

# Cytochrome P450: New Nomenclature and Clinical Implications

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*Many drug interactions are a result of inhibition or induction of cytochrome P450 enzymes (CYP450). The CYP3A subfamily is involved in many clinically significant drug interactions, including those involving nonsedating antihistamines and cisapride, that may result in cardiac dysrhythmias. CYP3A4 and CYP1A2 enzymes are involved in drug interactions involving theophylline. CYP2D6 is responsible for the metabolism of many psychotherapeutic agents. The protease inhibitors, which are used to treat patients infected with the human immunodeficiency virus, are metabolized by the CYP450 enzymes and consequently interact with a multitude of other medications. By understanding the unique functions and characteristics of these enzymes, physicians may better anticipate and manage drug interactions and may predict or explain an individual's response to a particular therapeutic regimen.*

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**T**he basic purpose of drug metabolism in the body is to make drugs more water soluble and thus more readily excreted in the urine or bile.<sup>1,2</sup> One common way of metabolizing drugs involves the alteration of functional groups on the parent molecule (e.g., oxidation) via the cytochrome P450 enzymes. These enzymes are most predominant in the liver but can also be found in the intestines, lungs and other organs.<sup>3-6</sup> These cytochrome P450 enzymes are designated by the letters "CYP" followed by an Arabic numeral, a letter and another Arabic numeral (e.g., CYP2D6).<sup>7</sup> Each enzyme is termed an isoform since each derives from a different gene. It should be noted, however, that structural similarity of enzymes cannot be used to predict which isoforms will be responsible for a drug's metabolism.

Drug interactions involving the cytochrome P450 isoforms generally result from one of two processes, enzyme inhibition or enzyme induction. Enzyme inhibition usually

involves competition with another drug for the enzyme binding site. This process usually begins with the first dose of the inhibitor,<sup>8,9</sup> and onset and offset of inhibition correlate with the half-lives of the drugs involved.<sup>9</sup>

Enzyme induction occurs when a drug stimulates the synthesis of more enzyme protein,<sup>9</sup> enhancing the enzyme's metabolizing capacity. It is somewhat difficult to predict the time course of enzyme induction because several factors, including drug half-lives and enzyme turnover, determine the time course of induction.

## Illustrative Case 1

A 74-year-old woman with insulin-dependent (type 2) diabetes had been taking metoprolol 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 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. The emergency department physician,

*Until genetic tests for isoform expression become available, a physician can often anticipate drug interactions in a patient by knowing which medications inhibit or induce P450 enzymes.*

SSRIs and cimetidine inhibit metabolism of tricyclic antidepressants, but the clinical significance of this finding depends on individual genetic variations and concomitant medications.

noting that paroxetine had recently been added to the medication regimen, changed the patient to fluoxetine, which he thought would be less sedating. Three days later, the patient was still very sedated and dizzy, and complained of difficulty urinating. She was again brought to the emergency department, where bladder catheterization yielded two liters of dark urine. Her International Normalized Ratio (INR) was 4.0.

On discussion with a colleague, the emergency department physician learned that both paroxetine and fluoxetine can inhibit cytochrome P450 enzymes (isoforms) responsible for the metabolism of the patient's other medications. This example illustrates the need to understand the cytochrome P450 isoforms responsible for drug metabolism and their inhibitors and inducers.

## Cytochrome P450 Isoforms CYP2D6

CYP2D6 has been studied extensively because it exhibits genetic polymorphism, meaning that distinct population differences are apparent in its expression or activity. Approximately 7 to 10 percent of Caucasians are poor metabolizers of drugs metabolized by CYP2D6.<sup>10</sup> Individuals with normal CYP2D6 activity are termed extensive metabolizers. Ethnic differences are indicated in this genetic polymorphism, since Asians and blacks are less likely than Caucasians to be poor metabolizers.<sup>11,12</sup> Poor metabolizers are at risk for drug accumulation and toxicity from drugs metabolized by this isoform. For example, one patient who suffered cardiotoxicity induced by desipramine (Norpramin) was found to be a poor metabolizer.<sup>13</sup> Poor metabolizers of CYP2D6 substrates are at risk for postural hypotension and antipsychotic side effects

