Metabolism

Metabolism: Introduction

Adsorption
Distribution
Metabolism
Excretion
Metabolism: Introduction

Pharmacodynamics

The action of the drug on the body

Metabolism

The action of the body on the drug

Adsorption

Distribution

Metabolism

Excretion

Pharmacokinetic Phase
**Metabolism: Introduction**

Sites of Drug Metabolism:
- Intestinal walls, liver (organs)

Sites of Drug Elimination:
- Kidneys (polar compounds), Bile, feces (lipophilic compounds), lung

**Metabolism: Enzymes**

For example ester hydrolysis (Acetylcholine)

![Diagram of enzyme reaction](image)

Organic Reaction

\[
\text{(H}_3\text{C})_3\text{N}^{+} + \text{OH}^- \rightarrow \text{CH}_3\text{COO}^- + \text{(H}_3\text{C})_3\text{NCH}_{2}\text{CH}_2\text{OH}
\]

Enzymatic Reaction

![Diagram of enzymatic reaction](image)

\[
\text{R} - \text{O}^- + \text{H}_2\text{O} \rightarrow \text{R} - \text{OH} + \text{H}_3\text{O}^+
\]
Metabolism: Enzymes

Energy Profile

Drug Metabolism

For Elimination of Xenobiotics, mainly in liver.
- Oxidation
- Hydrolysis
- Reduction

- Conjugation with small molecules \(\rightarrow\) Phase II

The most important phase I enzymes are the cytochrome P450 enzymes (CYPs).
**Drug Metabolism**

**Example 1: Benzene**

- Oxidation
- Phase I

\[ \text{OH} \quad \text{pK}_a = 10.0 \]

\[ \text{OSO}_3H \quad \text{pK}_a = 3.0 \]

\[ \text{(-OSO}_3\text{H)} \]

\[ \text{O-Glucuronide} \]

**Phase II**

**Drug Metabolism**

**Example 1: Aniline**

- Conjugation
- Oxidation

\[ \text{HN} \]

\[ \text{OH} \]

\[ \text{O-Glucuronide} \]
**Drug Metabolism: Hydrolysis**

- **Procaine**:
  - Reaction: O-O-N-Et → HO
  - $t_{1/2} = 30 - 40$ minutes (primarily in gut)
  - Products:
    - COOH
    - HO-N-Et

- **Procainamide**:
  - Reaction: O-H-N-Et → COOH
  - $t_{1/2} = 1.5 - 2$ hours
  - Products:
    - COOH
    - HO-N-Et

**Drug Metabolism: Hydrolysis**

- **Lidocaine**:
  - Reaction: HO-N-Et → No Hydrolysis
  - $t_{1/2} = 2 - 4$ hours
  - Products:
    - HO-N-Et
    - H$_3$C-CH$_3$-N-Et
**Drug Metabolism: Oxidation**

*Microsomal*

a. Aromatic hydroxylation
b. Aliphatic oxidation $\rightarrow$ alcohols, ketones, acids
c. N-dealkylation $\rightarrow$ alkyl oxidation
d. O- and S-Dealkylation
e. Epoxidation
f. N-Oxidation $\rightarrow$ hydroxylamine, amine oxides
g. S-Oxidation

*Non-microsomal*

h. Amine oxidation $\rightarrow$ to aldehydes and ketones
i. Alcohol/aldehyde oxidation

**Drug Metabolism: Oxidation**

*Cytochrome P450 isozymes*

Are microsomal heme monooxygenases with MW = 35-45 kD; there are 51 CYP families with up to 10 subfamilies.

