
  - Bound drug moves quickly
  - Free drug held in gel pores
- Determination of free and bound drug

Equilibrium Dialysis

- Free drug passes freely through membrane
- At equilibrium free concentration on each side of membrane is the same
- Equilibrium after 12 - 24 hours
- Drugs must be stable
- Concentrations can be determined on either side of the membrane
Chapter 29

Ultrafiltration

- Faster separation
- Free solution in solution is forced through membrane by centrifugation
- Filtrate contains free drug concentration

![Ultrafiltration apparatus](image)

Protein Binding Equilibria with One Type of Binding Site

\[
K_a = \frac{[D] + [nP - rP]}{[DP]}
\]

- [D] is free drug concentration
- [nP] total binding sites = n • [P]
- [rP] bound sites
- [nP - rP] is free protein binding site
Binding Sites

\[ \text{Ka} = \text{Association Constant} \]
\[ \text{Ka} = \frac{\text{[Concentration Bound]}}{\text{[Protein Free]}} \cdot \frac{[\text{rP}]}{[\text{D}]} = \frac{[\text{DP}]}{[\text{P}]_{\text{total}}} \cdot \frac{\text{[Drug Bound]}}{\text{[Total Protein]}} \]

where \( r = \frac{[\text{DP}]}{[\text{P}]_{\text{total}}} \)

Scatchard Plot

\[ r = \frac{n \cdot \text{Ka}}{[\text{D}]} \]

Double Reciprocal

\[ \frac{1}{r} = \frac{1}{n} \left( \frac{1}{\text{Ka}} \right) \left( \frac{1}{[\text{D}]} \right) \]
Data Analysis - Plots

- One type of binding site
  - straight line
  - use slope and intercept
- Two or more binding sites
  - curved line plot
  - curve fitting

Tissue Localization (Binding)

- Binding to intracellular molecules, drug receptor >> pharmacological effect
- Binding to tissue protein (albumin, etc.), nucleic acids, or dissolution in lipid
  - e.g. chloroquine in liver > DNA
  - barbiturates > adipose tissue
  - tetracycline > bone
- Difficult to measure - disrupt binding

Weight Consideration

- Apparent volume of distribution, V, often proportional to body weight
  - V often reported as xxx L/kg
- Appropriate if tissue proportions similar
- Very young or old could be quite different
- Overweight or underweight quite different
  - different proportions of adipose tissue
  - e.g. antipyrine 0.62 L/kg in normal weight and 0.46 L/kg in obese individuals
Protein Binding Interaction

- One drug may displace another from the same binding site
- One drug bound may alter binding of another
- Interactions can occur when one drug displaces another
- Free drug concentration usually the important factor with drug activity
- Higher free drug concentration often causes an increase in elimination

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