Pharmacology 659

Drug Absorption, Distribution, Metabolism, and Elimination

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What Happens to a Drug that Enters the Body?

Oral Ingestion

Drug

Intestine

Drug-plasma protein complex

Intestinal absorption

Blood

Adipose tissue storage

Drug-receptor Binding

Effector tissues, Metabolism

Liver, Drug Metabolism

Bile

Drug and metabolites in stool

Volatile drugs in inspired air

Drug and metabolites in urine

Peripheral tissues, Metabolism

Kidney

Lung
Drug Absorption
## Routes of Drug Administration

<table>
<thead>
<tr>
<th>Enteral</th>
<th>Special Utility</th>
<th>Limitations/Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (p. o.)</td>
<td>• Easy</td>
<td>• Relatively slow</td>
</tr>
<tr>
<td></td>
<td>• Usually safe</td>
<td>• Less predictable</td>
</tr>
<tr>
<td></td>
<td>• Economical</td>
<td>• First pass effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patient compliance</td>
</tr>
</tbody>
</table>

- Economical
The First Pass Effect

When drugs are administered orally, they are absorbed by the mesenteric veins. These veins drain into the portal vein from which blood flows into hepatic sinusoids. For some drugs, during their first pass through the liver, before they initially enter into the systemic circulation, a substantial portion of these drugs is metabolized by the hepatocytes. Also some drugs might be metabolized to a significant degree by gastrointestinal endothelial cells.
Anatomy of Abdominal Organs

- Portal vein
- Liver
- Duodenum
- Stomach
# Drug Absorption and Surface Area in the Small Intestine

<table>
<thead>
<tr>
<th>Modification</th>
<th>Surface area cm²</th>
<th>Area Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>None: plane tube</td>
<td>3300</td>
<td>1.0</td>
</tr>
<tr>
<td>Folding of surface</td>
<td>10000</td>
<td>3.0</td>
</tr>
<tr>
<td>Addition of villi</td>
<td>100,000</td>
<td>30</td>
</tr>
<tr>
<td>Addition of microvilli</td>
<td>2000000</td>
<td>600</td>
</tr>
</tbody>
</table>
# Routes of Drug Administration

<table>
<thead>
<tr>
<th>Enteral</th>
<th>Special Utility</th>
<th>Limitations/Risks</th>
</tr>
</thead>
</table>
| Oral (p. o.) | • Easy  
• Usually safe  
• Economical | • Relatively slow  
• Less predictable  
• First pass effect  
• Patient compliance |
| Sublingual | • Rapid response  
• No first pass effect  
• Bypasses GI acids and enzymes | • Many molecules do not penetrate oral mucosa  
• Not used for irritating substances |
| Rectal    | • Unconscious patients  
• Vomiting patients | • Irregular and incomplete absorption  
• Not used for irritating substances  
• Solutions must be isotonic |
### Routes of Drug Administration

<table>
<thead>
<tr>
<th>Parenteral</th>
<th>Special Utility</th>
<th>Limitations/Risks</th>
</tr>
</thead>
</table>
| Intravenous (i.v.) | • Most rapid response  
• Permits titration of dose  
• Most suitable for irritating substances and large volumes  
• Lowest intra-individual variability | • Greatest risks: anaphylaxis, overdose, infection, embolism, vascular injury, extravasation |
| Intramuscular (i.m.) | • Moderate volumes  
• More rapid absorption than s.q. | • Not used for irritating substances  
• Sterile abscesses  
• Might interfere with diagnostic tests  
• Not to be used with anticoagulant therapy |
| Subcutaneous (s.q.) | • Slower absorption than i.m.  
• Absorption may be slowed by vasoconstriction  
• Hyaluronidase speeds absorption | • Not used for irritating substances  
• Large volumes are painful |
## Routes of Drug Administration

<table>
<thead>
<tr>
<th>Parenteral</th>
<th>Special Utility</th>
<th>Limitations/Risks</th>
</tr>
</thead>
</table>
| Intraperitoneal *(i.p.)* | • Provides large absorbing surface  
                       | • Largely used on lab animals               | • First pass effect  
                       |                                                   | • Risks: adhesions, infection, injury             |
| Topical           | • Used for local effects  
                       | • Poisons and toxins                       | • Least effective for systemic absorption |
| Intrathecal *(i.t.)* | • Local anesthetics, antibiotics  
                       | • Bypasses BBB and blood-CSF barrier      | • Risks: infections, headaches             |
| Pulmonary         | • Useful for gases, vapors, aerosols  
                       | • Very rapid absorption                    | • Not used for irritating substances  
                       |                                                   | • Very difficult to control dose                 |
Membrane Structure
Lipid Bilayer

