

# 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*

Cytochrome P450 enzymes are essential for the metabolism of many medications. Although this class has more than 50 enzymes, six of them metabolize 90 percent of drugs, with the two most significant enzymes being CYP3A4 and CYP2D6. Genetic variability (polymorphism) in these enzymes may influence a patient's response to commonly prescribed drug classes, including beta blockers and antidepressants. Cytochrome P450 enzymes can be inhibited or induced by drugs, resulting in clinically significant drug-drug interactions that can cause unanticipated adverse reactions or therapeutic failures. Interactions with warfarin, antidepressants, antiepileptic drugs, and statins often involve the cytochrome P450 enzymes. Knowledge of the most important drugs metabolized by cytochrome P450 enzymes, as well as the most potent inhibiting and inducing drugs, can help minimize the possibility of adverse drug reactions and interactions. Although genotype tests can determine if a patient has a specific enzyme polymorphism, it has not been determined if routine use of these tests will improve outcomes. (*Am Fam Physician* 2007;76:391-6. Copyright © 2007 American Academy of Family Physicians.)

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Cytochrome P450 (CYP450) enzymes are essential for the production of cholesterol, steroids, prostacyclins, and thromboxane A<sub>2</sub>. They also are necessary for the detoxification of foreign chemicals and the metabolism of drugs. CYP450 enzymes are so named because they are bound to membranes within a cell (cyto) and contain a heme pigment (chrome and P) that absorbs light at a wavelength of 450 nm when exposed to carbon monoxide. There are more than 50 CYP450 enzymes, but the CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 enzymes metabolize 90 percent of drugs.<sup>1,2</sup> These enzymes are predominantly expressed in the liver, but they also occur in the small intestine (reducing drug bioavailability), lungs, placenta, and kidneys.<sup>2</sup>

## Pharmacogenetics

One out of every 15 white or black persons may have an exaggerated response to standard doses of beta blockers (e.g., metoprolol [Lopresor]), or no response to the analgesic tramadol (Ultram). This is because drug metabolism via CYP450 enzymes exhibits genetic variability (polymorphism) that influences a patient's response to a particular drug.<sup>3</sup>

A specific gene encodes each CYP450 enzyme. Every person inherits one genetic allele from each parent. Alleles are referred to as "wild type" or "variant," with wild type occurring most commonly in the general population. An "extensive" (i.e., normal) metabolizer has received two copies of wild-type alleles. Polymorphism occurs when a variant allele replaces one or both wild-type alleles. Variant alleles usually encode a CYP450 enzyme that has reduced or no activity.<sup>1</sup> Persons with two copies of variant alleles are "poor" metabolizers, whereas those with one wild-type and one variant allele have reduced enzyme activity. Finally, some persons inherit multiple copies of wild-type alleles, which results in excess enzyme activity. This phenotype is termed an "ultrarapid" metabolizer.<sup>4</sup>

CYP450 enzyme polymorphism is responsible for observed variations in drug response among patients of differing ethnic origins.<sup>4-6</sup> For example, 7 percent of white persons and 2 to 7 percent of black persons are poor metabolizers of drugs dependent on CYP2D6, which metabolizes many beta blockers, antidepressants, and opioids.<sup>7,8</sup> One in five Asian persons is a poor metabolizer

## SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>	<i>Comment</i>
Genotype testing may predict persons who are poor metabolizers or are nonresponsive to drugs metabolized by CYP450 enzymes.	C	1, 2, 6	Large, prospective trials needed to demonstrate that genotype testing improves outcomes and is cost-effective
Genetic variations in CYP450 metabolism should be considered when patients exhibit unusual sensitivity or resistance to drug effects at normal doses.	C	4, 35, 36	Studies demonstrate a link between adverse effects and variant CYP450 alleles
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.	C	10, 11, 14, 18, 31, 32	Well-recognized cause of clinically significant drug interactions
Severe toxicity can result if CYP450 enzyme-inhibiting drugs are added to the following medications: atypical antipsychotics, benzodiazepines, cyclosporine (Sandimmune), statins, or warfarin (Coumadin).	C	10, 11, 19, 24, 30	Particularly true if substrate drug depends on only one CYP450 enzyme for metabolism
Because they are known to cause clinically significant CYP450 drug interactions, always use caution when adding the following substances to medications that patients are taking: amiodarone (Cordarone), antiepileptic drugs, antidepressants, antitubercular drugs, grapefruit juice, macrolide and ketolide antibiotics, nondihydropine calcium channel blockers, or protease inhibitors.	C	10, 11, 14	Are either potent inhibitors or inducers of CYP450 enzymes

CYP = cytochrome P.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 323 or <http://www.aafp.org/afpsort.xml>.

of drugs dependent on CYP2C19, which metabolizes phenytoin (Dilantin), phenobarbital, omeprazole (Prilosec), and other drugs.<sup>9</sup> Variance in drug response among persons of different ethnic origins also can be caused by genetic variations in other drug-metabolizing enzymes, drug transporters, and drug receptors.<sup>3</sup>

