یاد تو مونس روآن

فارماکولوژی دامپزشکی

فارماکولوژی پایه

حذف و متابولیسم داروها

دکتر گودرز صادقی
دانشیار فارماکولوژی

دانشکده دامپزشکی
Introduction

- The **kidneys** are the major route by which drugs are excreted from the body.
- **Non-protein-bound** drugs: filtered at the glomerulus
- **Polar drugs**: no tubular reabsorption, excreted unchanged
- **Lipid-soluble drugs**: passively diffuse through the renal tubular cells back into the plasma
  - For excretion, these drugs must first undergo biotransformation
Drug-metabolizing enzymes are found:

- Primarily: in the smooth endoplasmic reticulum of the liver
- To a limited extent: in the GI tract, kidneys, and lungs.

Chemical reactions classes:

- Phase I reactions
- Phase II reactions
Biotransformation
Introduction - 2

- Phase I reactions:
  - Oxidation
  - Reduction
  - Hydrolysis

- Phase II reactions: conjugation reactions with:
  - Glucuronide
  - Sulfate
  - Acetate
  - Glutathione
  - Amino acids
Biotransformation
Phase I Reactions - 1

- Oxidation: the most important

**Aliphatic and Aromatic Hydroxylation**

- R\(\rightarrow\) R
  - O\(\rightarrow\) OH
  - RCH\(_2\)CH\(_3\) \(\rightarrow\) RCHCH\(_3\)

**Oxidative or N-Dealkylation**

- RNHCH\(_3\) \(\rightarrow\) RNH\(_2\) + CH\(_2\)O
- ROCH\(_3\) \(\rightarrow\) ROH + CH\(_2\)O

**Deamination**

- R\(_2\)CHNH\(_2\) \(\rightarrow\) R\(_2\)CO\(_3\) + NH\(_3\)

**Desulfuration**

- R\(_2\)CS \(\rightarrow\) R\(_2\)CO

**Sulfoxide Formation**

- RSR\(^\prime\) \(\rightarrow\) RSR\(^\prime\) \(\rightarrow\) RSR\(^\prime\) \(\rightarrow\) RSR\(^\prime\)
Biotransformation
Phase I Reactions - 2

- Majority of oxidation reactions: catalyzed by cytochrome P450 (CP450) enzymes
- Non-microsomally mediated oxidation reactions are catalyzed by:
  - Monoamine oxidases (MAOs),
  - Xanthine oxidase
  - Aldehyde dehydrogenase
Biotransformation
Phase I Reactions - 3

- Hydrolysis reactions: carried out by non-specific esterases present in the liver, plasma, and GI tract.
Biotransformation
Phase I Reactions - 4

- Reduction reactions: primarily in liver microsomes

\[
\begin{align*}
\text{Reduction} \\
\text{RN} + \text{NR}^{' \prime} & \rightarrow \text{RNNH}_2 + \text{R'NH}_2 \\
\text{RNO}_2 & \rightarrow \text{RNNH}_2
\end{align*}
\]
Biotransformation
Phase I Reactions - 5

- The products of phase I reactions: often inactive metabolites
- If phase I metabolism results in the production of an active metabolite:
  - Parent compound: pro-drug
Biotransformation
Phase II Reactions - 1

- Phase I metabolites or drugs containing a polar side group such as a hydroxyl, carboxyl, amino, or sulfhydryl group: substrates for phase II reactions.

Phase II Reactions
- Conjugation of OH, COOH, NH₂, or SH Group
  - Glucuronidation
  - Acetylation
  - Sulfate Conjugation
  - Glycine Conjugation
  - O, S, and N Methylation
  - Glutathione
Biotransformation
Phase II Reactions - 2

- Phase II reaction products: highly hydrophilic and more rapidly undergo renal elimination.
- Some phase II conjugates (particularly glucuronides): substrates for specific transporters in the renal tubule or biliary canalicular membrane.
- Phase II reaction products: almost always inactive.
Biotransformation
Phase II Reactions - 3

- Glucuronyl transferases: Microsomal enzymes, primarily in the liver and kidneys
- Cats: relatively low levels of this enzyme ⇒ very slow conjugation reactions
  - Able to conjugate endogenous substrates: bilirubin, thyroxine, and corticosteroids
  - Deficient in glucuronyl transferases for: phenols and aromatic amines
● **Acetyltransferases:**
  - Present in the cells of the reticulo-endothelial system, responsible for the addition of acetyl groups
  - Dogs: relatively deficient in ATs that catalyzes acetylation of aromatic amines.