such as oversedation, because several antipsychotic agents are metabolized by CYP2D6.<sup>14</sup> In a study of 45 elderly patients (five of whom were poor metabolizers) receiving perphenazine, side effects increased fivefold in the poor metabolizers compared with the extensive metabolizers.<sup>15</sup> 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. Codeine is O-demethylated to morphine by CYP2D6, which accounts at least partially for its analgesic effect.<sup>16</sup> Thus, poor metabolizers may have less response to codeine than other persons. The substrates and inhibitors of CYP2D6 are listed in *Table 1*.

*Psychotherapeutic Agents.* Many antidepressants are metabolized by CYP2D6, but other cytochrome P450 isoforms can also contribute to their metabolism (*Tables 1 through 6*). The clinical importance of this "dual metabolism" will be illustrated later. With respect to drugs inhibiting CYP2D6, cimetidine (Tagamet), the selective serotonin reuptake inhibitors (SSRIs) and some tricyclic antidepressants function as inhibitors of this P450 isoform.<sup>17-19</sup> Of the antidepressants, paroxetine (Paxil) appears to have the greatest ability to inhibit the metabolism of CYP2D6 substrates. This is followed by fluoxetine (Prozac) and norfluoxetine; sertraline (Zoloft) and desmethylsertraline; fluvoxamine (Luvox), nefazodone (Serzone) and venlafaxine (Effexor); clomipramine (Anafranil), and amitriptyline (Elavil).<sup>19</sup> This ranking is based on *in vitro* data, however, and the choice of an antidepressant should be based on factors other than the propensity to inhibit CYP2D6. Although sertraline appears to be less likely than the other SSRIs to inhibit CYP2D6, inhibition may still occur at doses greater than 50 mg. The clinical significance of the inhibition of tricyclics by SSRIs or cimetidine is subject to variation in enzyme activity between individuals, the degree to which the patient metabolizes and co-ingestion of other enzyme inhibitors.<sup>20</sup>

## CYP3A

*Inhibitors of CYP3A.* Members of the CYP3A subfamily are the most abundant cytochrome enzymes in humans. They account for 30 percent of the cytochrome P450 enzymes in the liver<sup>21</sup> and are also substantially expressed in the intestines. Members of this subfamily are involved in many clinically important drug interactions.<sup>1</sup> Substrates, inhibitors and inducers of CYP3A are listed in *Table 2*.

*Nonsedating Antihistamines.* High plasma concentrations of terfenadine (Seldane) and astemizole (Hismanal) have been associated with torsade de pointes, a life-threatening cardiac arrhythmia characterized by altered cardiac repolarization and a prolonged QT interval.<sup>22</sup> Terfenadine is a prodrug that undergoes complete first-pass metabolism to an active carboxymetabolite.<sup>23</sup> It is therefore unusual to detect terfenadine in the plasma of patients who take this drug at the recommended dosage. Since it is terfenadine rather than its active metabolite that is cardiotoxic, arrhythmias occur when a build-up of parent terfenadine takes place. This may occur when azole antifungal medications or macrolide antibiotics are taken concomitantly.<sup>22,24</sup> To counteract this problem, fexofenadine (Allegra), the active metabolite of terfenadine, is now marketed as a noncardiotoxic alternative to terfenadine. Like fexofenadine, loratadine (Claritin) does not appear to be cardiotoxic and thus is also a safe nonsedating antihistamine alternative.<sup>25</sup>

Ketoconazole (Nizoral), itraconazole (Sporanox) and fluconazole (Diflucan) inhibit CYP3A, although ketoconazole and itraconazole are more inhibiting than fluconazole.<sup>26</sup> Based on in vitro and in vivo studies, ketoconazole and itraconazole markedly inhibit metabolism of terfenadine, causing changes in the QT interval.<sup>22,27</sup> At dosages of 200 mg daily, fluconazole did not result in accumulation of parent terfenadine or changes in the QT interval.<sup>28</sup> However, an interaction with terfenadine and fluconazole coadministration

may occur in patients taking higher dosages of fluconazole or in patients with risk factors for ventricular arrhythmia. These two drugs should be used together with caution.