### Drug Interactions

Many drug interactions are the result of an alteration of CYP450 metabolism.<sup>10</sup> The non-sedating antihistamines terfenadine (Seldane) and astemizole (Hismanal), and the gastrointestinal motility agent cisapride (Propulsid), were all withdrawn from the U.S. market because metabolic inhibition by other drugs led to life-threatening arrhythmias.<sup>11</sup> The calcium channel blocker mibefradil (Posicor) was withdrawn from the U.S. market in 1998 because it was a potent enzyme inhibitor that resulted in toxic levels of other cardiovascular drugs.<sup>12</sup>

Drugs interact with the CYP450 system in several ways. Drugs may be metabolized by only one CYP450 enzyme (e.g., metoprolol by CYP2D6) or by multiple enzymes

(e.g., warfarin [Coumadin] by CYP1A2, CYP2D6, and CYP3A4).<sup>13</sup> Drugs that cause CYP450 metabolic drug interactions are referred to as either inhibitors or inducers (*Table 1*<sup>10,14-16</sup>). Inhibitors block the metabolic activity of one or more CYP450 enzymes. The extent to which an inhibitor affects the metabolism of a drug depends upon factors such as the dose and the ability of the inhibitor to bind to the enzyme. For instance, sertraline (Zoloft) is considered a mild inhibitor of CYP2D6 at a dose of 50 mg, but if the dose is increased to 200 mg, it becomes a potent inhibitor.<sup>17</sup> Inhibitory effects usually occur immediately.

Additionally, a drug can be both metabolized by and inhibit the same enzyme (e.g., erythromycin), or it can be metabolized by one enzyme and inhibit another enzyme (e.g., terbinafine [Lamisil]).<sup>18</sup> Drugs may be intentionally combined to take advantage of CYP450 inhibition. Ritonavir (Norvir), a protease inhibitor and potent CYP3A4 inhibitor, is added to lopinavir (Kaletra) to boost serum levels in patients with human immunodeficiency virus.<sup>14</sup>

Inducers increase CYP450 enzyme activity by increasing enzyme synthesis. Unlike metabolic inhibition, there is usually a delay before enzyme activity increases, depending on the half-life of the inducing drug. A decrease in the concentration of a drug metabolized by CYP2C9 can occur within 24 hours after the initiation of rifampin (Rifadin), an inducer with a short half-life, but can occur up to one week after the initiation of phenobarbital, an inducer with a very long half-life.<sup>10</sup> A drug also may be metabolized by the same CYP450 enzyme that it induces. Carbamazepine (Tegretol), a potent enzyme inducer, must be initiated at a low dose and then increased at weekly intervals as its half-life gradually decreases over time.

The following clinical scenario describes a case of drug interaction: A 68-year-old white woman taking warfarin, whose condition

was previously 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 (Diflucan) 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 International Normalized Ratio 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 account for a potential decrease or increase in metabolism. Information regarding a drug's CYP450 metabolism and its potential for inhibition or induction can be found on the drug label

**Table 1. Significant Cytochrome P450 Enzymes and Their Inhibitors, Inducers, and Substrates**

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

CYP=cytochrome P.

\*—These will slow down substrate drug metabolism and increase drug effect.

†—These will speed up substrate drug metabolism and decrease drug effect.

‡—Brand not available in the United States.

Information from references 10 and 14 through 16

and accessed through the U.S. Food and Drug Administration (FDA) or manufacturer's Web sites. The FDA has required this information for every drug approved since 1997. *Table 2*<sup>19-28</sup> lists examples of common drug-drug interactions and their potential clinical effects. *Table 3*<sup>14,16</sup> lists some useful CYP450 drug interaction resources.

### Adverse Drug Effects

Standard drug doses may cause adverse effects related to elevated drug serum levels if a person is a poor metabolizer or has a CYP450 enzyme inhibitor added to therapy.<sup>5,29</sup> Adverse effects are more likely to occur if a drug has a narrow safety range or is dependent on only one enzyme for metabolism.

Consider the following scenario: A 35-year-old white woman with panic disorder was treated with paroxetine (Paxil). She developed unrelated hypertension, for which the physician prescribed 50 mg daily of extended-release metoprolol (Toprol XL). The patient became symptomatically orthostatic after a few days and presented to the emergency department. In this example, metoprolol, which is metabolized solely by CYP2D6, was present in higher serum levels in the patient because of the use of paroxetine.

