Topic 6 Pharmacokinetics and Drug Metabolism

Chapter 8 Patrick
Drug candidate pharmaceutics are critical: ADME

- Absorption
- Distribution
- Metabolism
- Excretion
Drug candidate pharmaceutics are critical:

Drug Administration route-

1. Oral

2. Mucous membranes
   1. Rectal
   2. Oral (buccal)

3. Topical-transdermal

4. Inhaled

5. Injected
   1. Intravenous
   2. Intramuscular
   3. Subcutaneous
   4. Intrathecal-spinal
   5. Intraperitoneal
Drug candidate pharmaceutics are critical: Formulations

1. Pills, capsules
2. Liquid
3. Patch
4. Liposome/micelle
Pharmaceutics

Therapeutic Window must be maintained by dosing

Figure 35-12
Biochemistry, Sixth Edition
© 2007 W.H. Freeman and Company
Pharmaceutics

Therapeutic Window must be maintained by dosing
Absorption

Drug Absorption, Metabolism and Excretion
http://www.cc.nih.gov/training/training/principles/schedule.html
Drug molecule factors affecting absorption and distribution

1. Acid-base properties

2. Hydrophobicity/Functional groups

3. Size
Lipinski’s rules for lousy drug absorption:
1. MW > 500
2. H-bond donors > 5
3. H-bond acceptors > 10
4. log Partition coefficient > 5
   i.e. octanol / water > 100,000:1

A “good” drug
Morphine (C₁₇H₁₉O₃N)
   Molecular weight = 285
   log(P) = 1.27

A “lousy” drug: insulin
Distribution: Serum Albumin, The distributor of non polar drugs
Seeing distribution: e.g. fluconazole

PET scan of $^{18}$F fluconazole
Metabolism/excretion

Phase I Metabolism

Oxidation

Extrahepatic microsomal enzymes
(oxidation, conjugation)

Hepatic microsomal enzymes
(oxidation, conjugation)

Hepatic non-microsomal enzymes
(acetylation, sulfation, GSH, alcohol/aldehyde dehydrogenase, hydrolysis, ox/red)
Metabolism/excretion

1. Phase 1 metabolism - Liver microsomal system

- Oxidative Reactions: Cytochrome P450 mediated
  - Formation of an inactive polar metabolite
    - Phenobarbital

![Chemical structures]

phenobarbital  \(\rightarrow\)  p-hydroxyphenobarbital  \(\rightarrow\)  p-hydroxyphenobarbital-glucuronide
Metabolism/excretion

1. Phase 1 metabolism- Liver microsomal system

- Formation of a toxic metabolite
  - Acetaminophen – NAPQI
Metabolism/excretion

Acetaminophen Metabolism

HN\text{COCH}_3
\text{OH}
~60\%
CYP2E1*
CYP1A2
CYP3A11
~35%
HN\text{COCH}_3
\text{OH}
\text{SO}_3\text{H}
NAPQI
*induced by ethanol, isoniazid
Protein adducts,
Oxidative stress
Toxicity
N-acetyl-p-benzoquinone imine
# Metabolism/excretion

## Poisoning Fatalities U.S. 2006

Categories associated with largest numbers of fatalities

<table>
<thead>
<tr>
<th>Substance</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedative/hypnotics/antipsychotics</td>
<td>382</td>
</tr>
<tr>
<td>Opioids</td>
<td>307</td>
</tr>
<tr>
<td>Cardiovascular Drugs</td>
<td>252</td>
</tr>
<tr>
<td>Acetaminophen in combination</td>
<td>214</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>210</td>
</tr>
<tr>
<td>Stimulants and street drugs</td>
<td>203</td>
</tr>
<tr>
<td>Alcohols</td>
<td>139</td>
</tr>
<tr>
<td>Acetaminophen only</td>
<td>138</td>
</tr>
</tbody>
</table>

Excerpt from Table 18

“2006 Annual Report of the American Association of Poison Control Centers' National Poison Data System”

http://dx.doi.org/10.1080/15563650701754763
Metabolism/excretion

1. Phase 1 metabolism- Liver microsomal system

- Formation of an active metabolite
  - By Design: Purine & pyrimidine chemotherapy prodrugs

```
5-FU  \rightarrow  5-FUMP

5-FU

5-FUMP
```

