Cytochrome P450

Medicamentos
Toxicidad

Cytochrome P450

Cytochrome P450

Cytochrome P450
Why Learn about Adverse Drug Reactions (ADR)?

- Over 2 MILLION serious ADRs yearly
- 100,000 DEATHS yearly
- ADRs 4th leading cause of death ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents and automobile deaths
- Ambulatory patients ADR rate—unknown
- Nursing home patients ADR rate—350,000 yearly

Institute of Medicine, National Academy Press, 2000
Major Solvable Medical Problem ADR
US as an example since hardly any information... LA

- 2.2 million severe reactions/year (783,936 death/y 2003 report Death by Medicine)
- $177 billion in increased direct health care costs per year
- Cost leader for malpractice payouts

Leading Causes of Death in U.S.
- 100,000 by properly prescribed drugs
- plus 80,000 by improperly prescribed drugs
= 180,000 Deaths by prescription drugs

HEART DISEASE
CANCER
RX
STROKE
AUTO ACCIDENTS

Sources of data: U.S. Centers for Disease Control and Prevention and Journal of the American Medical Association (JAMA); links below.
Drugs

• Estimates of 700,000 people die worldwide annually from counterfeit drugs.

• Police arrested 600 people and seized $50 million in fake goods in 13 Latin American countries (October 2010, CNN).

• Forbes reports as much as 30 percent of drugs sold in Latin America are fake.
Xenobiotics

- Thousands of xenobiotics are ingested daily by man
- Between 1 and 3 million unique chemical are found on this planet. Several thousands of new chemical are synthesized per year.
- These substances either occur naturally (coffee > 500 compounds, red wine > 400, cooked beef > 300, cigarette smoke > 1000 or are synthetic (drugs, food, additives, agricultural chemicals, industrial products, etc.)
- How does our body deal with these foreign Chemicals?
Toxicity and Detoxification

Drug metabolism

• Refers to the process by drugs are converted in the body into one or more structural derivatives (drug metabolites).

• This process is sometimes referred to as biotransformation.

• Usually the metabolites have increased water solubility which promotes their excretion.

• Metabolism may change the pharmacological activity/toxicity of the molecule.
- Detoxification Mechanisms
- Brodie – in vitro, from late 40s till the 60s.
- Cytochrome P450 enzymes (hemeproteins) play an important role in the intracellular metabolism.
- Exist in prokaryotic and eukaryotic (plants insects fish and mammal, as well as microorganisms)
- Different P450 enzymes can be found in almost any tissue: liver, kidney, lungs and even brain.
- Plays important role in drugs metabolism and xenobiotics.
Cytochromes P-450

Hydrophobic: retained in kidney

11500
More than 1200 CYPs known

In humans: 55 CYP genes and 29 pseudogenes

Substrates:
- Cholesterol
- Steroids
- Bile Acids
- Lipids
- Drugs and other xenobiotics
- ...

Renal excretion

see: Nelson et al. (1996) Pharmacogenetics
http://drnelson.utmem.edu/cytochromep450.html
What and where, endoplasmic reticulum

prosthetic group
protoporphyrin IX

Isoalloxazine ring
redox group

Flavin adenine dinucleotide

NADPH → 2e− → [FAD]

N H3C

N H3C

N H3C

N H3C

N H3C

N H3C

N H3C
In the mitochondria, NADPH-adrenodoxin reductase
Ferrous positive reduction potential allows $O_2$ binding

2$^{nd}$ electron for $O_2$ cleavage

Cytochrome P450 Cycle

CO binding spectra
CLINICAL IMPORTANCE OF CYPs

What do P450s (CYPs) do?

Which ones do I have to know?

How are they regulated?

How do diseases affect CYPs?

Which diseases are caused by CYPs?

Gene therapy with CYPs? (Mikael Oscarson)
Effects of drug metabolism on pharmacological activity or toxicity

- Most often converts an active drug to an inactive metabolite
- Phenobarbital (CYP2B6) induces (CYP3A4)
- Sometimes converts an active drug into an active drug metabolite
- Sometimes converts an active drug into a toxic metabolite (acetaminophen)
- Sometimes converts an inactive drug into an active drug (pro-drug) Zidovudine, 5-Flurouracil (intracellular); Sulfasalazine (extracellular) anticancer cyclophosphamide
- Codeine to morphine (CYP2D6)
We divide metabolism into three phases

- Phase 1: Adds functional group
  - NH2, -OH, -SH, -COOH

- Phase 2: Adds water soluble substance to form conjugate
  - Example: sulfate, glucuronic acid, Glutathione
UDP-glucuronosyltransferase

Main type of phase 2 enzyme

Represents many isozymes in two evolutionarily-related families (UGT1 and UGT2), usually overlapping substrate specificities

Catalyze “glucuronidation” reactions

\[ \text{ROH} + \text{UDPGA} \rightarrow \text{R-O-Glucuronic acid} + \text{UDP} + \text{H}_2\text{O} \]

Located in smooth endoplasmic reticulum (microsomal fraction) of the cell, especially abundant in liver
Different types of phase 1 and phase 2 reactions

- Different types of phase 1 and phase 2 reactions are catalyzed by different enzymes.

- Oxidation – Enzymes in Cytochrome P450 family most common, many other enzymes can carry out oxidations but are less common.

- Hydrolysis – Esterases, Pseudocholinesterase, acetylcholesterase, others.

- Glucuronidation- UDP-glucuronosyltransferase family.

- Sulfation – Sulfotransferase family.

- GSH- Glutathione S-transferase.
**Aliphatic Hydroxylation**

\[
R-\text{CH}_2-\text{CH}_3 \rightarrow R-\text{CH}_2-\text{CH}_2-\text{OH} \\
R-\text{CH}_2-\text{CH}_3 \rightarrow R-\text{CH}_2\text{OH}-\text{CH}_3
\]

**Aromatic Hydroxylation**

\[
R-\begin{array}{c}
\text{O} \\
\text{H}
\end{array}
\rightarrow R-\begin{array}{c}
\text{O} \\
\text{H}
\end{array}
\]

**Epoxidation**

\[
R-\text{CH}=\text{CH}-\text{CH}_3 \rightarrow R-\text{CH}-\text{CH}-\text{CH}_3
\]

\[
R-\begin{array}{c}
\text{O} \\
\text{H}
\end{array} \\
\rightarrow R-\begin{array}{c}
\text{O} \\
\text{H}
\end{array}
\]

**Dealkylation Reactions**

- **N-dealkylation**
  \[
  R-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3 \rightarrow R-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2\text{OH} \rightarrow R-\text{CH}_2-\text{CH}_2-\text{NH}_2 + \text{HCHO}
  \]

- **O-dealkylation**
  \[
  R-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3 \rightarrow R-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2\text{OH} \rightarrow R-\text{CH}_2-\text{CH}_2-\text{OH} + \text{HCHO}
  \]

- **S-dealkylation**
  \[
  R-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_3 \rightarrow R-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2\text{OH} \rightarrow R-\text{CH}_2-\text{CH}_2-\text{S} + \text{HCHO}
  \]

**N-Oxidation Reactions**

- **Primary Amines**
  \[
  R-\text{CH}_2-\text{CH}_2-\text{NH}_2 \rightarrow R-\text{CH}_2-\text{CH}_2-\text{NH}-\text{OH}
  \]

- **Secondary Amines**
  \[
  R-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3 \rightarrow R-\text{CH}_2-\text{CH}_2-\text{NOH}-\text{CH}_3
  \]

**Sulfoxidation**

\[
R-\text{CH}_2-\text{S}-\text{CH}_2\text{R} \rightarrow R-\text{CH}_2-\text{S}-\text{CH}_2\text{R}
\]