CYP oxidations require NADPH$_2$/NADP.
Drug Metabolism: Oxidation

Aromatic Hydroxylation

\[
\begin{align*}
R & \rightarrow \text{O} \\
& \rightarrow \text{OH}
\end{align*}
\]

verses

Drug Metabolism: Oxidation

\[
\begin{align*}
& \\
& H
\end{align*}
\]
Polycyclic Aromatic Hydrocarbons (PAH)

- Benzo[a]pyrene is an important PAH which has been studied extensively.
- Benzo[a]pyrene is found in chimney soot, barbecued meat and cigarette smoke.
- Metabolites of benzo[a]pyrene form adducts with DNA.
**Polycyclic Aromatic Hydrocarbons (PAH)**

Liver Enzymes → epoxide hydrolase → DNA

**Drug Metabolism: Oxidation**

*Aliphatic Hydroxylation*

R → R-OH → R-CO

2 CO₂ + R-CO → R-CO₂H
Drug Metabolism: Oxidation

- If there is a choice between an aromatic oxidation and an aliphatic oxidation, the aliphatic position is the one that is more easily oxidized.

Drug Metabolism: Oxidation

*N-Dealkylation*

\[
\begin{align*}
\text{NH}_2 & \quad \rightarrow \quad \text{C}=\text{O} \\
\text{N} & \quad \text{CH}_2\text{CH}_2\text{N}^+ \text{CH}_3 & \quad \rightarrow \quad \text{CH}_2\text{CH}_2\text{N}^+ \text{CH}_3 \quad + \quad \text{NH}_3
\end{align*}
\]
Drug Metabolism: Oxidation

S-Dealkylation

Cimetidine

Drug Metabolism: Oxidation

N- Verses O-Dealkylation in an Alkaloid

10% unchanged
40% conjugated
10% norcodeine (N-demethylation)
10% morphine (O-demethylation)
[1% of all morphine is converted to heroin]
**Drug Metabolism: Oxidation**

*General Mechanism of Dealkylations: α-Hydroxylation*

\[
\begin{align*}
RNHCH_2R^1 & \xrightarrow{[O]} \left[\begin{array}{c} R \textcolor{red}{H} \ N \textcolor{blue}{C} \ R^1 \end{array}\right] \leftrightarrow RNH_2 + O\textcolor{red}{H}R^1 \\
ROCH_2R^1 & \xrightarrow{[O]} \left[\begin{array}{c} R \textcolor{red}{O} \ H \textcolor{blue}{C} \ R^1 \end{array}\right] \leftrightarrow ROH + O\textcolor{red}{H}R^1 \\
RSCH_2R^1 & \xrightarrow{[O]} \left[\begin{array}{c} R \textcolor{red}{S} \ H \textcolor{blue}{C} \ R^1 \end{array}\right] \leftrightarrow RSH + O\textcolor{red}{H}R^1
\end{align*}
\]

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**Drug Metabolism: Oxidation**

*Epoxidation*

1. Benzene (oxidation) \(\xrightarrow{\text{oxidation}}\) Diphenyl oxide (oxidation) \(\xrightarrow{\text{oxidation}}\) Hydroquinone
2. Cyclohexane (oxidation) \(\xrightarrow{\text{oxidation}}\) Cyclohexene oxide
3. Diethylstibestrol (DES) (oxidation) \(\xrightarrow{\text{oxidation}}\) Oxysterol
Drug Metabolism: Oxidation

**N-Oxidation**

Aniline $\rightarrow$ Hydroxylamine $\rightarrow$ N-Nitrosoamine

$\text{PhNH}_2 \ [O] \rightarrow \text{PhNHOH}$

$\text{PhNHR} \ [O] \rightarrow \text{PhNHR}$

$\text{PhNR}_2 \ [O] \rightarrow \text{PhN}_2\text{R}$

**S-Oxidation**

$\text{RSR}^1 \ [O] \rightarrow \text{RSR}^1 \ [O] \rightarrow \text{RSR}^1$

Thioether  →  Sulfoxide  →  Sulfone
**Drug Metabolism: Oxidation**

**Non-Microsomal Oxidations**

**Amine Oxidation**

\[
\text{RCH}_2\text{NH}_2 \xrightarrow{H_2} \text{RCH}=\text{NH} \xrightarrow{H_2O} \text{RCH}=\text{D} \xrightarrow{H_2N} \]

