Understanding CYP2D6 and Its Role in Tamoxifen Metabolism

Edith Caroline Smith, MSN, CNM, WHNP-C

The gene CYP2D6 has an extremely important role in drug metabolism. "Cytochrome P450, family 2, subfamily D, polypeptide 6" is the official name of CYP2D6. The gene is located at position 13.1 on the long (q) arm of chromosome 21 and encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases that are heavily involved in drug metabolism (Genetics Home Reference, 2013), and many drugs are activated into their biologically active compounds. Because of numerous polymorphisms, the gene also has significant person-to-person variability. To date, more than 80 distinct CYP2D6 alleles and specific types and frequencies have been associated with different ethnic groups. CYP2D6*4 is the most common variant allele in Caucasians and, in that population, has a frequency of about 25%. On the other hand, CYP2D6*10 is common in the Asian population (Stearns & Rae, 2008).

Metabolism Categories

Because of the tremendous variability in CYP2D6 genotypes, people are categorized as being poor metabolizers, intermediate metabolizers, extensive metabolizers, or ultrarapid metabolizers. