

*Principles of Cytochrome P-450
Drug Interactions*

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Pre-Test

1. What 6 cytochrome enzymes have been estimated to be responsible for 90% or more of human drug oxidation?
2. Name 4 factors that affect the cytochrome P-450 system.
3. True or False: Enzyme induction tends to occur more quickly than enzyme inhibition
4. Which antifungal would least-likely interact with simvastatin?
 1. Itraconazole
 2. Terbinafine
 3. Ketoconazole
 4. Fluconazole
5. Which is a characteristic of CYP1A2?
 1. Broad substrate specificity
 2. Subject to genetic polymorphism
 3. Inhibited by cigarette smoke
 4. High substrate specificity

The Adverse Drug Event Prevention Study estimated an overall event rate of 6.5 per 100 admissions in U.S. hospitals, of which 28% were judged preventable.

Ref 1

Retrospective prescription audits of community-based practices have shown prevalence rates of potential drug interactions in the range of 4-6%.

Ref 2

Although only an estimated 10-15% of potential interactions are clinically significant, they may be serious enough to account for approximately 3% of medical hospital admissions.

Ref 2

Case Study
Ref 3

- 45 y/o premenopausal female diagnosed w/major depressive disorder 10 year ago
- Treated w/fluoxetine successfully for 12 months & has been free of depressive symptoms for 8-9 years
- 1 year ago, diagnosed with estrogen receptor positive invasive breast cancer

Case Study (cont.)

Ref 3

- Underwent
 - Surgery
 - Chemotherapy
 - Radiation therapy
- Treated with tamoxifen for past 6 months
- Tolerated tamoxifen well except for hot flashes
- Recently experienced depressive symptoms and sought treatment from her psychiatrist

Case Study Questions:

Ref 3

- What drugs are effective against both depression and hot flashes in women with breast cancer?
- Would any of these drugs compromise the efficacy of tamoxifen or increase its toxicity through a drug-drug interaction?

Objectives

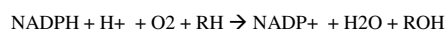
- To define the cytochrome P-450 enzyme system
- To recognize factors affecting the system
- To describe characteristics of hepatic CYP-450 isoenzymes
- To predict drug interactions
- To identify strategies to avoid and manage drug interactions

The CYP-450 enzyme system is a system of enzymes responsible for the formation of several endogenous chemicals and in the oxidative metabolism of exogenous drugs.

Ref 4

P-450 is involved in the metabolism of:

- Drugs
- Steroids
- Carcinogens



Ref 5

CYP family of enzymes

- Found in liver, small intestine, lungs, kidneys, placenta
- Consists of > 50 isoforms
- Major source of catalytic activity for drug oxidation
- Only a few enzymes are involved in drug metabolism

Ref 6

It's been estimated that 90% or more of human drug oxidation can be attributed to 6 main enzymes:

- CYP1A2
- CYP2C9
- CYP2C19
- CYP2D6
- CYP2E1
- CYP3A4

Ref 7

Nomenclature: CYP1A2

- CYP = Cytochrome
- 1 = Family (>40% homology of amino acid sequence)
- A = Subfamily (>59% homology of amino acid sequence)
- 2 = Gene

Ref 4

Definitions:

- Substrate = the substance acted upon
- High substrate specificity = only a few drugs fit into the active site of the isoenzyme
- Broad substrate specificity = a greater number of drugs fit into the active site of the isoenzyme

Factors affecting the CYP450 system:

- Environment (cigarette smoke)
- Diet (char-broiled foods, grapefruit juice)
- Other drugs (enzyme inducers/inhibitors)
- Genetics

Genetic polymorphism

- A gene's ability to exist in an alternate form or alternate gene forms
- May cause people to be slow or fast metabolizers
- Has been shown to affect 2C9, 2C19, and 2D6

Ref 8

CYP-450 Genetic Polymorphisms

Ref 9

Enzyme	Genetic Polymorphism	Examples of Drugs
CYP2D6	2D6	Codeine, Oxycodone, Tricyclic Antidepressants
CYP2C9	2C9	Warfarin, Phenytoin, NSAIDs
CYP2C19	2C19	Pantoprazole, Rabeprazole
CYP2D6	2D6	Codeine, Oxycodone, Tricyclic Antidepressants
CYP3A4	3A4	Statins, Benzodiazepines, Immunosuppressants

