Drug Elimination

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Elimination

Zero Order

First Order

Plasma Concentration vs. Time
Zero Order Elimination

- Constant rate of elimination per time
- No dependence/variation with [drug]
- No constant half life

\[ \text{Rate} = 5 \times [\text{Drug}]^0 \]

- Ethanol
- Phenytoin
- Aspirin
First Order Elimination

- Rate varies with concentration of drug
- Percent (%) change with time is constant (half life)
- Most drugs 1\textsuperscript{st} order elimination

\[
\text{Rate} = C \cdot [\text{Drug}]^1
\]
### Zero Order Elimination

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Amount (g)</th>
<th>Change (g)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>5</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>5</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>5</td>
<td>25%</td>
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</tbody>
</table>
# First Order Elimination

<table>
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<td>0</td>
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<td>1</td>
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<td>2</td>
<td>2.5</td>
<td>2.5</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>1.25</td>
<td>1.25</td>
<td>12.5</td>
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</tbody>
</table>
Special Types of Elimination

- Flow-dependent
- Capacity-dependent
Flow-dependent Elimination

• Some drugs metabolized so quickly that blood flow to organ (usually liver) determines elimination
• These drugs are “high extraction” drugs
• Example: Morphine
• Patients with heart failure will have ↓ clearance
Capacity-dependent Elimination

- Follows Michaelis-Menten kinetics
- Rate of elimination = \( V_{\text{max}} \cdot C / (K_m + C) \)
- “Saturatable” → High C leads to \( V_{\text{max}} \) rate
- When this happens zero order elimination occurs
- Three classic drugs:
  - Ethanol
  - Phenytoin
  - Aspirin
Urine pH

- Many drugs are weak acids or weak bases

Weak Acid: $HA \leftrightarrow A^- + H^+

Weak Base: $BOH \leftrightarrow B^+ + OH^-$
Urine pH

- Drugs filtered by glomerulus
- Ionized form gets “trapped” in urine after filtration
- Cannot diffuse back into circulation

Weak Acid: HA $\leftrightarrow$ $A^-$ + $H^+$

Weak Base: BOH $\leftrightarrow$ $B^+$ + $OH^-$
Urine pH

- Urine pH affects drug excretion
- Weak acids: Alkalinize urine to excrete more drug
- Weak bases: Acidify urine to excrete more drug

Weak Acid: $HA \leftrightarrow A^- + H^+$

Weak Base: $BOH \leftrightarrow B^+ + OH^-$
Examples

• **Weak acid drugs**
  • Phenobarbital, aspirin
  • Sodium bicarbonate to alkalinize urine in overdose

• **Weak base drugs**
  • Amphetamines, quinidene, or phencyclidine
  • Ammonia chloride (NH$_4$Cl) to acidify urine in overdose
  • Historical: Efficacy not established, toxicity severe acidosis
Drug Metabolism

• Many, many liver reactions that metabolize drugs
• Liver “biotransforms” drug
• Usually converts lipophilic drugs to hydrophilic products
  • Creates water-soluble metabolites for excretion
• Reactions classified as Phase I or Phase II
Phase I Metabolism

• Reduction, oxidation, or hydrolysis reactions
• Often creates active metabolites
• Two key facts to know:
  • Phase I metabolism can slow in elderly patients
  • Phase I includes cytochrome P450 system
Cytochrome P450

- Intracellular enzymes
- Metabolize many drugs (Phase I)
- If inhibited → drug levels rise
- If induced → drug levels fall
Cytochrome P450

- Inhibitors are more dangerous
  - Can cause drug levels to rise
  - Cyclosporine, some macrolides, azole antifungals
- Luckily, many P450 metabolized drugs rarely used
  - Theophylline, Cisapride, Terfenadine
- Some clinically relevant possibilities
  - Some statins + Inhibitor → Rhabdo
  - Warfarin
P450 Drugs
Some Examples

Inducers
- Chronic EtOH
- Rifampin
- Phenobarbital
- Carbamazepine
- Griseofulvin
- Phenytoin

Inhibitors
- Isoniazid
- Erythromycin
- Cimetidine
- Azoles
- Grapefruit juice
- Ritonavir (HIV)
Phase II Metabolism

• Conjugation reactions
  • Glucuronidation, acetylation, sulfation
• Makes very polar inactive metabolites
Slow Acetylators

- Genetically-mediated ↓ hepatic N-acetyltransferase
- Acetylation is main route isoniazid (INH) metabolism
- Also important sulfasalazine (anti-inflammatory)
- Procainamide and hydralazine
  - Can cause drug-induced lupus
  - Both drugs metabolized by acetylation
  - More likely among slow acetylators