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Get to Know an Enzyme: CYP2D6

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In previous issues of *Pharmacy Times* we have discussed the cytochrome P450 (CYP450) enzymes CYP1A2, CYP2C9, and CYP2C19. In this issue, we will discuss CYP2D6?an enzyme that is involved in the metabolism of numerous drugs. CYP2D6 also is involved in the activation of some drugs, so these drugs may have reduced efficacy when patients with inadequate CYP2D6 activity take them. Another important property of CYP2D6 is that its activity is affected by genetic variability?some individuals are CYP2D6 deficient; others have normal CYP2D6 activity; and still others have increased activity.

Genetics of CYP2D6

The genetics of CYP2D6 has been extensively studied, and individuals can be divided into 4 groups. Patients who are poor metabolizers (individuals with no CYP2D6 activity) or ultrarapid metabolizers (individuals with genetically elevated CYP2D6 activity) can have markedly altered response to drugs that are CYP2D6 substrates. Note that ethnic differences exist in CYP2D6 activity. Genetic testing for CYP2D6 activity can be performed, but it is not yet a routine procedure.

Table 1

Genetics of CYP2D6

Genetic Type	CYP2D6 Activity	Ethnic Differences (Approximate)
Poor metabolizers	None	Caucasians 6%-10%
		Mexican Americans 3%-6%
		African Americans 2%-5%
		Asians ~1%
Intermediate metabolizers	Low	Not established
Extensive metabolizers	Normal	Most people are extensive metabolizers
Ultrarapid metabolizers	High	Finns and Danes 1%
		North Americans (white) 4%
		Greeks 10%
		Portuguese 10%
		Saudis 20%
		Ethiopians 30%

CYP2D6 Substrates

Drugs metabolized by CYP2D6 are called CYP2D6 substrates (see Table 2 at right). Keep in mind that many drugs are metabolized by more than one CYP450 enzyme, and CYP2D6 may represent only one pathway. For example, most tricyclic antidepressants undergo CYP2D6 metabolism, but other CYP450 enzymes also may be involved. Many other psychotherapeutic drugs are substrates for or inhibitors of CYP2D6, so this enzyme is of particular interest for patients on such drugs. For some CYP2D6 substrates (eg, thioridazine), increased plasma concentrations can increase the risk of serious adverse consequences.

Table 2

CYP2D6 Substrates
Amitriptyline (Elavil, etc)
Atomoxetine (Strattera)
Carvedilol (Coreg)
Chlorpheniramine
Chlorpromazine
Clomipramine (Anafranil)
Codeine*
Desipramine (Norpramin)
Dextromethorphan
Dihydrocodeine*
Diphenhydramine (Benadryl)
Dolasetron (Anzemet)
Doxepin (Sinequan)
Duloxetine (Cymbalta)
Flecainide (Tambocor)
Fluoxetine (Prozac)
Fluvoxamine
Haloperidol (Haldol)
Hydrocodone (Vicodin)*
Imipramine (Tofranil)
Maprotiline (Ludiomil)
Metoclopramide (Reglan)
Metoprolol (Lopressor)
Mexiletine (Mexitil)
Nortriptyline (Pamelor)
Palonosetron (Aloxi)
Paroxetine (Paxil)
Perhexiline (Pexid)
Promethazine (Phenergan)
Propafenone (Rythmol)
Propranolol (Inderal)
Protriptyline (Vivactil)
Risperidone (Risperdal)
Tamoxifen (Nolvadex)
Thioridazine (Mellaril)
Timolol (Blocadren)
Tolterodine (Detrol)
Tramadol (Ultram)*
Trazodone (Desyrel)
Venlafaxine (Effexor)

* Converted by CYP2D6 to active metabolite.

CYP2D6 Inhibitors

Drugs that inhibit CYP2D6 activity are likely to increase the plasma concentrations of certain medications, and, in some cases, adverse outcomes will occur (see Table 3 below right for a list of known inhibitors). Some drugs, such as fluoxetine, paroxetine, and quinidine, are particularly potent inhibitors of CYP2D6; patients on these drugs may have almost no CYP2D6 activity. Note that in patients genetically deficient in CYP2D6 who are taking a CYP2D6 substrate, the addition of a CYP2D6 inhibitor will not result in any change in the plasma concentrations of the substrate.

CYP2D6 Inducers

The evidence suggests that, unlike most other CYP450 enzymes, CYP2D6 is not very susceptible to enzyme induction. Thus, genetics, rather than drug therapy, accounts for most ultrarapid CYP2D6 metabolizers.

Drugs Activated by CYP2D6

Codeine

Codeine is largely a prodrug, and its activity is primarily dependent on its conversion to morphine. Patients who have little CYP2D6 activity, therefore, are likely to have little response to codeine. The number of people with low CYP2D6 activity is substantial, when one considers the people genetically deficient in CYP2D6, plus the many patients who are taking CYP2D6 inhibitors. A more dangerous situation, however, occurs when ultrarapid metabolizers take codeine. They may develop moderate-to-severe adverse effects from excessive morphine concentrations in the blood. In one tragic case, a healthy breast-feeding

newborn infant developed fatal morphine toxicity; his mother was an ultrarapid metabolizer who was taking codeine, and her milk contained toxic amounts of morphine.

Tamoxifen

Tamoxifen has a complex set of metabolic pathways, but CYP2D6 is primarily responsible for the production of its active metabolite. Growing evidence suggests that breast cancer patients with low CYP2D6 activity do not respond as well to tamoxifen therapy and are more likely to have cancer relapse. Thus, assessing the CYP2D6 genotype for patients taking tamoxifen in order to identify those with low activity is of growing interest. For the same reason, it also would be prudent to avoid CYP2D6 inhibitors in patients taking tamoxifen.

Table 3

CYP2D6 Inhibitors
Amiodarone (Cordarone)
Bupropion (Wellbutrin)
Chloroquine (Aralen)
Cinacalcet (Sensipar)
Diphenhydramine (Benadryl)
Fluoxetine (Prozac)
Haloperidol (Haldol)
Imatinib (Gleevec)
Paroxetine (Paxil)
Propafenone (Rythmol)
Propoxyphene (Darvon)
Quinidine (Quinidex, etc)
Terbinafine (Lamisil)
Thioridazine (Mellaril)

Summary

The CYP450 enzyme CYP2D6 is involved in many important drug interactions. For those drugs that are metabolized by CYP2D6 to inactive metabolites, CYP2D6 inhibitors may result in toxicity. For drugs that are converted to active metabolites by CYP2D6, the addition of a CYP2D6 inhibitor will tend to inhibit the efficacy of the drug. Genetic variability in CYP2D6 activity also can affect the outcome of CYP2D6 drug interactions.