**Dehalogenation**

\[
F_3C-\text{CHBrCl} \rightarrow F_3C-\text{COOH} + \text{HCl} + \text{HBr}
\]
CYTOCHROME P450 ENZYMES IN BIOLOGY AND MEDICINE

- polymorphisms
- drug design
- mutagen activation
- therapy design
- promoters
- chemothrapeutics
- drug interactions
- endocrine disruptors
- susceptibility
- pesticides
- pollutants
- natural products
- environmental toxicology
- P450 enzymes
- carcinogenesis
- reactive oxygen
- gene regulation
- growth factors
- juvenile hormone
- retinoids
- bioteknology
- selective biocides
- flower color
- novel catalysts
- bile acids
- vitamin D
- fatty acids
- Ca++
- homeostasis
- endocrinology
- androgens
- estrogens
- adrenal steroids
- ecdysones
- phytosteroids
- progesterones
- ketones
- eicosanoids
The CYP-gene superfamily

- More than 11,000 sequences known
- Humans have 57 sequenced CYP genes and
- 59 pseudo-genes about 18 families

- *Nomenclature*
- These are grouped in 18 families (>40 % amino acid identity) and 42 (>55 %) subfamilies
Cytochrome P450 Nomenclature

CYP 3A4

- GENE for mammalian cytochrome
- Specific enzyme
- Subfamily
- Family

- CYP Substrates
- CYP Inducers
- CYP Inhibitors
<table>
<thead>
<tr>
<th>Family</th>
<th>Function</th>
<th>Members</th>
<th>Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1</td>
<td>drug and steroid (especially estrogen) metabolism</td>
<td>3 subfamilies, 3 genes, 1 pseudogene</td>
<td>CYP1A1, CYP1A2, CYP1B1</td>
</tr>
<tr>
<td>CYP2</td>
<td>drug and steroid metabolism</td>
<td>13 subfamilies, 16 genes, 16 pseudogenes</td>
<td>CYP2A6, CYP2A7, CYP2A13, CYP2B6, CYP2C3, CYP2C9, CYP2C18, CYP2C19, CYP2D8, CYP2E1, CYP2F1, CYP2J2, CYP2R1, CYP2S1, CYP2U1, CYP2W1</td>
</tr>
<tr>
<td>CYP3</td>
<td>drug and steroid (including testosterone) metabolism</td>
<td>1 subfamily, 4 genes, 2 pseudogenes</td>
<td>CYP3A4, CYP3A5, CYP3A7, CYP3A43</td>
</tr>
<tr>
<td>CYP4</td>
<td>arachidonic acid or fatty acid metabolism</td>
<td>6 subfamilies, 12 genes, 10 pseudogenes</td>
<td>CYP4A11, CYP4A22, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4F22, CYP4V2, CYP4X1, CYP4Z1</td>
</tr>
<tr>
<td>CYP5</td>
<td>thromboxane A2 synthase</td>
<td>1 subfamily, 1 gene</td>
<td>CYP5A1</td>
</tr>
<tr>
<td>CYP7</td>
<td>bile acid biosynthesis 7-alpha hydroxylase of sterol nucleus</td>
<td>2 subfamilies, 2 genes</td>
<td>CYP7A1, CYP7B1</td>
</tr>
<tr>
<td>CYP8</td>
<td>varied</td>
<td>2 subfamilies, 2 genes</td>
<td>CYP8A1 (prosacyclin synthase), CYP8B1 (bile acid biosynthesis)</td>
</tr>
<tr>
<td>CYP11</td>
<td>steroid biosynthesis</td>
<td>2 subfamilies, 3 genes</td>
<td>CYP11A1, CYP11B1, CYP11B2</td>
</tr>
<tr>
<td>CYP17</td>
<td>steroid biosynthesis, 17-alpha hydroxylase</td>
<td>1 subfamily, 1 gene</td>
<td>CYP17A1</td>
</tr>
<tr>
<td>CYP19</td>
<td>steroid biosynthesis: aromatase synthesizes estrogen</td>
<td>1 subfamily, 1 gene</td>
<td>CYP19A1</td>
</tr>
<tr>
<td>CYP20</td>
<td>unknown function</td>
<td>1 subfamily, 1 gene</td>
<td>CYP20A1</td>
</tr>
<tr>
<td>CYP21</td>
<td>steroid biosynthesis</td>
<td>2 subfamilies, 1 gene, 1 pseudogene</td>
<td>CYP21A2</td>
</tr>
<tr>
<td>CYP24</td>
<td>vitamin D degradation</td>
<td>1 subfamily, 1 gene</td>
<td>CYP24A1</td>
</tr>
<tr>
<td>CYP26</td>
<td>retinoic acid hydroxylase</td>
<td>3 subfamilies, 3 genes</td>
<td>CYP26A1, CYP26B1, CYP26C1</td>
</tr>
<tr>
<td>CYP27</td>
<td>varied</td>
<td>3 subfamilies, 3 genes</td>
<td>CYP27A1 (bile acid biosynthesis), CYP27B1 (vitamin D3 1-alpha hydroxylase, activates vitamin D3), CYP27C1 (unknown function)</td>
</tr>
<tr>
<td>CYP39</td>
<td>7-alpha hydroxylation of 24-hydroxycholesterol</td>
<td>1 subfamily, 1 gene</td>
<td>CYP39A1</td>
</tr>
<tr>
<td>CYP46</td>
<td>cholesterol 24-hydroxylase</td>
<td>1 subfamily, 1 gene</td>
<td>CYP46A1</td>
</tr>
<tr>
<td>CYP51</td>
<td>cholesterol biosynthesis</td>
<td>1 subfamily, 1 gene, 3 pseudogenes</td>
<td>CYP51A1 (lanosterol 14-alpha demethylase)</td>
</tr>
</tbody>
</table>
THE HUMAN P450 KARYOGRAM
Different members of cytochrome P450 family and “substrate specificities”