● **Sulfate**
  - Pigs: Relative deficiency
  - Cats: Easily saturated
Biotransformation
Factors Influencing Drug Biotransformation - 1

- Genetic factors
- Environmental factors
- Physiological factors

Factors Affecting Drug-Metabolizing Enzymes

<table>
<thead>
<tr>
<th>Individual Genetic Diversity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species Variation</td>
</tr>
<tr>
<td>Cats ↓ Glucuronyl transferases</td>
</tr>
<tr>
<td>Dogs ↓ Acetyltransferases</td>
</tr>
<tr>
<td>Pigs ↓ Sulfate conjugation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activation by Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
</tr>
<tr>
<td>Phenylbutazone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhibition by Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
</tr>
<tr>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Quinidine</td>
</tr>
<tr>
<td>Organophosphates</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
</tr>
</tbody>
</table>

↓ Activity in Neonatal and Geriatric Patients
↓ Activity in Chronic Hepatic Failure
Biotransformation
Factors Influencing Drug Biotransformation - 2

- Genetic polymorphism: in the expression of the CP450 enzymes

- Environmental agents and drugs:
  - Drugs that inhibit:
    - Cimetidine, chloramphenicol, quinidine, and organophosphates
  - Drugs that induce:
    - The barbiturates and phenylbutazone
Older individuals and neonates: lower enzyme activity

Liver disease: compromise the enzyme activity

Saturation of hepatic biotransformation pathways:
- Too much drug: slow drug elimination
- 2 drugs compete: slowed elimination
- **γ-Glutamyl transpeptidase:**
  - Conjugation of xenobiotics to glutathione.
  - Not an important player
  - Important in inactivating unstable and toxic intermediates.
  - Some products of phase I oxidation reactions $\Rightarrow$ reactive toxic intermediates
    - Rapid conjugation to glutathione $\Rightarrow$ ↓ toxicity.
Drug Elimination - 1

- Renal excretion: Most common mechanism for the elimination of polar drugs or their metabolites.

---

R = Side Chain  
BPD = Biotransformed Polar Drug  
PP = Plasma Protein  
D = Drug  
ND = Nonpolar Drug  
PD = Polar Drug
Drug Elimination - 2

• For most drugs or metabolites:
  - Renal elimination: filtration of non-protein-bound drugs at the glomerulus $\Rightarrow$ tubular excretion

• Some drugs:
  - Actively secreted into the tubular
  - Example: organic acids (penicillins, furosemide) and glucuronide drug metabolites
  - Excreted via the uric acid transport system
Drug Elimination - 3

- **Organic bases:**
  - Examples: Procainamide, trimethoprim, dopamine
  - Transported by a carrier that excretes histamine and choline
- **The extent of reabsorption:** Modified by changing urine pH.
Drug Elimination - 4

- Urine alkalinization: weak acids are excreted more rapidly.
  - The converse is true for weak bases.
- Renal disease: decrease the rate of drug elimination ⇒ prolongation of drug action
Other routes of drug elimination:
  - Biliary and fecal excretion

The biliary membrane: transporters for LMW organic anions and cations.

Drugs excreted in bile:
  - Excreted in the feces
  - Passively reabsorbed
Drug Elimination - 6

- Glucuronide conjugates: in GIT undergo hydrolysis by intestinal $\beta$-glucuronidases and the lipid-soluble parent drug reabsorbed.
  - This process is called enterohepatic cycling.
  - It may prolong the action of some drugs.
- Species differences in biliary excretion:
  - Good: Dogs
  - Fair: Cats
  - Poor: Humans