- Inadvertent: terfenadine – fexofenadine

```
Terfenadine
(Seldane)

Fexofenadine
(Allegra)
```
Metabolism/excretion
Cytochrome P450 Isoforms (CYPs) - An Overview

- NADPH + H⁺ + O₂ + Drug → NADP⁺ + H₂O + Oxidized Drug
- Carbon monoxide binds to the reduced Fe(II) heme and absorbs at 450 nm (origin of enzyme family name)
- CYP monooxygenase enzyme family is major catalyst of drug and endogenous compound oxidations in liver, kidney, G.I. tract, skin, lungs
- Oxidative reactions require the CYP heme protein, the reductase, NADPH, phosphatidylcholine and molecular oxygen
- CYPs are in smooth endoplasmic reticulum in close association with NADPH-CYP reductase in 10/1 ratio
- The reductase serves as the electron source for the oxidative reaction cycle
Metabolism/excretion

Electron flow in microsomal drug oxidizing system
Metabolism/excretion

CYP Families

• Multiple CYP gene families have been identified in humans, and the categories are based upon protein sequence homology
• Most of the drug metabolizing enzymes are in CYP 1, 2, & 3 families.
• CYPs have molecular weights of 45-60 kDa.
• Frequently, two or more enzymes can catalyze the same type of oxidation, indicating redundant and broad substrate specificity.
• **CYP3A4** is very common to the metabolism of many drugs; its presence in the GI tract is responsible for poor oral availability of many drugs
ROLE OF CYP ENZYMES IN HEPATIC DRUG METABOLISM

RELATIVE HEPATIC CONTENT OF CYP ENZYMES

- CYP 2C: 17%
- CYP 1A2: 12%
- CYP 3A4-5: 26%
- OTHER: 36%
- CYP2D6: 2%
- CYP2E1: 7%

% DRUGS METABOLIZED BY CYP ENZYMES

- CYP 3A4-5: 33%
- CYP 2C9: 14%
- CYP 2C19: 11%
- CYP 1A2: 14%
- CYP2D6: 23%
- CYP2E: 5%
## Human Liver Drug CYPs

<table>
<thead>
<tr>
<th>CYP enzyme</th>
<th>Level (% total)</th>
<th>Extent of variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>~13</td>
<td>~40-fold</td>
</tr>
<tr>
<td>1B1</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>2A6</td>
<td>~4</td>
<td>~30 - 100-fold</td>
</tr>
<tr>
<td>2B6</td>
<td>&lt;1</td>
<td>~50-fold</td>
</tr>
<tr>
<td>2C</td>
<td>~18</td>
<td>25-100-fold</td>
</tr>
<tr>
<td>2D6</td>
<td>Up to 2.5</td>
<td>&gt;1000-fold</td>
</tr>
<tr>
<td>2E1</td>
<td>Up to 7</td>
<td>~20-fold</td>
</tr>
<tr>
<td>2F1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2J2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3A4</td>
<td>Up to 28</td>
<td>~20-fold</td>
</tr>
<tr>
<td></td>
<td>30-60*</td>
<td>90-fold*</td>
</tr>
<tr>
<td>4A, 4B</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S. Rendic & F.J. DiCarlo, Drug Metab Rev 29:413-80, 1997  
L. Wojnowski, Ther Drug Monit 26: 192-199, 2004
## Participation of the CYP Enzymes in Metabolism of Some Clinically Important Drugs

<table>
<thead>
<tr>
<th>CYP Enzyme</th>
<th>Examples of substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A1</td>
<td>Caffeine, Testosterone, <strong>R-Warfarin</strong></td>
</tr>
<tr>
<td>1A2</td>
<td>Acetaminophen, Caffeine, Phenacetin, <strong>R-Warfarin</strong></td>
</tr>
<tr>
<td>2A6</td>
<td>17β-Estradiol, Testosterone</td>
</tr>
<tr>
<td>2B6</td>
<td>Cyclophosphamide, Erythromycin, Testosterone</td>
</tr>
<tr>
<td>2C-family</td>
<td>Acetaminophen, Tolbutamide (2C9); Hexobarbital, S-Warfarin (2C9,19); Phenytoin, <strong>Testosterone</strong>, <strong>R-Warfarin</strong>, Zidovudine (2C8,9,19);</td>
</tr>
<tr>
<td>2E1</td>
<td>Acetaminophen, Caffeine, Chlorzoxazone, Halothane</td>
</tr>
<tr>
<td>2D6</td>
<td>Acetaminophen, Codeine, Debrisoquine</td>
</tr>
<tr>
<td>3A4</td>
<td>Acetaminophen, Caffeine, Carbamazepine, Codeine, Cortisol, Erythromycin, Cyclophosphamide, S- and <strong>R-Warfarin</strong>, Phenytoin, <strong>Testosterone</strong>, Halothane, Zidovudine</td>
</tr>
</tbody>
</table>

