Cytochrome P-450
Drug Interactions
Dr. Janell Mayer, Pharm.D., CGP

Learning Objectives
Recognize the cytochrome P450 isoenzymes that are most responsible for drug metabolism

Describe the mechanisms of action of drug interactions involving cytochrome P450 enzymes

Predict the change in plasma concentration for a substrate when an inducer or inhibitor is added

Drug Metabolism
Biotransformation
Changes molecule from lipid soluble to more water soluble
The liver utilizes 2 sets of chemical reactions
Phase I reactions
Cytochrome P450
Oxidation
Reduction
Phase II reactions
Conjugation
Cytochrome P450 Enzymes
Superfamily of heme-containing enzymes
Located primarily in the liver but also found in the small intestines, brain, lung, and kidney
More than 50 different CYPs have been identified in humans

Cytochrome P450 Enzymes
Subject to inhibition and induction
Subject to genetic polymorphisms pharmacogenomics

Cytochrome P450 Nomenclature
CYP 3 A 4
GENE for mammalian cytochrome
Family
Subfamily
Specific enzyme

GENE for mammalian cytochrome
Enzyme Inhibition

Competition for the same limited quantity of enzymes

Inhibitor + Substrate = ↓ metabolism of substrate

↓ metabolism = ↑ blood levels
Increased SE
Increased toxicity

Enzyme Induction

The opposite of enzyme inhibition
Caused when one drug increases production of the CYP enzyme

Inducer + substrate = ↑ metabolism of substrate

↑ metabolism = ↓ blood levels
Loss of efficacy

Meet the CYP’s
Cytochrome P450 Isoenzymes

CYP2C19
CYP1A2
CYP2C9
CYP2D6
CYP3A4

P450 Enzyme Content in the Liver

- CYP2E1 (9%)
- CYP2A6 (6%)
- CYP2D6 (2%)
- CYP2C (25%)
- CYP1A2 (18%)
- CYP3A4 (40%)
Proportion of Drugs Metabolized by P450 Enzymes

- CYP3A4/5: 36%
- CYP2D6: 19%
- CYP2C9: 16%
- CYP1A2: 11%
- CYP2E1: 4%
- CYP2A6: 3%
- CYP2B6: 3%
- CYP2C19: 8%

CYP2C19
Responsible for metabolizing ~ 8% of currently prescribed medications

CYP2C19
INHIBITORS
- Chloramphenicol
- Cimetidine
- Citalopram
- Esomeprazole
- Fluconazole
- Fluoxetine
- Fluoxamine
- Omeprazole
- Ticlopidine

INDUCERS
- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifampin
- St. John’s Wort
**CYP2C19 Substrates**

- Amitriptyline
- Citalopram
- Clopidogrel
- Desipramine
- Doxepin
- Esomeprazole
- Imipramine
- Methadone
- Thioridazine

---

**CYP1A2**

Responsible for the metabolism of ~11% of currently prescribed medications

---

**CYP1A2**

**INHIBITORS**

- Ciprofloxacin
- Verapamil
- Cimetidine
- Fluvoxamine
- Ethinyl estradiol
- Isoniazid

**INDUCERS**

- Rifampin
- Tobacco
- Carbamazepine
- Phenytoin
- Ritonavir
- Char-grilled meat
CYP1A2 Substrates

- Alosetron
- Clomipramine
- Clozapine
- Desipramine
- Duloxetine
- Haloperidol
- Imipramine
- Methadone
- Mexiletine
- Olanzapine
- Pamidomide
- Propranolol
- Ramelteon
- Rasagiline
- Roflumilast
- Theophylline
- Tizanidine
- (R) Warfarin
- Zolmitriptan

CYP2C9

Responsible for the metabolism of ~16% of currently prescribed medications

CYP2C9 INHIBITORS
- Amiodarone
- Sulfamethoxazole
- Metronidazole
- Fluconazole
- Fluoxetine
- Fluvasitatin
- Fluvoxamine
- Gemfibrozil

CYP2C9 INDUCERS
- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifampin
- St. John’s Wort
CYP2C9 Substrates
Amitriptyline  Carvedilol  Clomipramine  Fluvasatin  Imipramine  Phenytoin  Ramelteon  Voriconazole  (S) Warfarin

CYP2D6

2% of enzyme content in the liver
Responsible for metabolizing ~ 19% of currently prescribed medications.
Most polymorphic
83 variants

CYP2D6 INHIBITORS
Bupropion  Cinacalcet  Darifenacin  Dronedarone  Duloxetine  Fluoxetine  Mirabegron  Paroxetine  Quinidine  Sertraline  Terbinafine