<table>
<thead>
<tr>
<th>Isozyme</th>
<th>Substrate examples</th>
<th>Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A1</td>
<td>benzo[a]pyrene</td>
<td>hydroxylation</td>
</tr>
<tr>
<td></td>
<td>7-ethoxyresorufin</td>
<td>0-de-ethylations</td>
</tr>
<tr>
<td>1A2</td>
<td>acetylaminofluorene</td>
<td>N-hydroxylation</td>
</tr>
<tr>
<td></td>
<td>phenacitin</td>
<td>0-de-ethylations</td>
</tr>
<tr>
<td>CYP2A1</td>
<td>testosterone</td>
<td>7α-hydroxylation</td>
</tr>
<tr>
<td>2A2</td>
<td>testosterone</td>
<td>15α-hydroxylation</td>
</tr>
<tr>
<td>2A3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2B1</td>
<td>hexobarbital</td>
<td>hydroxylation</td>
</tr>
<tr>
<td></td>
<td>7-pentoxyresorufin</td>
<td>0-de-ethylations</td>
</tr>
<tr>
<td>2B2</td>
<td>7-pentoxyresorufin</td>
<td>0-de-ethylations</td>
</tr>
<tr>
<td></td>
<td>7,12-dimethylbenzantrachene</td>
<td>12-methyl-hydroxylation</td>
</tr>
<tr>
<td>CYP2C</td>
<td>S-mephenytoin</td>
<td>hydroxylation</td>
</tr>
<tr>
<td>CYP2D</td>
<td>debrisoquine</td>
<td>alicyclic hydroxylation</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>p-nitrophenol</td>
<td>hydroxylation</td>
</tr>
<tr>
<td></td>
<td>aniline</td>
<td>hydroxylation</td>
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<tr>
<td>CYP3A</td>
<td>ethylmorphine</td>
<td>N-demethylation</td>
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<tr>
<td></td>
<td>aminopyrine</td>
<td>N-demethylation</td>
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<tr>
<td>CYP4A1</td>
<td>lauric acid</td>
<td>ω-hydroxylation</td>
</tr>
<tr>
<td></td>
<td>lauric acid</td>
<td>ω-1-hydroxylation</td>
</tr>
</tbody>
</table>
Metabolism of therapeutic drugs by CYPs