Isoenzyme induction:

- Generally hastens the metabolism and diminishes the duration and intensity of drugs metabolized by the induced enzyme
- May increase a drug's pharmacologic effect if the drug's metabolites are active
- May hasten the conversion of pro-drugs to their active forms, thus increasing their effect

Strong enzyme-inducing compounds include:

- Barbiturates
- Rifampin
- Griseofulvin
- Phenytoin
- Carbamazepine
- Chronic EtOH
- PAH's (poly-aromatic hydrocarbons)

Time course for induction:

- Depends on drug dose & pharmacokinetics
- Is related to time taken to reach steady state plasma levels (approx. 5 half-lives) and rate of enzyme synthesis

Ref 4

Isoenzyme inhibition:

- Generally slows the metabolism & increases the duration & intensity of drugs metabolized by the inhibited enzyme.
- May increase the pharmacologic effect if a drug's metabolites are inactive
- May slow the metabolism of pro-drugs to their active forms & decrease their effect
– e.g. tamoxifen (2D6), clopidogrel (2C19, 3A4)

Isoenzyme inhibition:

- Drugs can inactivate isoenzymes
- Drugs can compete for binding at the active sites of the enzyme
- Enzyme inhibition tends to occur more quickly than induction

Ref 4

Enzyme-inhibiting drugs:

- Quinolone antibiotics
- Cimetidine (but not famotidine, nizatidine, ranitidine)
- Macrolides
- Antifungals
- Valproate

Ref 4

The players:

- CYP1A2
- CYP2C9
- CYP2C19
- CYP2D6
- CYP3A4

CYP1A2

- High substrate specificity
- Primarily responsible for demethylating methylxanthines like caffeine and theophylline *Ref 10*
- Genetic polymorphisms are rare

CYP1A2 Substrates of note:

- Caffeine
- Theophylline
- Clozapine
- Tacrine
- Olanzapine
- Rasagiline

CYP1A2 Inducers of note:

- Char-broiled foods
- Cigarette smoke
- Carbamazepine
- Barbiturates
- Phenytoin
- Rifampin

CYP1A2 Inhibitors of note:

- Fluvoxamine
- Mexiletine
- Quinolones
- Tacrine
- Zafirlukast
- Zileuton

Ref 9

Drug interactions of note associated with 1A2:

- Theophylline with 1A2 inhibitors/inducers
- Use of tacrine in Alzheimers patients can double theophylline levels *Ref 4*
- Quinolones can increase caffeine levels
- Response to clozapine should be monitored whenever an inhibitor/inducer co-administered

The 2C subfamily:

- Comprises about 20% of all the CYP450s in the liver
- The most abundant of six 2C isozymes is 2C9
- 2C9 metabolizes ASA, many NSAIDs, sulfonamides, phenytoin, & S-warfarin
- 2C19 metabolizes diazepam, omeprazole, and the TCAs
- 2C9 & 2C19 are subject to genetic polymorphism

Ref 11

2C9 Substrates of note:

- Many NSAIDs
- Losartan (activation)
- S-warfarin
- Glyburide, glimepiride, glipizide
- Phenytoin

CYP2C9 Inducers of note:

- Barbiturates
- Rifampin
- Carbamazepine

CYP2C9 Inhibitors of note:

- Isoniazid
- Fluconazole
- Metronidazole
- Co-trimoxazole
- Amiodarone

Drug interactions of note associated with 2C9:

- Monitor patients on anti-coagulation therapy with warfarin when inhibitor/inducer is co-administered
- Monitor patients on phenytoin therapy when inhibitor/inducer is co-administered

Ref 9

CYP2C19 Substrates of note:

- Diazepam
- Lansoprazole/Omeprazole/Rabeprazole
- Amitriptyline (minor)
- Imipramine
- Clopidogrel

CYP 2C19 Inducers of note:

- Rifampin
- Barbiturates
- Phenytoin
- Primidone
- St. John's Wort

Ref 9

CYP2C19 Inhibitors of note:

- Fluoxetine
- Fluvoxamine
- Fluconazole
- Omeprazole
- Oxcarbazepine
- Isoniazid
- Clopidogrel