In addition to the azole antifungal medications, the macrolide antibiotics can also inhibit terfenadine metabolism, resulting in the development of torsade de pointes. Erythromycin and clarithromycin (Biaxin) have been shown to alter terfenadine metabolism, but this does not appear to occur with azithromycin (Zithromax).<sup>29</sup> Thus, a patient who is taking terfenadine and needs macrolide antibiotic therapy should be given azithromycin to avoid possible cardiac consequences.

**TABLE 1**  
**Substrates and Inhibitors of CYP2D6**

Substrates	Inhibitors
Antidepressants*	Antidepressants
Amitriptyline (Elavil)	Paroxetine > fluoxetine > sertraline (Zoloft) > fluvoxamine (Luvox),
Clomipramine (Anafranil)	Nefazodone (Serzone),
Desipramine (Norpramin)	Venlafaxine > clomipramine (Anafranil) > amitriptyline
Doxepin (Adapin, Sinequan)	Cimetidine (Tagamet)
Fluoxetine (Prozac)	Fluphenazine (Prolixin)
Imipramine (Tofranil)	Antipsychotics
Nortriptyline (Pamelor)	Haloperidol
Paroxetine (Paxil)	Perphenazine
Venlafaxine (Effexor)	Thioridazine
Antipsychotics	
Haloperidol (Haldol)	
Perphenazine (Etrafon, Trilafon)	
Risperidone (Risperdal)	
Thioridazine (Mellaril)	
Beta blockers	
Metoprolol (Lopressor)	
Penbutolol (Levitol)	
Propranolol (Inderal)*	
Timolol (Blocadren)	
Narcotics	
Codeine, tramadol (Ultram)	

\*—Other enzymes are also involved.

NOTE: Inhibitors will decrease metabolism of substrates and generally lead to increased drug effect (unless the substrate is a prodrug). Inducers will increase metabolism of substrates and generally lead to decreased drug effect (unless the substrate is a prodrug).

# Cytochrome P450

The SSRIs are 28 to 775 times less potent as inhibitors of terfenadine metabolism than ketoconazole.<sup>30</sup> With respect to ability to inhibit CYP3A, the following order of the SSRIs is observed: nefazodone is greater than fluvoxamine, and norfluoxetine is greater than fluoxetine, which is greater than sertraline, desmethylsertraline, paroxetine and venlafaxine.<sup>31</sup> Several clinically important cardiac events have been reported in patients receiving

fluoxetine or fluvoxamine with terfenadine or astemizole.<sup>30,32,33</sup> The use of fluvoxamine or nefazodone with terfenadine or astemizole is contraindicated, and the U.S. Food and Drug Administration is currently considering requiring a contraindication against the use of other SSRIs with the nonsedating antihistamines.<sup>30</sup> The package insert for sertraline contains a warning against its use with terfenadine and astemizole.<sup>34</sup> In patients who need to take an

**TABLE 2**  
**Substrates, Inhibitors and Inducers of CYP3A**

### Substrates

Amitriptyline\* (Elavil)  
Benzodiazepines  
  Alprazolam (Xanax)  
  Triazolam (Halcion)  
  Midazolam (Versed)  
Calcium blockers  
Carbamazepine (Tegretol)  
Cisapride (Propulsid)  
Dexamethasone (Decadron)  
Erythromycin  
Ethinyl estradiol (Estraderm, Estrace)  
Glyburide (Glynase, Micronase)  
Imipramine\* (Tofranil)  
Ketoconazole (Nizoral)  
Lovastatin (Mevacor)  
Nefazodone (Serzone)  
Terfenadine (Seldane)  
Astemizole (Hismanal)  
Verapamil (Calan, Isoptin)  
Sertraline (Zoloft)  
Testosterone  
Theophylline\*  
Venlafaxine (Effexor)  
Protease inhibitors  
  Ritonavir (Norvir)  
  Saquinavir (Invirase)  
  Indinavir (Crixivan)  
  Nelfinavir (Viracept)