- CYP3A4/5: 36%
- CYP2D6: 19%
- CYP2C8/9: 16%
- CYP1A2: 11%
- CYP2C19: 8%
- CYP2E1: 4%
- CYP2B6: 3%
- CYP2A6: 3%
Most important cytochrome P450 in Humans

- CYP3A4 metabolizes 36% of therapeutic drugs
- CYP2D6  19%
- CYP2C9, 16% CYP2C19 6% = 25%
- CYP1A2, 11% CYP2A6, 3% CYP2B6 3%
- The activities of certain CYP enzymes have been associated with increased risk for cancer
The Cytochromes P450 of Human Liver

- CYP 3A: 30%
- CYP 1A2: 13%
- CYP 2C: 18%
- CYP 2A6: 4%
- CYP 2B6: 0.2%
- CYP 2D6: 1-2%
- CYP 2E1: 7%
- Unknown: 28%

P450 3 Family (1)

CYP3A4 – metabolizes 1/3 of all clinically important drugs, is the most abundant of the liver isozymes (also present in the intestine, lung, uterus, placenta, kidney, and brain). It is glucocorticoid and phenobarbital inducible. 3A5 is also present in adults.

- Its presence in the intestine, in combination with P-glycoprotein on enterocytes, is likely to govern oral bioavailability(*) of drugs
- 3A4 induction by Phenobarbital may explain the DDI between barbiturates & other drugs

CYP3A7 is present in fetal livers (ca. 50% of the total fetal P450 enzymes). It metabolizes Dehydroepiandrosterone-3-sulfate (16α-hydroxylation), as well as allylic & benzylic carbons.

(*) Oral bioavailability is the combined result of (passive) intestinal absorption and first-pass metabolism (in the liver).
CYP2E1 — known as microsomal ethanol oxidizing system (MEOS) or benzene hydroxylase, metabolizes few drugs (mostly halogenated hydrocarbons) and a range of low-MW organic compounds, e.g., dimethylformamide, acetonitrile, acetone, ethanol, benzene. **Most of its metabolites are toxic or carcinogenic.** It is expressed in liver, kidney, intestine and lung.

- Metabolizes:
  - Acetaminophen, activated to N-acetyl-para-benzoquinoneimine; Zoxazolamine.
  - General anesthetics: Enflurane, Halothane, Methoxyflurane, etc.
  - Styrene (epoxidation), Chloroform, Methylenechloride
  - Miscellaneous solvents: ethanol, glycerine, acetone, diethylether, aniline, benzene, acetonitrile, pyridine.

- Inducible by Ethanol, Isoniazid, 4-Methylpyrazole, also by diabetes and fasting.

- Ketogenic diets (high serum levels – low carb/high fat) enhance halogenated hydrocarbons metabolism in rats. **Chronic alcoholism increases the hepatotoxicity of halogenated hydrocarbons.**

- Polymorphism is mostly studied in Chinese-Asians.
Cytochrome P450scc
side chain cleavage (20-22)
CYP11A1

Cholesterol (C-27) → 22-Hydroxycholesterol → 20,22-Dihydroxycholesterol → Isocaproic aldehyde + Pregnenolone (C-21)
The role of cytochrome p450 in steroid synthesis

- Cholesterol → CYP11A1 (Mitochondria, adrenal cortex)
- Pregnenolone → CYP17
  - 3B hydroxysteroid (cytosol) dehydrogenase/ isomerase
- Progesterone → CYP17
- 11-Deoxycorticosterone → CYP21A2 (endoplasmic reticulum)
  - (DOC)
- Corticosterone → CYP11B1 (mitochondria)
  - (19 carbons + acetyl group)
- 18-OH-Corticosterone → CYP11B2 (mitochondria)
- Androgenic hormones → CYP17 (cytochrome b5 seems to be important in cleavage)
  - (DHEA)
- Cortisol → CYP11B1
- Congenital deficiencies
  - (Adrenal Hyperplasia, CAHs, +ACTH +androgenic hormones)
- Mineralocorticoid, regulates salt and water balance
- Glucocorticoid, protein, carbohydrate and lipid metabolism
Synthesis of estrogens
CYP aromatase (P450\textsubscript{arom})

