Cytochrome P450
Effects of its metabolism on Drug Response, Interactions, and Adverse Effects

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Variance in drug response among persons of different ethnic origins depend on:

- CYP450 enzyme polymorphism (genetic variability)
- Genetic variations in other drug-metabolizing enzymes, drug transporters, and drug receptors.

Cytochrome P450 (CYP450) enzymes are essential for:

- Synthesis of cholesterol, steroids, prostacyclins, and TX A2.
- Detoxification of foreign chemicals
- Metabolism of drugs
- CYP450 enzymes are bound to membranes in cells (Cyto), contain a Heme Pigment (chrome and P) that absorbs light at a wavelength of 450 nm.

- Expressed in liver, small intestine (reducing drug bioavailability), lungs, placenta, and kidneys.

- > 50 enzymes present, but 6 of them metabolize 90% of drugs, 2 most significant are CYP3A4 and CYP2D6.

- Genetic variability in CYP450 influence the response to drugs.
CYP450 can be inhibited or induced by drugs \(\rightarrow\) drug-drug interactions \(\rightarrow\) adverse reactions or therapeutic failures.

Interactions with warfarin, antidepressants, antiepileptic and statins often involve CYP450 enzymes.

Knowledge in this regard helps minimize the possibility of adverse drug reactions and interactions.

Genotype tests can determine the specific enzyme polymorphism, but its routine use may not improve the overall outcomes.
Pharmacokinetics

- 1/15 persons may exaggerate response to standard doses of beta blockers or no response to tramadol due to CYP450 genetic variability (polymorphism).

- A specific gene encodes each CYP450 enzyme.

- Every person inherits one genetic allele from each parent.

- (Wild Type) in normal individuals and (Variant) in those with reduced or no activity.
Polymorphism occurs when a variant allele replaces one or both wild-type alleles.

- Two copies of variant alleles = poor metabolizers
- One wild-type and one variant allele have reduced enzyme activity
- Multiple copies of wild-type alleles, which results in excess enzyme activity. This phenotype is termed an “ultrarapid” metabolizer.
A 68 y/o F taking warfarin, whose condition was well controlled on a stable dose, has recently been difficult to anticoagulate to a therapeutic level. Review of her medications reveals the addition of monthly fluconazole for recurrent vulvovaginal candidiasis. The physician recognizes the drug interaction between warfarin and fluconazole as a potential cause and switches the patient to an alternate antifungal agent. The patient’s INR quickly stabilizes.

As shown in this example, physicians should be cautious when prescribing a drug known to be a CYP450 inhibitor or inducer.

The target drug may need to be substituted or the dose adjusted to prevent a potential decrease or increase in metabolism.
A 35 y/o F with panic disorder was treated with paroxetine. She developed unrelated hypertension, for which the physician prescribed 50 mg ER metoprolol per day. The patient became symptomatically orthostatic after a few days and presented to the emergency department. In this example, metoprolol, metabolized by CYP2D6, was present in higher serum levels in the patient because of the use of paroxetine.

Daily usual dose of simvastatin can cause myopathy and rhabdomyolysis if a potent CYP450 inhibitor is added.

Some drugs, such as tramadol or losartan, are not therapeutic until they are metabolized to active compounds. They may cause an exaggerated therapeutic effect or adverse effect when a CYP450 inducer is added.

Conversely, if a CYP450 inhibitor is combined with a prodrug, or a person is a poor metabolizer of a prodrug, therapeutic failure is likely to result because of little or no production of the active drug.
Drug Interactions

- Many drug interactions are due to an altered CYP450 metabolism.

- Terfenadine, astemizole, and cisapride were withdrawn from the U.S. market because its metabolic inhibition by other drugs led to fatal arrhythmias.

- The CCB (mibefradil) was withdrawn from the U.S. market due to its potent enzyme inhibitory effect that resulted in toxic levels of other cardiovascular drugs.

- Drugs interact with the CYP450 system in several ways.
  - Drugs may be metabolized by one or multiple CYP450 enzymes.
Drugs that affect CYP450 metabolism are called either inhibitors or inducers.

The extent of inhibition by CYP450 inhibitors depends on the dose and the ability of the inhibitor to bind to the enzyme.

Inhibitory effects usually occur immediately.
- Drugs may be intentionally combined to take advantage of CYP450 inhibition. Ritonavir is added to lopinavir to increase its level in serum.

- Inducers increase CYP450 activity by increasing enzyme synthesis thus induction effects happen delayed due to the half life of inducer, for example:
  - Rifampin (short half life) effects onset in 24 hours
  - Phenobarbital (long half life) effects onset in one week
CYP450 Inhibitors

- Amiodarone
- Cimetidine
- Ciprofloxacin
- Metronidazole
- Ritonavir
- Trimethoprim/Sulfamethoxazole
- Isoniazid
- Erythromycin, Clarithromycin
- Itraconazole, Fluconazole, Ketoconazole
- Terbinafine

- Paroxetine, Fluxitin
- Quinidine
- Diltiazem, Verapamil
- Grapefruit juice
- Diphenhydramine
- Gemfibrozil
- Acute alcohol use
CYP450 Inducers

- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifampin
- Tobacco
- St. John's Worts
- Modafinil
- Griseofulvin
- Chronic alcohol use
Examples of Drug Interactions Involving CYP450 System

- Amiodarone and metronidazole (CYP3A4 and 2C9 inhibitors) increase the level of Warfarin and thus increased risk of bleeding.