### Inhibitors

Antidepressants  
  Nefazodone > fluvoxamine (Luvox) > fluoxetine (Prozac) > sertraline  
  Paroxetine (Paxil)  
  Venlafaxine  
Azole antifungals  
  Ketoconazole (Nizoral) > itraconazole (Sporanox) > fluconazole (Diflucan)  
Cimetidine (Tagamet)†  
Clarithromycin (Biaxin)  
Diltiazem  
Erythromycin  
Protease inhibitors

### Inducers

Carbamazepine  
Dexamethasone  
Phenobarbital  
Phenytoin (Dilantin)  
Rifampin (Rifadin, Rimactane)

\*—Other enzymes are involved.

†—Does not inhibit all CYP3A substrates; does not inhibit terfenadine metabolism.

NOTE: Inhibitors will decrease metabolism of substrates and generally lead to increased drug effect (unless the substrate is a prodrug). Inducers will increase metabolism of substrates and generally lead to decreased drug effect (unless the substrate is a prodrug).

antidepressant and a nonsedating antihistamine concurrently, paroxetine, venlafaxine and tricyclic antidepressants may be safe options, since they inhibit CYP3A more weakly.<sup>35,36</sup> Conversely, fexofenadine or loratadine, neither of which are associated with arrhythmias, could be prescribed, thus permitting more freedom in the choice of an antidepressant.

**Cisapride.** Serious ventricular arrhythmias have been reported in patients taking cisapride (Propulsid) and drugs that inhibit CYP3A, the isoform responsible for metabolism of cisapride.<sup>37</sup> Ketoconazole, fluconazole,

*Erythromycin, clarithromycin and ketoconazole inhibit CYP3A, causing build-up of drugs metabolized by the same enzyme. Terfenadine and cisapride are examples of drugs that can rise to cardiotoxic levels.*

itraconazole, metronidazole, erythromycin and clarithromycin have been associated with cisapride-induced torsade de pointes.<sup>37</sup> Concurrent use of cisapride with fluoxetine, sertraline, fluvoxamine and nefazodone might be problematic because of CYP3A inhibition.<sup>38</sup>

**Theophylline.** Erythromycin<sup>39</sup> and clarithromycin<sup>40</sup> (but not azithromycin<sup>41</sup>) decrease theophylline metabolism by inhibiting CYP3A. The interaction between erythromycin and theophylline is most likely to occur in patients receiving higher dosages of erythromycin and increases with the duration of therapy.

**Inducers of CYP3A.** Because of the resurgence of tuberculosis in the United States, rifampin (Rifadin, Rimactane), an inducer of the CYP3A subfamily, is being prescribed more widely than in previous years. Of particular clinical relevance is the potential reduction of oral contraceptive efficacy by rifampin, since estradiol levels can be reduced by rifampin-mediated CYP3A induction.<sup>42</sup> In addition to rifampin, potent glucocorticoids such as dexamethasone (Decadron) are also inducers of CYP3A, but lower-potency glucocorticoids, such as prednisolone, have minimal effect.<sup>43</sup>

**TABLE 3**  
**Substrates, Inhibitors**  
**and Inducers of CYP1A2**

**Substrates**

- Amitriptyline\* (Elavil)
- Clomipramine (Anafranil)\*
- Clozapine (Clozaril)\*
- Imipramine (Tofranil)\*
- Propranolol (Inderal)\*
- R-warfarin\*
- Theophylline\*
- Tacrine (Cognex)

**Inhibitors**

- Fluvoxamine (Luvox)
- Grapefruit juice
- Quinolones
  - Ciprofloxacin (Cipro)
  - Enoxacin (Penetrex) > norfloxacin (Noroxin) > ofloxacin (Floxin) > lomefloxacin (Maxaquin)

**Inducers**

- Omeprazole (Prilosec)
- Phenobarbital
- Phenytoin (Dilantin)
- Rifampin (Rifadin, Rimactane)
- Smoking
- Charcoal-broiled meat\*

\*—Other enzymes involved.