CYP2D6 INDUCERS
Not inducible
CYP2D6 Substrates

- Amitriptyline
- Aripiprazole
- Chlorpromazine
- Codeine
- Desipramine
- Dextromethorphan
- Donepezil
- Doxepin
- Duloxetine
- Flecainide
- Fluphenazine
- Iloperidone
- Imipramine
- Metoprolol
- Nortriptyline
- Perphenazine
- Risperdone
- Tamoxifen
- Trazodone

CYP3A4

- Responsible for the metabolism of ~36% of currently prescribed medications
- Major isoenzyme found in the intestines
- Substrates, inducers, and inhibitors for CYP3A4 are often substrates, inducers, and inhibitors for P-glycoprotein

CYP3A4 INHIBITORS

- Amiodarone
- Clarithromycin
- Diltiazem
- Erythromycin
- Fluconazole
- Grapefruit
- Itraconazole
- Ketoconazole
- Protease Inhibitors
- Voriconazole

CYP3A4 INDUCERS

- Carbamazepine
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rifampin
- St. John’s Wort
**CYP3A4 Substrates**

- Aliskiren
- Alprazolam
- Amiodarone
- Atorvastatin
- Buspirone
- Colchicine
- Cyclophosphamide
- Cyclosporine
- Haloperidol
- Paroxetine
- Prednisone
- Nifedipine
- Quinidine
- Simvastatin
- Tacrolimus
- (R) Warfarin

**P-Glycoprotein**

**Efflux pump**

- Pumps molecules out of the cell

**Located**

- Intestinal epithelium
- Liver cells
- Kidney
- Blood-brain barrier

**Crystal structure of human P-Glycoprotein**

**P-Glycoprotein Substrates**

- Amiodarone
- Clarithromycin
- Cyclosporine
- Erythromycin
- Digoxin
- Itraconazole
- Lovastatin
- Phenytoin
- Paroxetine
- Pravastatin
- Quinidine
- Risperidone
- Simvastatin
- Tacrolimus
- Tamoxifen
- Verapamil
P-Glycoprotein

**INHIBITORS**
- Amiodarone
- Clarithromycin
- Diltiazem
- Erythromycin
- Grapefruit
- Fluconazole
- Itraconazole
- Ketoconazole
- Telithromycin
- Verapamil

**INDUCERS**
- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifampin
- St. John’s Wort
- Venlafaxine

---

**CYP450 Inhibitors**
- Erythromycin
- Clarithromycin
- Ciprofloxacin
- Fluconazole
- Itraconazole
- Ketoconazole
- Amiodarone
- Fluoxetine
- Paroxetine
- Fluvoxamine
- Grapefruit juice
- Protease inhibitors

---

**CYP450 Inducers**
- Carbamazepine
- Phenytoin
- Phenobarbital
- Rifampin
- St. John’s Wort
Resources
Indiana University:
http://medicine.iupui.edu/clinpharm/ddis/main-table/

FDA:
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

CYP450 Drug Interactions

CYP2C19
Clopidogrel (Plavix®) + Omeprazole (Prilosec®)
Clopidogrel = substrate
Omeprazole = inhibitor

Clopidogrel $\xrightarrow{CYP2C19}$ Active metabolite
Clopidogrel + Omeprazole = $\downarrow$ Effectiveness of clopidogrel
**CYP1A2**
Theophylline (Uniphyl®) + Ciprofloxacin (Cipro®)
Theophylline = substrate
Ciprofloxacin = Inhibitor

Theophylline $\xrightarrow{\text{CYP1A2}}$ Inactive metabolite
Theophylline + Ciprofloxacin $\xrightarrow{\uparrow}$ Increased toxicity of theophylline

**CYP2C9**
Sulfamethoxazole (Bactrim®) + Warfarin (Coumadin®)
Sulfamethoxazole = Inhibitor
Warfarin = substrate
Warfarin = (S)warfarin + (R)warfarin
(S)warfarin $\rightarrow$ CYP2C9
(R)warfarin $\rightarrow$ CYP3A4

(S)Warfarin $\xrightarrow{\text{CYP2C9}}$ Inactive metabolite
Sulfamethoxazole + Warfarin $\xrightarrow{\uparrow}$ INR

**CYP2D6**
Tamoxifen (Nolvadex®) + Fluoxetine (Prozac®)
Tamoxifen = substrate
Fluoxetine = Inhibitor

Tamoxifen (prodrug) $\xrightarrow{\text{CYP2D6}}$ Active metabolite

Tamoxifen + Fluoxetine $\xrightarrow{\downarrow}$ Effectiveness of tamoxifen
Summary

Major drug interactions are caused by either inhibition or induction of drug metabolizing enzymes.

Understanding the mechanism of the drug-drug interaction allows the practitioner to predict the change in plasma concentration.

Recognizing medications that are either strong inhibitors or inducers allows for alternative therapies to avoid drug-drug interactions.
### References