Adapted from: *S. Rendic Drug Metab Rev* 34: 83-448, 2002  
*Also D.F.V. Lewis, Current Medicinal Chemistry, 2003, 10, 1955-1972*
Non-nitrogenous Substances that Affect Drug Metabolism

- **Grapefruit juice** - CYP 3A4 inhibitor; highly variable effects; fucocoumarins

- **St John’s wort, other herbal products**

- **Isosafrole, safrole**
  - CYP1A1, CYP1A2 inhibitor; found in root beer, perfume
EXAMPLE: a Ca^{2+} channel blocker for hypertension

Effect of Grapefruit Juice on Felodipine Plasma Concentration

5mg tablet with juice

without

EXAMPLE: a Ca\textsuperscript{2+} channel blocker for hypertension

First-Pass Metabolism after Oral Administration of a Drug, as Exemplified by Felodipine and Its Interaction with Grapefruit Juice

Human Drug Metabolizing CYPs Located in Extrahepatic Tissues

<table>
<thead>
<tr>
<th>CYP Enzyme</th>
<th>Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A1</td>
<td>Lung, kidney, GI tract, skin, placenta, others</td>
</tr>
<tr>
<td>1B1</td>
<td>Skin, kidney, prostate, mammary, others</td>
</tr>
<tr>
<td>2A6</td>
<td>Lung, nasal membrane, others</td>
</tr>
<tr>
<td>2B6</td>
<td>GI tract, lung</td>
</tr>
<tr>
<td>2C</td>
<td>GI tract (small intestine mucosa) larynx, lung</td>
</tr>
<tr>
<td>2E1</td>
<td>Lung, placenta, others</td>
</tr>
<tr>
<td>2F1</td>
<td>Lung, placenta</td>
</tr>
<tr>
<td>2J2</td>
<td>Heart</td>
</tr>
<tr>
<td>3A</td>
<td>GI tract, lung, placenta, fetus, uterus, kidney</td>
</tr>
<tr>
<td>4B1</td>
<td>Lung, placenta</td>
</tr>
<tr>
<td>4A11</td>
<td>Kidney</td>
</tr>
</tbody>
</table>
CYP Biotransformations

• Chemically diverse small molecules are converted, generally to more polar compounds.

• Reactions include:
  – Aliphatic hydroxylation, aromatic hydroxylation
  – Dealkylation (N-, O-, S-)
  – N-oxidation, S-oxidation
  – Deamination
  – Dehalogenation
Non-CYP Drug Biotransformations

- **Oxidations**
- **Hydrolyses**
- **Conjugation (Phase 2 Rxs)**
  - Major Conjugation Reactions
    - **Glucuronidation** (high capacity)
    - **Sulfation** (low capacity)
    - **Acetylation** (variable capacity)
      - Examples: Procainamide, Isoniazid
  - Other Conjugation Reactions: O-Methylation, S-Methylation, Amino Acid Conjugation (glycine, taurine, glutathione)
  - Many conjugation enzymes exhibit polymorphism
Phase II Metabolism

Conjugation Reactions
Glucuronidation

UDP-α-D-glucuronic acid

\[ \text{UDP} + \text{ROH} \quad \text{or} \quad \text{R}_3\text{N} \rightarrow \text{UGT} \]

O-glucuronide

N⁺-glucuronide

Liver has several soluble UDP-Gluc-transferases
Metabolism/excretion

Conjugation examples

- Cyclophosphamide-glutathione conjugate
- Morphine glucuronidate
- Minoxidil sulfate