NOTE: Inhibitors will decrease metabolism of substrates and generally lead to increased drug effect (unless the substrate is a prodrug). Inducers will increase metabolism of substrates and generally lead to decreased drug effect (unless the substrate is a prodrug).

**CYP1A2**

CYP1A2 can be induced by exposure to polycyclic aromatic hydrocarbons, such as those found in charbroiled foods and cigarette smoke.<sup>44</sup> This is the only P450 isoform affected by tobacco. Cigarette smoking can result in an increase of as much as threefold in CYP1A2 activity.<sup>44</sup> Theophylline is metabolized in part by CYP1A2,<sup>45</sup> which explains why smokers require higher doses of theophylline than non-smokers. Table 3 lists the substrates, inhibitors and inducers of CYP1A2.

**Quinolones.** Certain quinolone antibiotics can inhibit theophylline metabolism,<sup>46-48</sup> although this effect is highly variable. The interaction between enoxacin (Penetrex) or ciprofloxacin (Cipro) and theophylline<sup>47</sup> is most significant in patients with plasma theophylline concentrations at the upper end of normal. Conversely, norfloxacin (Noroxin) and ofloxacin (Floxin) have little effect on theophylline concentrations,<sup>46</sup> and lomefloxacin (Maxaquin) does not appear to alter the pharmacokinetics of theophylline.<sup>49</sup> Since cimetidine is an inhibitor of CYP1A2,<sup>17</sup> additive inhibition of theophylline metabolism occurs when cimetidine is combined with a fluoroquinolone.

## CYP2E1

This isoform is inducible by ethanol and isoniazid and is responsible in part for the metabolism of acetaminophen.<sup>50</sup> The product of acetaminophen's cytochrome P450 metabolism is a highly reactive intermediate that must be detoxified by conjugation with glutathione.<sup>51</sup> Patients with alcohol dependence may be at increased risk for acetaminophen hepatotoxicity because ethanol induction of CYP2E1 increases formation of this reactive intermediate, and glutathione concentrations are decreased in these patients.<sup>52</sup> Cimetidine exhibits only moder-

**TABLE 4**  
Substrates, Inhibitors  
and Inducers of CYP2E1

### Substrates

Acetaminophen (Tylenol)  
Ethanol

### Inhibitors

Disulfiram (Antabuse)

### Inducers

Ethanol  
Isoniazid (Laniazid)

NOTE: Inhibitors will decrease metabolism of substrates and generally lead to increased drug effect (unless the substrate is a prodrug). Inducers will increase metabolism of substrates and generally lead to decreased drug effect (unless the substrate is a prodrug).

ate affinity for this isoform and produces no significant inhibition of the production of acetaminophen's toxic metabolite.<sup>17</sup> Table 4 lists the substrates, inhibitors and inducers of CYP2E1.

## CYP2C9

**S-Warfarin.** Warfarin is produced as a racemic mixture of R-warfarin and S-warfarin, but the predominance of pharmacologic activity resides in the S-enantiomer.<sup>53</sup> Most metabolism of S-warfarin is by means of CYP2C9,<sup>54</sup> and inhibition of this isoform results in several clinically important drug interactions. Fluconazole, metronidazole, miconazole and amiodarone are a few examples of the many drugs that profoundly inhibit S-warfarin metabolism and produce marked increases in prothrombin time measurements.<sup>55-58</sup> Interestingly, cimetidine, a very weak inhibitor of CYP2C9,<sup>17</sup> has been shown to have very little effect on warfarin concentrations.<sup>59</sup> The substrates, inhibitors and inducers of CYP2C9 are listed in Table 5.