Hydrophobic Fatty Acid Chains

Lipid

Aqueous Pore

25 Å

7-10 Å

Proteins

Lipid

Lipid Bilayer
Type of transport

Diffusion
Non-electrolytes and unionized forms of weak acids and weak bases

Filtration and bulk flow
Molecules of varying sizes

Endocytosis

Ion pair

Facilitated or active
Saturable carrier mediated
selective
competitive blocking drugs

Drug
Drug-carrier complex

Membrane
Absorbed molecules
Membrane Transport of Drugs
Passive Transport

1. Convective solute flow (solvent drag)
2. Simple diffusion
3. Channel-mediated diffusion
4. Carrier-mediated (facilitated) diffusion (uniport)

Mediated Transport
Membrane Transport of Drugs
Active Transport (Mediated)

5 ATP-mediated transport
6 symport (cotransport)
7 antiport (countertransport)

Primary Active Transport
Secondary Active Transport
Membrane Types.

Blood capillaries and renal glomerular membranes. These membranes are quite porous allowing non-polar and polar molecules (up to a fairly large size, just below that of albumin, Mol.Wt. 69,000) to pass through. This is especially useful in the kidney since it allows excretion of polar (drug and waste compounds) substances.

Renal tubules. In the kidney there are a number of regions important for drug elimination. In the tubules drugs may be reabsorbed. However, because the membranes are relatively non-porous, only lipid-soluble compounds or non-ionized species (dependent on pH and pKa) are reabsorbed.

Blood-brain barrier. The membranes between the blood and brain have effectively no pores. This will prevent many polar materials (often toxic materials) from entering the brain. However, smaller lipid materials or lipid soluble materials, such as diethyl ether, halothane, can easily enter the brain. These compounds are used as general anesthetics.
Non-brain capillary

Pinocytosis of compounds > ~25,000 daltons

Endothelial cells

Solutes move through fenestrations by passive diffusion

Brain capillary

Ion pumps (Na⁺,K⁺-ATPase)

Endothelial cells

Solutes must diffuse through two membranes
Characteristics of Drug Molecules that Influence Drug Transport Across Membranes

Lipid Solubility
Charge
Polarity
Molecular Weight
Drug in oil phase

Drug in water phase

\[ \text{Po/w} = \frac{C_{\text{oil}}}{C_{\text{water}}} \text{equilibrium} \]
Non-polar Functional Groups (lipophilic or fat soluble)

- Propane
- Cyclohexane
- Benzene
- Diethylether

- Ketones
- Carboxylic acid esters
- Halogens (F, Cl, Br)
- Amides of carboxylic acid esters
Polar Functional Groups (hydrophilic or water soluble)

- O
- NO₂

\[ \text{CO}_2\text{H} \]

- OH
- SO₃H
- NH₂
Oil/Water Partition Coefficients for a Series of Salicylic Acid Derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>$P_{o/w}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylic acid</td>
<td>0.01</td>
</tr>
<tr>
<td>Acetylsalicylic acid (Aspirin)</td>
<td>0.1</td>
</tr>
<tr>
<td>Methylsalicylate</td>
<td>0.4</td>
</tr>
<tr>
<td>Salicylamide</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Chemical structures:
- Salicylic acid
- Acetylsalicylic acid (Aspirin)
- Methylsalicylate
- Salicylamide
Partition ratio = 1

Partition ratio = 10
Comparison of Intestinal Absorption to Oil / Water Partition Coefficients for Non-dissociated Forms of Various Drugs

<table>
<thead>
<tr>
<th>Substance</th>
<th>Absorption (%)</th>
<th>Solubility in chloroform ($P_{HCCl_3}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>thiopentone</td>
<td>67</td>
<td>100</td>
</tr>
<tr>
<td>aniline</td>
<td>54</td>
<td>26.4</td>
</tr>
<tr>
<td>acetanilide</td>
<td>43</td>
<td>7.6</td>
</tr>
<tr>
<td>acetylsalicylic acid</td>
<td>21</td>
<td>2.0</td>
</tr>
<tr>
<td>barbituric acid</td>
<td>5</td>
<td>0.008</td>
</tr>
<tr>
<td>mannitol</td>
<td>&lt;2</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>

Influence of lipid solubility on absorption from the stomach

The number above each bar is the oil/water equilibrium partition coefficient.