Similar to CYP11A1
one enzyme involved in two hydroxylation before cleavage

Other endogenous substrates
CYP27B1  25-Hydroxy-vitamin D\textsubscript{3} to 1,25 hydroxy
CYP4F3    Leukotriene B4 less active 20 hydroxy
CYP2J2, CYP2B6, CYP4A11  Arachidonic acid
CYP26A1    Retinoic acid
Cooperativity of Cytochrome P450s in fetal and maternal organs

The placenta cannot synthesize estrogen from cholesterol lack of CYP 17.

1000 times more estrogen in pregnancy
- 15-20 mg estradiol
- 50-100 mg estriol
- 250 mg progesterone

- After 4 weeks
  - 3β hydroxysteroid (cytosol) dehydrogenase/isomerase

- Maternal circulation

- Ovaries
  - Estrogen first few weeks
  - Estriol

- Fetal adrenal gland with CYP17
  - Cholesterol to DHEA (lacks CYP17 17α-hydroxylation & cleavage (C17-20))

- Placenta
  - CYP arom (CYP19)

- Progesterone and estrogens
  - 8 weeks
  - Progesterone by the CYPscc

- Cooperativity of Cytochrome P450s in fetal and maternal organs
Receptors

Binding of ligand (L) to specific receptor (R) (AhR, CAR, PXR, or PPAR)

Binding of heterodimeric receptor partner (Arnt or RXR) to form ligand–heterodimeric receptor complex

Recognition of DNA response elements of specific P450 genes by receptor complex

Regulation of gene transcription
Increased mRNA synthesis of P450 genes
Medications that interact with the CYP450 system do so in 1 of 3 ways:

- **Inhibition** – Generally leads to decreased rates of metabolism of other drugs metabolized by the same enzyme, resulting in higher drug levels and increased potential for toxicity.
- Inhibition is usually reversible, irreversible inhibition can occur, requiring new CYP450 enzyme to be synthesized.
- Inhibition tends to occur quickly with maximal effect occurring when highest concentrations of the inhibitor are reached.
- **Example:** Ritonavir (PI) and Midazolam = ↑ sedation
Medications that interact with the CYP450 system do so in 1 of 3 ways:

- **Induction** – results in the increased clearance of concomitant medications metabolized by the same enzyme.
- The body responds by increasing the production of specific enzymes of the CYP450 system.
- ↑ enzyme production can lead to ↑ metabolism and ↓ drug concentrations
- Example: Efavirenz and methadone = withdrawal symptoms
Medications that interact with the CYP450 system do so in 1 of 3 ways:

- **Substrates** – occupy the active site of a specific CYP450 enzyme.

- The medication’s metabolism is then affected by other medications that either induce or inhibit the CYP450 enzyme system.

- Example: NNRTIs and PIs are substrates at CYP3A4 and are therefore prone to drug interactions. (Non-Nucleoside Reverse Transcriptase Inhibitors) (protease Inhibitors)

- [http://www.youtube.com/watch?v=RUUyd5bE9vQ](http://www.youtube.com/watch?v=RUUyd5bE9vQ)
Drug Interactions (Liver)

- CYP Substrate
- CYP Inhibitor

CYP Substrate → ↑ Substrate concentration → ↑ Toxicity

CYP Substrate → ↓ Substrate concentration → ↓ Efficacy

CYP Inducer
Drugs with established clinical Drug-gene Interactions and Therapeutic Recommendations