Peak serum levels of simvastatin (Zocor), which is metabolized solely by CYP3A4, also can increase by many times in patients who are poor metabolizers or with the addition of a potent inhibitor (e.g., verapamil [Calan], nefazodone [Serzone; brand not

**Table 2. Examples of Common Drug-Drug Interactions Involving the Cytochrome P450 Enzyme System**

<i>Drug(s)/product</i>	<i>Enzyme inhibitor or inducer</i>	<i>Drug(s)</i>	<i>Metabolizing enzyme</i>	<i>Possible clinical effect</i>
Amiodarone (Cordarone)	CYP2C9 and CYP3A4 inhibitor	Warfarin (Coumadin)	CYP2C9	Increased risk of bleeding caused by increased warfarin level <sup>19</sup>
Carbamazepine (Tegretol), phenobarbital, phenytoin (Dilantin)	CYP3A4 inducer	Ethinyl estradiol-containing contraceptives	CYP3A4	Unplanned pregnancy caused by reduced estradiol level <sup>20</sup>
Clarithromycin (Biaxin), erythromycin, telithromycin (Ketek)	CYP3A4 inhibitor	Simvastatin (Zocor), verapamil (Calan)	CYP3A4	Myopathy or rhabdomyolysis caused by increased simvastatin level <sup>21</sup> Hypotension and QT interval prolongation caused by increased verapamil level <sup>22</sup>
Diltiazem (Cardizem), verapamil	CYP3A4 inhibitor	Prednisone	CYP3A4	Immunosuppression caused by increased prednisolone serum levels <sup>23</sup>
Fluoxetine (Prozac), paroxetine (Paxil),	CYP2D6 inhibitor	Risperidone (Risperdal), tramadol (Ultram)	CYP2D6	Increased risk of extrapyramidal adverse effects caused by increased risperidone level <sup>24</sup> ; decrease in analgesic effect caused by low level of active metabolite <sup>25</sup>
Grapefruit juice	CYP3A4 inhibitor	Buspirone (Buspar)	CYP3A4	Dizziness and serotonin syndrome caused by increased buspirone level <sup>26</sup>
Metronidazole (Flagyl)	CYP2C9 inhibitor	Warfarin	CYP2C9	Increased risk of bleeding caused by increased warfarin level <sup>27</sup>
Terbinafine (Lamisil)	CYP2D6 inhibitor	Amitriptyline	CYP2D6	Dry mouth, dizziness, and cardiac toxicity caused by prolonged increase in amitriptyline and nortriptyline (Pamelor) levels <sup>28</sup>

CYP=cytochrome P.

Information from references 19 through 28.

**Table 3. Cytochrome P450 Drug Interaction Resources**

Source	Comment
Concise Guide to Drug Interaction Principles for Medical Practice: Cytochrome P450s, UGTs, P-glycoproteins <sup>14</sup>	Comprehensive guide to drug interactions with useful charts and representative cases
Indiana University School of Medicine drug interaction table ( <a href="http://medicine.iupui.edu/flockhart/table.htm">http://medicine.iupui.edu/flockhart/table.htm</a> ) <sup>16</sup>	Continually updated table of important substrates, inhibitors, and inducers with direct links from each drug name to a PubMed list of citations
Drugs section in the Lexi-Complete PDA software package from Lexi-Comp	This PDA software includes a section on cytochrome P450 enzyme activity for each drug narrative

UGT = uridine diphosphate-glucuronosyltransferase; PDA = personal digital assistant.

Information from reference 14 and 16.

available in the United States]), increasing the risk of myopathy and rhabdomyolysis at usual doses.<sup>30</sup>

Some drugs, such as tramadol or losartan (Cozaar), are not therapeutic until they are metabolized to active compounds. These medications, known as prodrugs, 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.<sup>31,32</sup>

### Genotype Testing

Genotyping for CYP450 polymorphism has primarily been used for research purposes or clinical drug trials. Recently, the FDA approved the first genotype test designed for use by physicians to guide the selection of medications metabolized by CYP450 enzymes. The Amplichip CYP450 test is a DNA microarray that can detect 29 polymorphisms of CYP2D6 and two polymorphisms of CYP2C19 using a blood sample.<sup>33</sup> Roche Diagnostics currently charges laboratories \$500 per test, and most major insurance companies do not cover the cost.<sup>34</sup> Although there is evidence of a link between adverse effects and polymorphisms coding for reduced CYP450 activity, large prospective clinical trials are needed to determine whether use of genotyping in clinical practice is cost-effective and improves clinical outcomes by preventing adverse drug effects or identifying poor responders.<sup>5,7,35,36</sup>

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Andrea E. Gordon, MD, Tufts University Family Medicine Residency Program at Cambridge Health Alliance, Malden, Mass.

### The Authors

TOM LYNCH, PharmD, is an associate professor in the Department of Family and Community Medicine at Eastern Virginia Medical School in Norfolk. He graduated from the University of Arkansas for Medical Sciences School of Pharmacy in Little Rock. Dr. Lynch has been a pharmacist in family medicine residency programs for the past eight years, and is a board-certified pharmacotherapy specialist.

AMY PRICE, MD, is an assistant professor in the Department of Family and Community Medicine at Eastern Virginia Medical School, and is the medical director of the Maryview Foundation Healthcare Center, a free primary care center in Portsmouth, Va. She graduated from the University of Tennessee College of Medicine in Memphis, and completed a family medicine residency and faculty development fellowship at the University of Virginia in Charlottesville.

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Address correspondence to Tom Lynch, PharmD, Department of Family and Community Medicine, Eastern Virginia Medical School, 721 Fairfax Ave., Rm. 324, Norfolk, VA 23507. Reprints are not available from the authors.

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