**Phenytoin.** Phenytoin is primarily metabolized via CYP2C9,<sup>60</sup> although CYP2C19 may also play a small role.<sup>61</sup> As stated above, cimetidine is a weak inhibitor of CYP2C9. It is

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most likely to cause clinically significant inhibition of phenytoin metabolism at cimetidine dosages greater than 1,200 mg in patients at the upper end of the phenytoin therapeutic range.<sup>62</sup> In patients with nonlinear metabolism of phenytoin at relatively low serum levels, the risk of interaction with cimetidine is increased. However, it is difficult to identify these patients in a clinical situation.

### CYP2C19

Like CYP2D6, CYP2C19 has been shown to exhibit genetic polymorphism.<sup>63,64</sup> This enzyme is completely absent in 3 percent of Caucasians and 20 percent of Japanese. Drugs metabolized by this isoform include omeprazole (Prilosec),<sup>65</sup> lansoprazole (Prevacid)<sup>66</sup> and diazepam (Valium).<sup>67</sup> However, clinical examples of excessive or adverse drug effects in people who are CYP2C19-deficient are lacking. Table 6 lists the substrates and inhibitors of CYP2C19.

### Illustrative Case 2

A 47-year-old man recently diagnosed with HIV infection visited his physician with flushing, dizziness and swelling of the feet and ankles. He had been taking sustained-release nifedipine for treatment of hypertension for about three years. Approximately two weeks earlier, his physician had prescribed a combination of lamivudine, zidovudine and the protease inhibitor ritonavir.

The HIV-1 protease inhibitors ritonavir, indinavir, saquinavir and nelfinavir all inhibit the CYP3A subfamily of enzymes, thus increasing the serum levels of other drugs that are metabolized by this pathway, including nifedipine. It is likely that the addition of ritonavir to this patient's medical regimen resulted in an increase in the serum level of nifedipine and the subsequent symptoms of flushing and dizziness. Of the currently available protease inhibitors, ritonavir, because of its ability to both inhibit and induce CYP450 enzymes, is associated with the most drug-drug interactions.<sup>68</sup>

**TABLE 5**  
**Substrates, Inhibitors**  
**and Inducers of CYP2C9**

#### Substrates

Nonsteroidal anti-inflammatory drugs  
Phenytoin (Dilantin)  
S-warfarin  
Torsemide (Demadex)

#### Inhibitors

Fluconazole (Diflucan)  
Ketoconazole (Nizoral)  
Metronidazole (Flagyl)  
Itraconazole (Sporanox)  
Ritonavir (Norvir)

#### Inducers

Rifampin (Rifadin, Rimactane)

NOTE: *Inhibitors will decrease metabolism of substrates and generally lead to increased drug effect (unless the substrate is a prodrug). Inducers will increase metabolism of substrates and generally lead to decreased drug effect (unless the substrate is a prodrug).*

**TABLE 6**  
**Substrates and Inhibitors**  
**of CYP2C19**

#### Substrates

Clomipramine (Anafranil)\*  
Diazepam (Valium)\*  
Imipramine (Tofranil)\*  
Omeprazole (Prilosec)  
Propranolol (Inderal)\*

#### Inhibitors

Fluoxetine (Prozac)  
Sertraline (Zoloft)  
Omeprazole  
Ritonavir (Norvir)

\*—Other enzymes involved also.

NOTE: *Inhibitors will decrease metabolism of substrates and generally lead to increased drug effect (unless the substrate is a prodrug). Inducers will increase metabolism of substrates and generally lead to decreased drug effect (unless the substrate is a prodrug).*

## Final Comment

Physicians who become familiar with the role of the various cytochrome P450 enzymes in drug metabolism can often predict the consequences of drug interactions and explain patients' responses to medication regimens. Although tests for isoform expression are not widely available, it is conceivable that such testing may become standard practice in the future, given the clinical importance of isoform deficiencies. In the future, testing may help to identify individuals at risk for drug interactions and adverse events.

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