Ref 9

Proton Pump Inhibitors & Clopidogrel

Ref 12

- Available data suggest that omeprazole is the proton pump inhibitor most likely to have a significant interaction with clopidogrel
 - Further studies are needed to determine that an interaction between the other PPIs and clopidogrel does not exist
 - If both a PPI and clopidogrel are indicated, pantoprazole should be used since it is the PPI least likely to interact with clopidogrel
- (Some sources recommend an H₂-blocker instead of a PPI but it may offer less effective gastric protection)

CYP2D6

- 2D6 is subject to genetic polymorphism
- Accounts for only 4% of hepatic CYP enzymes but is more unique in its metabolic profile (*Ref 7*)
- Is involved in the metabolism of a large number of drugs
- There are no known inducers of 2D6

Ref 4

One study in Kentucky indicated that 1/5th of its subjects had genotypes associated with extremes in 2D6 that may have affected their response to 2D6 medications.

Ref 13

CYP2D6 Substrates of note:

- Thioridazine/haloperidol/risperidone
- Many antidepressants
- Codeine/DM/hydrocodone/oxycodone/tramadol
- Encainide/flecainide/propafenone
- Some Beta-blockers
- Tamoxifen

CYP2D6 Inducers of note:

- None known

CYP2D6 Inhibitors of note:

Ref 9

- Quinidine
- Some SSRI's
- Terbinafine
- Haloperidol
- Amiodarone
- Bupropion
- Duloxetine
- Diphenhydramine

Drug interactions of note associated with 2D6:

- Antiarrhythmics' (e.g. flecainide, mexiletine, propafenone) effect may be increased with co-administration of 2D6 inhibitors
- Tamoxifen and 2D6 inhibitors
- Amitriptyline/imipramine with SSRI's (Paroxetine & fluoxetine, especially)
- Paroxetine/fluoxetine with thioridazine

When TCAs are used with fluoxetine, the TCA dose should be reduced by 75% when 20mg/day of fluoxetine is added.

Ref 4

CYP3A4

- The most common isoenzyme found in the liver
- Broad substrate specificity
- Also found in the small bowel
- Does not exhibit polymorphism but patients can have widely differing drug plasma levels because of varying amounts of enzyme production

Ref 4

CYP3A4 Substrates of note:

- Alprazolam/diazepam/triazolam/Zolpidem
- Cyclosporin
- Diltiazem/verapamil
- Nifedipine/amlodipine/felodipine
- R-warfarin
- Quinidine/disopyramide/propafenone
- Clopidogrel
- Amiodarone
- Statins (not fluvastatin or pravastatin)
- Buspirone
- CBZ
- Nefazodone
- Quetiapine
- Fentanyl
- Theophylline
- Protease inhibitors
- Efavirenz

CYP3A4 Inducers of note:

- CBZ
- Barbiturates
- Phenytoin
- Rifampin
- Griseofulvin

CYP 3A4 Inhibitors of note:

- Imidazole antifungals
- Macrolides
- Isoniazid
- Nefazodone
- Diltiazem/verapamil
- Fluvoxamine
- Delavirdine/indinavir/nelfinavir/ritonavir/saquinavir
- Cyclosporin
- Zafirlukast
- Grapefruit juice

Drug interactions of note associated with 3A4:

- Ventricular arrhythmias associated with QT interval prolongation have been seen when 3A4 inhibitors are co-administered with terfenadine, astemizole, cisapride.
- Rhabdomyolysis has been associated with co-administration of statins and 3A4 inhibitors

Ref 14

Drug interactions of note associated with 3A4 (cont.):

- Symptomatic hypotension may occur when 3A4 inhibitors are given with some dihydropyridine calcium antagonists
- Excessive sedation may result from co-administration of 3A4 inhibitors with some benzodiazepines (midazolam, triazolam, alprazolam, or diazepam) or non-benzodiazepines (zolpidem, buspirone)

Ref 14

Drug interactions of note associated with 3A4 (cont.):

- Ataxia can occur with carbamazepine following addition of a 3A4 inhibitor
- Ergotism can occur with ergot alkaloids following addition of a 3A4 inhibitor

Ref 14

Beneficial drug interactions with 3A4:

- Co-administration of a 3A4 inhibitor with cyclosporin
- Some HIV protease inhibitors (saquinavir) have low bioavailability that can be increased by the addition of ritonavir

Ref 14

Strategies:

By comparison

HMG-CoA reductase inhibitors:

Associated with 2 uncommon but important S.E.s

1. Asymptomatic elevation in liver enzymes
2. Skeletal muscle abnormalities

Ref 11

*Not all statins are cleared by
CYP3A4.*

Statin substrates for 3A4:

- Simvastatin
- Lovastatin
- Atorvastatin

*Fluvastatin and rosuvastatin are
metabolized by 2C9. Thus, they're
not affected by 3A4 inhibition.*

*Pravastatin is not metabolized
by CYP-450 isozymes.*

Ref 9

Pravastatin

There are no known interactions where it is recommended to avoid concomitant use.