78% of drugs with guidance are processed by the main 3 CYPs

**CYP2D6**
Amitriptyline, Aripiprazole, Atomoxetine, Carvedilol, Clomipramine, Codeine, Doxepin, Duloxetine, Flecainide, Haloperidol, Imipramine, Metoprolol, Mirtazapine, Nortriptyline, Oxycodone, Paroxetine, Propafenone, Risperidone, Tamoxifen, Tramadol, Venlafaxine, Zuclopenthixol

**CYP2C9**
Acenocoumarol, Glibenclamide, Gliclazide, Glimepiride, Phenprocoumon, Phenytoin, Tolbutamide

**CYP2C19**
Citalopram/Escitalopram, Clopidogrel, Esomeprazole, Imipramine, Lansoprazole, Moclobemide, Omeprazole, Pantoprazole, Rabeprazol, Sertraline, Voriconazole

Note: Many other drugs have drug-gene interactions but clinically confirmed therapeutic recommendations are still being determined.
http://www.nature.com/clpt/journal/v89/n5/full/clpt201134a.html
## Frequency of Genetic Variation in the Cytochromes P450s

<table>
<thead>
<tr>
<th>Gene</th>
<th>Normal</th>
<th>Intermediate</th>
<th>Poor</th>
<th>Ultra</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>48%</td>
<td>35%</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>~60%</td>
<td>&gt;35%</td>
<td>2-4%</td>
<td>N/A</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>14-44%</td>
<td>24-36%</td>
<td>2-20%</td>
<td>30%</td>
</tr>
</tbody>
</table>

*There is wide variability among populations. People of Asian and African ancestry have a greatly increased prevalence of poor metabolizer. These frequencies are not well studied in the Hispanic populations.*
DISEASES CAUSED BY DEFECTS IN CYPs

CYP

• CYP1B1

• CYP11A1, CYP11B1, CYP11B2, CYP17, CYP21

• Various CYPs

DISEASE

Congenital glaucoma

Various endocrine syndromes

Risk factor for cancer
Drug Drug Interactions (3)

- **Can DDIs be lethal?** When 3A4 substrates/inhibitors are co-administered with astemizole, cisapride, pimozide or terfenadine, this can lead to QT prolongation (on the ECG signal), which in turn can lead to **fatal ventricular arrhythmia** (known as ‘Torsade des pointes’).

- As a result, Terfenadine and Cisapride are no longer in clinical use.

- The Terfenadine metabolite, Fexofenadine, is marketed as Allegra.

- **Can DDIs be beneficial?** When co-administered with Cyclosporine (a very expensive drug), 3A4 inhibitors can reduce the cost of immunosuppressive therapy. This is also valid for most HIV-1 protease inhibitors (Ritonavir, Saquinavir).

- E.g., the (poor) oral bioavailability of Saquinavir can be increased by combination with Ritonavir (3A4 inhibitor). This lead to Kaletra, a new drug combination of Ritonavir (3A4 inhibitor) and Lopinavir (3A4 substrate).
Poor metabolizers of CYP2D6 substrates are at risk for postural hypotension and antipsychotic side effects such as over sedation, because several antipsychotic agents are metabolized by CYP2D6. In a study of 45 elderly patients (five of whom were poor metabolizers) receiving perphenazine, side effects increased five fold in the poor metabolizers compared with the extensive metabolizers. Conversely, when formation of an active metabolite is essential for drug action, poor metabolizers of CYP2D6 can exhibit less response to drug therapy compared with extensive metabolizers.
Case Studies
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A 56-year-old teacher with a seizure disorder had been virtually seizure free for the past 10 years while taking phenytoin (Dilantin), 300 mg/day (blood level, 14.5 μg/mL). One summer, he received the news that he would not be rehired by the school for the coming academic year. This event, along with the recent death of his spouse from pancreatic cancer, led him into his first severe depressive episode. His friends advised him to visit a psychiatrist, and he accepted their advise. During the intake, he ruminated about how he had attended the same school as a teenager, and in his day he had been the class president and the starting quarterback. Now he was being rejected by a place he had considered a kind of home. His obsessional ruminations about his “lost glories,” as well as a full array of neurovegetative depressive symptoms, led the psychiatrist to start the patient on fluvoxamine (Luvox), with the plan to titrate to a dosage of 150 mg/day and then wait a few weeks for a possible response.
During this fluvoxamine dosage titration, the patient progressively more sedated and slightly unsteady, but he did not want to be a “complainer,” and he decided to just “stick it out,” assuming that these were transient side effect of his new medicine that would soon abate.

