Pharmacokinetics & Pharmacodynamics

- Pharmacokinetics: Bioavailability
- Pharmacodynamics: Drug-Target Interactions

Pharmacokinetic Factors that Determine Bioavailability of Drugs

**Pharmacokinetic Factors**

- General Principles of Passage of Drugs Across Biological Barriers
  - Route of Administration
  - Absorption & Distribution
    - Size
    - Lipid Solubility
    - Ionization Constant
    - Blood-Brain Barrier
The time course of drug blood level depends on route of administration.

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (PO)</td>
<td>Safe, self-administered; economical; no needle-related complications</td>
<td>Slow and highly variable absorption; subject to first-pass metabolism; less predictable blood levels</td>
</tr>
<tr>
<td>Intravenous (IV)</td>
<td>Most rapid, most accurate blood concentration</td>
<td>Onset of action cannot be readily monitored; requires sterile needles and medical technique</td>
</tr>
<tr>
<td>Intramuscular (IM)</td>
<td>Slow and even absorption</td>
<td>Localized irritation at site of injection; needs sterile equipment</td>
</tr>
<tr>
<td>Subcutaneous (SC)</td>
<td>Slow and prolonged absorption</td>
<td>Variable absorption depending on blood flow</td>
</tr>
<tr>
<td>Inhalation</td>
<td>Large absorption surface; very rapid onset</td>
<td>Irritation of nasal passages; small particles inhaled may cause lung injury</td>
</tr>
<tr>
<td>Topical</td>
<td>Localized action and effects; easy to self-administer</td>
<td>May be absorbed into general circulation</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Controlled and prolonged absorption</td>
<td>Local irritation; useful only for lipid-soluble drugs</td>
</tr>
<tr>
<td>Episoral</td>
<td>Bypasses first-pass liver; very rapid effect on CNS</td>
<td>Non-overdoses result in anticonvulsant effects; possible nerve damage</td>
</tr>
</tbody>
</table>
Pharmacokinetic Factors

- General Principles of Passage of Drugs Across Biological Barriers
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Absorption – Passive Diffusion Across Membranes & Lipid Solubility

Biological membranes are phospholipid bilayers.

Absorption – Passive Diffusion Across Membranes & Lipid Solubility

Aqueous solutions are polar environments: H₂O, dissociated inorganic electrolytes (Na⁺, Cl⁻, Mg²⁺, etc...), proteins.

Oxygen has six valence electrons and two "holes." Thus, can bond with two hydrogens. Therefore, the chemical formula for water is H₂O. Oxygen’s other four valence electrons are referred to as unshared pairs of electrons. Oxygen shares electrons with hydrogen, but pulls just a little harder on the electrons. The electrons are just a little closer to the oxygen than the hydrogens, so this is called a polar covalent bond. The sort-of positive ends on one water molecule are attracted to the sort-of negative ends on another water molecule. This is called hydrogen bonding.
Absorption – Passive Diffusion Across Membranes & Lipid Solubility

• Influence of Lipid Solubility on Rate of Absorption

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Partition Coefficient</th>
<th>% Absorbed from Stomach in 1 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbital</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Secobarbital</td>
<td>52</td>
<td>30</td>
</tr>
<tr>
<td>Thiopental</td>
<td>580</td>
<td>46</td>
</tr>
</tbody>
</table>

1 Concentration in organic (non-polar) solvent, methylene chloride, divided by concentration in water.

Pharmacokinetic Factors

• General Principles of Passage of Drugs Across Biological Barriers
  – Route of Administration
  – Absorption & Distribution
    • Size
    • Lipid Solubility
    • Ionization Constant
pH = -log[H⁺]

Most Compounds of Pharmacological Interest are Weak Electrolytes, even H₂O.

2H₂O = H₃O⁺ + OH⁻

Even in plain, distilled water, because of the hydrogen bonding, sometimes one of the hydrogen protons from one water molecule "jumps over" to one of the pairs of unshared electrons in another water molecule (leaving its electron behind). Thus ions of H₃O⁺ (hydronium ion) and OH⁻ (hydroxide ion) are formed. Somebody figured out that in one liter of pure, distilled water, there will be 0.0000001 M each of H₃O⁺ (often written as H⁺) and of OH⁻ present; pH = 7.

Absorption – Passive Diffusion Across Membranes & Ionization

Ionization of Amines by Coordinate Covalent Bond Formation.

Amines are weak electrolytes that ionize by accepting a proton (H⁺ ion). Certain atoms like O, S, and N can donate an electron pair to the naked proton of the hydrogen ion to form a coordinate covalent bond and retain the positive charge associated with the hydrogen ion. Since many drugs are organic compounds containing N, this type of reaction plays an important role in absorption of drugs by passive diffusion.