Absorbed from stomach in 1 hr (% of dose)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Oil/Water Partition Coefficient</th>
<th>% Absorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturate</td>
<td>Approximately 1</td>
<td>Approximately 52</td>
</tr>
<tr>
<td>Secobarbiturate</td>
<td>Approximately 52</td>
<td>Approximately 580</td>
</tr>
<tr>
<td>Thiopental</td>
<td>Approximately 580</td>
<td>Approximately 580</td>
</tr>
</tbody>
</table>

The $pK_a$ values for these substances are as follows:

- Barbiturate: $pK_a 7.8$
- Secobarbiturate: $pK_a 7.9$
- Thiopental: $pK_a 7.6$
Characteristics of Drug Molecules that Influence Drug Transport Across Membranes

- Charge
- Polarity
- Molecular weight
- Lipid solubility
Acids and Bases

Acid – A compound that in aqueous solution can dissociate and release a hydrogen ion

\[ \text{RCOOH} \quad \text{RCOO}^- \]

Base – A compound that in aqueous solution can take up a hydrogen ion

\[ \text{RNH}_3^+ \quad \text{RNH}_2 \]
Henderson-Hasselbach Equation

\[ \text{HA} \rightleftharpoons A^- + H^+ \quad K_a = \frac{[A^-][H^+]}{[\text{HA}]} \]

\[ \text{BH}^+ \rightleftharpoons B^- + H^+ \quad K_a = \frac{[B^-][H^+]}{[\text{BH}^+]} \]

\(-\log K_a = -\log [H^+] - \log \frac{[A^-]}{[\text{HA}]}
\)

\(-\log K_a = -\log [H^+] - \log \frac{[B^-]}{[\text{BH}^+]}
\)
By definition, pH is the negative log of the hydrogen ion concentration \([H^+]\) and \(pK_a\) is the negative log of the equilibrium dissociation constant, \(K_a\)

\[
\begin{align*}
\text{pH} &= pK_a + \log \frac{[A^-]}{[HA]} \\
\text{pH} &= pK_a + \log \frac{[B]}{[BH^+]} \\
\text{pH} - pK_a &= \log \frac{[A^-]}{[HA]} \\
\text{pH} - pK_a &= \log \frac{[B]}{[BH^+]} 
\end{align*}
\]
Effect of pH on Ionization of Acids and Bases

- Non-ionized form (%)
- Low pH
- High pH
- pH - pK\(_a\)
Absorption of a Weak Acid ($pK_a = 4.4$)

Gastric juice (pH = 1.4) \[ \text{RCOOH} \quad \text{RCOO}^- \]

Plasma (pH = 7.4) \[ \text{RCOO}^- \quad \text{RCOOH} \]

\[
1.4 - 4.4 = \log \frac{[\text{RCOO}^-]}{[\text{RCOOH}]} = -3
\]

\[
\frac{[\text{RCOO}^-]}{[\text{RCOOH}]} = \frac{0.001}{1}
\]

Amount in gastric juice = 1.001

Gastric juice : Plasma = 1.001 : 1001

\[
7.4 - 4.4 = \log \frac{[\text{RCOO}^-]}{[\text{RCOOH}]} = 3
\]

\[
\frac{[\text{RCOO}^-]}{[\text{RCOOH}]} = \frac{1000}{1}
\]

Amount in plasma = 1001
Absorption of a Weak Base (pK\textsubscript{a} = 4.4)

Gastric juice (pH = 1.4) & Plasma (pH = 7.4) \\ & \\

\[ \text{RNH}_2 \] & \[ \text{RNH}_2 \] \\
\[ \downarrow \] & \[ \downarrow \] \\
\[ \text{RNH}_3^+ \] & \[ \text{RNH}_3^+ \]

\[
1.4 - 4.4 = \log \frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = -3
\]

\[
\frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = \frac{1}{1000}
\]

Amount in gastric juice = 1001

\[
7.4 - 4.4 = \log \frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = 3
\]

\[
\frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = \frac{1}{.001}
\]