However, 1 week after reaching 150 mg/day, the patient lost his balance and fell down a flight of stairs in his home. He was too delirious and debilitated to summon help himself, and he basically lay there until a friend happened to drop by 6 hours later. He was immediately taken to the local emergency room, where his phenytoin blood lever was found to be 46.7 ug/mL (Mamiya et al. 2001). (check drug interactions what can you say)
PANICKED AND CONFUSED
A 35-year-old man with long-standing schizoaffective disorder, bipolar type, and alcohol dependence in full remission was being stably maintained on haloperidol (Haldol), 10mg qhs, and divalproex sodium (Depakote), 1,000 mg bid. Benztropine (Cogentin), 2 mg bid, alleviated his haloperidol-induced tremor and stiffness without causing any further side effects.
Over the previous 2 years, both of his parents died from medical causes, this led to the emergence of frequent and debilitating panic attacks.

His psychiatric hoped to alleviate these panic attacks by adding paroxetine (Paxil), 20 mg qhs, to the patient regimen; the psychiatrist declined to use benzodiazepines to avoid rekindling the patient alcohol use.

Within 5 days, the patient experienced new-onset blurring of his vision, urinary retention, and mild memory impairment.

After taking a nap and waking in the early evening, he could not remember what day it was or whether it was morning or evening, thus inducing another severe panic attack.
The psychiatrist told the patient to stop taking the paroxetine and sent him to have blood levels drawn for his medications. His haloperidol and divalproex levels were essentially unchanged and in the normal range, but his benztropine level (no baseline) was 42 ng/ml. (Levels of 25 ng/ml, are considered toxic) (Specialty Laboratories 2001). On receiving this result, the psychiatrist held the patient benztropine, and his anticholinergic symptoms abated over the next 3 days (Armstrong and Schweitzer 1997).
DISCUSSION

This is an example of an inhibitor added to a substrate.

Benztropine is believed to be a 2D6 substrate, and there have been several documented instances that suggest that 2D6-inhibiting selective serotonin reuptake inhibitors such as paroxetine (von Moltke et al. 1995) inhibit benztropine’s metabolism. The addition of paroxetine to the regimen impaired the ability of 2D6 to efficiently metabolize the benztropine, which led to an increase in the blood level of benztropine, even though the benztropine dosage had not been changed. The increased benztropine level led to the emergence of several anticholinergic symptoms (blurry vision due to mydriasis, urinary retention, and mild confusion).
Practice exercise
Clinical Case Study

A 74-year-old woman with insulin-dependent (type 2) diabetes had been taking metoprolol (Lopressor) and warfarin for atrial fibrillation and amitriptyline, 50 mg at bedtime, for diabetic neuropathy, for several years. On the death of her husband, she presented with symptoms of depression, and paroxetine was added to her medication regimen with the rationale that paroxetine would cause fewer side effects than an increase in the amitriptyline dosage. Three days after the initiation of paroxetine (Paxil) therapy, the woman was brought to the emergency department by her daughter, who had found her asleep at 11 a.m. On awakening, the patient complained of dry mouth and dizziness. Her International Normalized Ratio (INR) was 4.0.
ADD THESE 3 DRUGS TO THE LIST ON THE RIGHT

(Atrial fibrillation)
1. Metoprolol, beta blocker (Lopressor)
2. Warfarin

(diabetic neuropathy (antidepressant))
3. Amitriptyline

Let's look for possible drug interactions
Now lets add paroxetine (antidepressant) also known as Paxil to the list and look for drug interactions