Absorption – Passive Diffusion Across Membranes & Ionization

pH = -log[H⁺]

### TABLE 1.2 pH of Body Fluids

<table>
<thead>
<tr>
<th>Fluid</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach fluid</td>
<td>1.0–3.0</td>
</tr>
<tr>
<td>Small intestine</td>
<td>5.0–6.6</td>
</tr>
<tr>
<td>Blood</td>
<td>7.35–7.45</td>
</tr>
<tr>
<td>Kidney urine</td>
<td>4.5–7.5</td>
</tr>
<tr>
<td>Saliva</td>
<td>6.2–7.2</td>
</tr>
<tr>
<td>CSF</td>
<td>7.3–7.4</td>
</tr>
</tbody>
</table>
Passive Diffusion - Effect of Ionization on Drug Absorption, ex. Aspirin

- Weak Electrolytes
  - Acids, proton donors
  - Bases, proton acceptors
- Ionization Constant ($pK_a$)
  - $HA = H^+ + A^-$
  - $B + H^+ = BH^+$
- Law of Mass Action
  - $[H^+] \times [A^-] = \text{a constant}$
  - $[BH^+] = \text{a constant}$
- $pH = -\log[H^+]$

Passive Diffusion - Effect of Ionization on Drug Absorption

- Effect of pH on Rate of Absorption of Strychnine from the Stomach
  - Ionization Constant ($pK_a$) = pH at which 50% of weak electrolyte is ionized

<table>
<thead>
<tr>
<th>pH of Solution in Stomach</th>
<th>% Undissociated Strychnine</th>
<th>Interval to Death Following Injection (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>54.0</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>150</td>
</tr>
<tr>
<td>3</td>
<td>0.001</td>
<td>Survived</td>
</tr>
</tbody>
</table>

Pharmacokinetic Factors

- General Principles of Passage of Drugs Across Biological Barriers
  - Route of Administration
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    - Ionization Constant
    - Blood-Brain Barrier
The Blood-Brain Barrier Limits Movement of I onized Molecules from Blood to Brain

Specialized Transport Processes

- Passive Diffusion
- Facilitated Diffusion
- Active Transport

Pharmacodynamics: Ligand – Receptor Interactions
Pharmacodynamic Factors

- Ligand - Receptor Binding
  - Selective
  - Specific
  - Reversible

Radioligand Binding to Receptors – Drug Potency

\[ K_d = \text{affinity/potency} \]

Concentration of ligand resulting in 50% maximal binding (\( B_{\text{max}} \))

Bioassays: Dose-Response Curve – Drug Potency

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Maximum response

Threshold

ED\(_{50}\)

ED\(_{30}\)

Dose
Dose–Response Curves for Four Analgesic Agents

Drug Antagonism – Competition Studies

Drug Efficacy versus Drug Potency
Functional Selectivity: Conformational Model of GPCRs

1. Spontaneous equilibrium
2. Ligand intrinsic efficacy

- Full agonist
- Partial agonist
- Antagonist
- Full inverse agonist

From Intrinsic Efficacy to Functional Selectivity

GPCR Functional Selectivity has Therapeutic Impact
GPCR Signal Transduction

Functional Selectivity could Improve Therapeutic Profile

Drug Safety: Comparison of ED_{50} and TD_{50}
Drug Interactions

(A) Physiological antagonism

(B) Additive effects

(C) Potentiation

TABLE 1.8 Significant Characteristics of Tolerance

Reversible when drug use stops
Dependent on dose and frequency of drug use and drug-taking environment
May occur rapidly, or after long periods of chronic use, or never
Not all effects of a drug show the same amount of tolerance
Several different mechanisms explain multiple forms of tolerance

TABLE 1.9 Types of Tolerance Exhibited by Selected Drugs

<table>
<thead>
<tr>
<th>Drug or drug class</th>
<th>Drug disposition tolerance</th>
<th>Pharmacodynamic tolerance</th>
<th>Behavioral tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Alcohol</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Morphine</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cocaine</td>
<td>-</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Caffeine</td>
<td>-</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Nicotine</td>
<td>-</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>LSD</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Behavioral Tolerance to Morphine-Induced Hyperthermia

Drug Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Psychoactive drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS stimulants</td>
<td>Amphetamine, Cocaine, Nicotine</td>
</tr>
<tr>
<td>CNS depressants</td>
<td>Barbiturates, Alcohol</td>
</tr>
<tr>
<td>Analgesics</td>
<td>Morphine, Codeine</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>Methadone, LSD, Psilocybin</td>
</tr>
<tr>
<td>Psychotherapeutics</td>
<td>Prozac, Thioridazine</td>
</tr>
</tbody>
</table>