(Ref 15)



AntiFungals

Ketoconazole & itraconazole are potent inhibitors of 3A4.

Clinical interactions with fluconazole & 3A4 substrates are of lesser magnitude and are generally observed only with fluconazole doses of $\geq 200\text{mg/day}$.

Ref 16

Fluconazole & miconazole are potent inhibitors of 2C9.

They may therefore interact with phenytoin, warfarin, sulfamethoxazole, and losartan.

Ref 16



Terbinafine

- Is a potent inhibitor of 2D6
- Remember that tamoxifen is metabolized by 2D6 to its active metabolite

Terbinafine (cont.)

Ref 9

- Terbinafine may increase levels/effects of:
 - TCAs
 - Selected beta-blockers
 - Carvedilol
 - Metoprolol
 - Propranolol
 - Flecainide, mexiletine, propafenone
 - Thioridazine
 - Other 2D6 substrates



The Macrolides

Macrolide/CYP-450 drug interactions of note:

Macrolide/benzodiazepines

- Alprazolam
- Midazolam
- Triazolam
- Diazepam
- (non-benzodiazepines zolpidem & buspirone)

Macrolide/Benzodiazepines

- Clarithromycin & erythromycin enhanced all the pharmacodynamic effects of triazolam. The greatest impairment was associated with clarithromycin. Azithromycin produced no effect on the kinetics or dynamics of triazolam.

Ref 17

Macrolide/Benzodiazepines

- Erythromycin showed a 3 fold increase in Cmax & > 4 fold increase in AUC with midazolam
- Clarithromycin reduced clearance of midazolam & a 3.6 fold increase in AUC with midazolam
- Azithromycin showed no interaction

Ref 17

Macrolide/Benzodiazepines

- Erythromycin showed a 62% increase in AUC, 60% reduction in clearance, and > 2 fold increase in elimination half-life of alprazolam
- Conclusion: Co-administration of macrolides (except azithromycin) should be avoided or dose of BZD substantially reduced

Ref 17

Macrolide/Quinidine

- Erythromycin decreased total clearance & increased the inhibition of both hepatic & intestinal 3A4
- Quinidine serum concentrations should be closely monitored

Ref 17

Macrolide/Statins

- Erythromycin increased AUC of simvastatin in serum 6 fold. Erythromycin should be avoided with pts on simvastatin.
- In order to reduce the risk of rhabdomyolysis, it's been suggested that when giving erythromycin, lovastatin daily dose should be reduced to 20mg/day.

Ref 17

Macrolides/Statins (cont.)

Case reports in a systematic screening of the World Health Organization ADR database, Vigibase, are suggestive that interactions between azithromycin and statins resulting in rhabdomyolysis may occur.

Ref 25

Macrolide/Warfarin

- The unpredictability of macrolide interactions with warfarin requires careful monitoring

Ref 17

Macrolide/Theophylline

- Erythromycin & clarithromycin decreased theophylline clearance by 20-25%
- In one study the kinetics of theophylline was not altered by azithromycin BUT a case report has been published of a moderate interaction of azithromycin with theophylline
- Recommend monitoring theophylline levels

Ref 17

Macrolide/Ergot alkaloids

- Ergot alkaloids are contraindicated with erythromycin and clarithromycin
- No cases yet reported with azithromycin but all are best avoided

Ref 17

Benzodiazepines

Metabolism of benzodiazepines

- Mainly by 3A4 including hydroxylation (triazolam, midazolam, diazepam, alprazolam), demethylation (diazepam), and nitroreduction (clonazepam)
- 3-OH benzodiazepines are not metabolized by CYPs but directly conjugated (lorazepam, oxazepam, temazepam)

Ref 18

Benzodiazepines

- Cimetidine significantly increased the plasma AUC of alprazolam & triazolam
- Omeprazole reduced the clearance of diazepam 27% and its half-life increased by 36%

Ref 18

Grapefruit juice anyone?