- Carbamazepine, phenobarbital, phenytoin (CYP3A4 inducers) and cause unplanned pregnancy who take OCPs containing Ethinyl estradiol.

- Clarithromycin, erythromycin, telithromycin (CYP3A4 inhibitors) cause myopathy or rhabdomyolysis if used with Simvastatin. Or may cause hypotension and QT prolongation if used with Verapamil.
- Diltiazem and verapamil are CYP3A4 inhibitors and may cause immunosuppression if used with prednisolone.

- Fluoxetine and Paroxetine (CYP2D6 inhibitors) may increase extrapyramidal effects of Risperidone, or may decreased the effects of Tramadol if used together.

- Grapefruit juice is a CYP3A4 inhibitor and may cause dizziness and serotonin syndrome if added to Buspirone.

- Terbinafine is a CYP2D6 inhibitor and increase the level of amitryptalin and nortriptyline thus leads to increased dry mouth, dizziness, and cardiac toxicity.
Key Recommendations for Practice

1. Genotype testing may predict persons who are poor metabolizers or are nonresponsive to drugs metabolized by CYP450 enzymes.

2. Genetic variations in CYP450 metabolism should be considered when patients exhibit unusual sensitivity or resistance to drug effects at normal doses.

3. Patients should be monitored closely for the development of adverse drug effects or therapeutic failures when a potent CYP450 enzyme inhibitor or inducer is added to drugs metabolized by one or more CYP450 enzymes.
4. Severe toxicity can result if CYP450 enzyme inhibiting drugs are added to:

- atypical antipsychotics
- Benzodiazepines
- Cyclosporine
- Statins
- Warfarin
5. Always use caution when adding the following substances to medications that patients are taking:

- Amiodarone
- Antiepileptic drugs
- Antidepressants
- Anti-TB drugs
- Grapefruit juice
- Macrolide
- Ketolide antibiotics
- Calcium channel blockers
- Protease inhibitors.
<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Potent inhibitors*</th>
<th>Potent inducers†</th>
<th>Substrates</th>
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</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Amiodarone (Cordarone), cimetidine (Tagamet), ciprofloxacin (Cipro), fluvoxamine (Luvox$)</td>
<td>Carbamazepine (Tegretol), phenobarbital, rifampin (Rifadin), tobacco</td>
<td>Caffeine, clozapine (Clozaril), theophylline</td>
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<tr>
<td>CYP2C9</td>
<td>Amiodarone, fluconazole (Diflucan), fluoxetine (Prozac), metronidazole (Flagyl), ritonavir (Norvir), trimethoprim/sulfamethoxazole (Bactrim, Septra)</td>
<td>Carbamazepine, phenobarbital, phenytoin (Dilantin), rifampin</td>
<td>Carvedilol (Coreg), celecoxib (Celebrex), glipizide (Glucotrol), ibuprofen (Motrin), irbesartan (Avapro), losartan (Cozaar)</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Fluvoxamine, isoniazid (INH), ritonavir</td>
<td>Carbamazepine, phenytoin, rifampin</td>
<td>Omeprazole (Prilosec), phenobarbital, phenytoin</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Amiodarone, cimetidine, diphenhydramine (Benadryl), fluoxetine, paroxetine (Paxil), quinidine, ritonavir, terbinafine (Lamisil)</td>
<td>No significant inducers</td>
<td>Amitriptyline, carvedilol, codeine, donepezil (Aricept), haloperidol (Haldol), metoprolol (Lopressor), paroxetine, risperidone (Risperdal), tramadol (Ultram)</td>
</tr>
<tr>
<td>CYP3A4 and CYP3A5</td>
<td>Clarithromycin (Biaxin), diltiazem (Cardizem), erythromycin, grapefruit juice, itraconazole (Sporanox), ketoconazole (Nizoral), nefazodone (Serzone$), ritonavir, telithromycin (Ketek), verapamil (Calan)</td>
<td>Carbamazepine, <em>Hypericum perforatum</em> (St. John’s wort), phenobarbital, phenytoin, rifampin</td>
<td>Alprazolam (Xanax), amlodipine (Norvasc), atorvastatin (Lipitor), cyclosporine (Sandimmune), diazepam (Valium), estradiol (Estrace), simvastatin (Zocor), sildenafil (Viagra), verapamil, zolpidem (Ambien)</td>
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Reference

- AAFP.ORG PULICATION: The Effect of Cytochrome P450 Metabolism on Drug Response, Interactions, and Adverse Effects TOM LYNCH, PharmD, and AMY PRICE, MD, Eastern Virginia Medical School, Norfolk, Virginia
Thank You