Amount in plasma = 1.001

Gastric juice : Plasma = 1001 : 1.001
## pH of Some Body Fluids

<table>
<thead>
<tr>
<th>Fluids</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric juice</td>
<td>1.0 - 3.0</td>
</tr>
<tr>
<td>Small intestine: duodenum</td>
<td>5.0 - 6.0</td>
</tr>
<tr>
<td>Small intestine: ileum</td>
<td>8.0</td>
</tr>
<tr>
<td>Large intestine</td>
<td>8.0</td>
</tr>
<tr>
<td>Plasma</td>
<td>7.4</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>7.3</td>
</tr>
<tr>
<td>Urine</td>
<td>4.0 - 8.0</td>
</tr>
<tr>
<td>Body Fluid</td>
<td>pH Range</td>
</tr>
<tr>
<td>------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Urine</td>
<td>5.0 – 8.0</td>
</tr>
<tr>
<td>Breast milk</td>
<td>6.4 – 7.6</td>
</tr>
<tr>
<td>Contents</td>
<td></td>
</tr>
<tr>
<td>Jejunum, ileum</td>
<td>7.5 – 8.0</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.92 – 2.59</td>
</tr>
<tr>
<td>Secretions</td>
<td></td>
</tr>
<tr>
<td>Prostatic</td>
<td>6.45 – 7.4</td>
</tr>
<tr>
<td>Vaginal</td>
<td>3.4 – 4.2</td>
</tr>
</tbody>
</table>
Acids ionized: some in stomach and almost fully in intestine or in blood; therefore may be absorbed from stomach and trapped in blood.

Bases ionized: some in stomach but almost none in intestine or blood; therefore absorbed mainly from intestine.

pKa

1. antipyrine
2. diazepam
3. salicylic acid
4. phenylbutazone
5. warfarin
6. aminopyrine
7. ergotamine
8. lidocaine
9. procainamide
10. amphetamine
11. mecamylamine

Acids ionized: almost none in stomach, a little in intestine, and more in blood; therefore absorbed from stomach.

Bases ionized: almost fully in stomach and some in intestine and blood; therefore absorbed mainly from intestine; also secreted into stomach and trapped there.

C. B. Smith, M.D., Ph.D.
Effect of Acidosis (Acidification of Plasma) on Distribution of Phenobarbital – a Weak Acid with pKa = 7.3

Anesthesia deepens

Blood

Brain

Non-ionized (NI) >> Ionized (I)
Effect of Alkalosis (Alkanization of Plasma) on Distribution of Phenobarbital – a Weak Acid with pKa = 7.3
Acidic compounds (phenobarbital and salicylates)

1. are cleared much more rapidly in alkaline than in acidic urine.

2. are particularly sensitive to changes in urinary pH if the pKa is within the range of 3.0 to 7.5

3. Intravenous sodium bicarbonate is used to alkalinize the urine.

Basic compounds (amphetamines)

1. can be cleared more rapidly in acidic than in alkaline urine.

2. are particularly sensitive to changes in urinary pH if its pKa is within the range of 7.5 to 10.5

3. Acidification can be accomplished by the administration of ammonium chloride or ascorbic acid
Comparison of Chemical Properties of Drugs to Penetration into Cerebrospinal Fluid

<table>
<thead>
<tr>
<th>Drug</th>
<th>pKa</th>
<th>Partition Coefficient</th>
<th>Observed Penetration half time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopental acid</td>
<td>7.6</td>
<td>3.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>8.1</td>
<td>0.05</td>
<td>4.0</td>
</tr>
<tr>
<td>Barbital acid</td>
<td>7.5</td>
<td>0.002</td>
<td>27.0</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>3.0</td>
<td>0.12</td>
<td>115.0</td>
</tr>
<tr>
<td>Antipyrine base</td>
<td>1.4</td>
<td>0.005</td>
<td>5.8</td>
</tr>
<tr>
<td>Drug</td>
<td>pKₐ</td>
<td>Fraction non-ionized at pH 7.4</td>
<td>Partition coefficient of non-ionized form</td>
</tr>
<tr>
<td>---------------</td>
<td>-----</td>
<td>-------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Thiopental a</td>
<td>7.6</td>
<td>0.61</td>
<td>3.3</td>
</tr>
<tr>
<td>Pentobarbital a</td>
<td>8.1</td>
<td>0.83</td>
<td>0.05</td>
</tr>
<tr>
<td>Barbital a</td>
<td>7.5</td>
<td>0.56</td>
<td>0.002</td>
</tr>
<tr>
<td>Salicylic acid a</td>
<td>3.0</td>
<td>0.00004</td>
<td>0.12</td>
</tr>
<tr>
<td>Antipyrine b</td>
<td>1.4</td>
<td>&gt;0.999</td>
<td>0.005</td>
</tr>
</tbody>
</table>

a  Acid  

b  Base  

c  Effective Partition Coefficient = (Fraction non-ionized at pH 7.4) x (Partition Coefficient of non-ionized form) x 1000