Grapefruit juice

- 1989: Report of decreased clearance of felodipine with grapefruit juice
- Both reversible & irreversible inhibition of 3A4
- Substrate must be that of 3A4 w/a low oral bioavailability due to extensive 1st pass metabolism

Ref 19

Grapefruit juice

- The substrate's biotransformation by 3A4 in the g.i. tract must account for a major component of this presystemic extraction
- It affects only p.o. drugs, not parenteral

Ref 19

Large magnitude of grapefruit interaction

- Lovastatin
- Simvastatin
- Buspirone
- Amiodarone

Ref 19

Moderate magnitude of grapefruit juice interaction

- Felodipine
- Nicardipine
- Nifedipine
- Atorvastatin
- Cyclosporin
- Tacrolimus
- Diazepam
- Carbamazepine
- Nefazodone
- Midazolam
- Quetiapine
- Sildenafil

Ref 19

Other Combinations

Repaglinide with gemfibrozil

- Repaglinide in combination with gemfibrozil is contraindicated according to gemfibrozil prescribing information
- Repaglinide is a substrate for CYP2C8 and gemfibrozil inhibits 2C8; increased repaglinide AUC 8.1-fold
- Combined use of repaglinide, gemfibrozil, and itraconazole increased repaglinide AUC 19.4-fold

Ref 20

Colchicine: Non-dihydropyridine Calcium Channel Blockers

- Diltiazem & verapamil are CYP3A4 inhibitors
 - The 1st study to evaluate drug-drug interactions between verapamil & colchicine
 - Similar to other studies with diltiazem
 - Recommend alternative Ca-channel blocker or colchicine dose reduction for pts on verapamil or diltiazem
- Watch out for other 3A4 inhibitors too

(Ref 26)

Herbals

- Phenylzine = avoid ginseng
- TCAs = avoid yohimbine
- Liquorice = may potentiate action of corticosteroids
- Betel nuts have cholinergic effects

Ref 21

Herbals (cont.)

- Warfarin = avoid ginkgo, garlic, dong quai or danshen, others
- St. John's Wort may interact with SSRIs, alprazolam, verapamil, cyclosporin, digoxin, & case reports of oral contraceptives
 - SJW induces 3A4 & P-GP
 - Watch for evidence of serotonin syndrome w/SSRIs

Ref 9

Discontinuing Drugs

- Don't overlook drug interactions that may occur when drugs are discontinued
- Consider the effect of smoking cessation on prescribed medications *Ref 22*
 - Warfarin
 - Olanzapine
 - Clozapine
 - Theophylline

Software

- How often is it updated?
- Is information in the system from a primary source or is a recognized drug interaction text used?
- Are flags cross-referenced with text you can read more on?
- Is there a phone contact for questions you may have?

Ref 23

Software (cont.)

- How are urgent items or "Dear Health Professional" letters from manufacturers entered into the system?
- Does the pharmacy maintain a procedure to update pharmacists on interactions that are not in the computer yet?

Ref 23

Consider:

- The pharmacist should be the primary gate-keeper to drug interactions
- Pts receiving potentially toxic drugs should receive baseline & ongoing monitoring of drug blood levels & renal & liver function
- More up-to-date, detailed computer programs linking pt, lab, and drug data should be developed to prevent significant ADEs
- Well-designed epidemiologic studies of significant ADEs are needed

Ref 24

Case Study Revisited:

Ref 3

- What drugs are effective against both depression and hot flashes in women with breast cancer?
- Would any of these drugs compromise the efficacy of tamoxifen or increase its toxicity through a drug-drug interaction?

Questions?

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Post-Test

1. Which cytochrome enzyme is responsible for metabolizing tamoxifen to its active metabolite?
2. Which drug would most likely present a problem for a patient taking clopidogrel?
 1. Cetirizine
 2. Omeprazole
 3. Ranitidine
 4. Pantoprazole
3. Which of the following drugs are best avoided if a person is taking repaglinide?
 1. Hydrochlorothiazide
 2. Lisinopril
 3. Gemfibrozil
 4. Atorvastatin
4. Name 3 benzodiazepines largely glucuronidated and unlikely to be affected by 3A4 inhibitors.
5. Which of the following statins is not metabolized by the CYP-450 system?
 1. Lovastatin
 2. Pravastatin
 3. Rosuvastatin
 4. Simvastatin