**Alcohol/aldehyde Oxidation**

\[
\text{NAD} + \text{CH}_3\text{CH}_2\text{OH} \xrightarrow{\text{dehydrogenase}} \text{NADH}_2 + \text{CH}_3\text{CHO} \xrightarrow{\text{dehydrogenase}} \text{CH}_3\text{COOH} \]

**Drug Metabolism: Reduction**

\[
\text{R-NO}_2 \rightarrow \text{R-NH}_2 \quad \text{RR}^1\text{C}=\text{O} \rightarrow \text{RR}^1\text{CH-OH} \]

\[
\text{RN}=\text{NR}^1 \rightarrow \text{RHN-NHR}^1 \quad \text{R-X} \rightarrow \text{R-H} \]

Clonazepam
**Drug Metabolism: Conjugation**

- Conjugation reactions constitute phase II metabolic processes.
- These coupling reactions usually complete the degradation of a xenobiotic for excretion.
- Sometimes these are referred to as ‘building’ reactions because they are designed to further increase the aqueous solubility of a metabolized molecule.

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**Glucuronide Formation**

\[ \text{drug} - XH + \text{uridine diphosphate glucuronate (UDP)} \rightarrow \text{glycoside conjugate} \]

\( X = N, O, S \)
**Drug Metabolism: Conjugation**

**Sulfate Conjugation**

\[
\text{HO} \quad \rightarrow \quad \text{HOSO}_3
\]

**Glutathione Conjugation**

\[
\text{glutathione} \quad \rightarrow \quad \text{glutathione conjugate} \quad \rightarrow \quad \text{mercapturic acid conjugate}
\]
Drug Metabolism: Conjugation

**Acetylation**

\[
\begin{align*}
RNH_2 & \quad + \quad H_3C\text{S-CoA} & \quad \rightarrow \quad R\text{N}CH_3 \\
RCO_2H & \quad + \quad R^1\text{S-CoA} & \quad \rightarrow \quad R\text{CO}_2\text{H} \quad + \quad H_2NCH_2CO_2H
\end{align*}
\]

Factors affecting ADME Properties: Absorption

- Three factors influence absorption of a drug; solubility, concentration, and route of administration.
- Dissolution of solid dosages depend significantly on four factors.
  1. Water solubility
  2. pH of the medium
  3. The pKₐ of the drug
  4. The formulation
Factors affecting ADME Properties:

Absorption

<table>
<thead>
<tr>
<th>Route</th>
<th>Absorption Pattern</th>
<th>Limitations/Precautions/Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteral (oral)</td>
<td>Variable</td>
<td>Absorption potentially erratic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absorption potentially incomplete</td>
</tr>
<tr>
<td>Parenteral (non-oral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>Absorption circumvented</td>
<td>Immediate effects. Increase risk of adverse effects</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Prompt from aqueous soln.</td>
<td>Not suitable for large volume (suspension) Possible pain, edema</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>Prompt from aqueous soln.</td>
<td>Over or underweight patients exhibit unusual patterns of absorption Slow and sustained (suspension)</td>
</tr>
</tbody>
</table>

Factors affecting ADME Properties:

Metabolism

- Age
- Disease
- Species Differences
- Gender
- Pregnancy
- Environmental
- Enzyme Induction
- Enzyme Inhibition
- Diet
- Heredity/Genetics
Factors affecting ADME Properties: Metabolism

Enzyme Induction

Acetaminophen \[\xrightarrow{\text{CYP}}\] Ethanol \[\overset{\text{p-Quinone imine}}{\longrightarrow}\] TOXIC

Factors affecting ADME Properties: Metabolism

Enzyme Inhibition

Terfenadine (Seldane) \[\xrightarrow{\text{Erythromycin Ketoconazole}}\] Fexofenadine
Factors affecting ADME Properties: Metabolism

Diet

![Molecular structure of Terfenadine (Seldane), CYP, and Fexofenadine]

Heredit/Genetics

- "Slow Acetylators" 50% Caucasians and African-Americans
- "Fast Acetylators" Eskimos and Asian-Americans
- Egyptians and Europeans oxidation

![Molecular structures of Isoniazid and its derivatives]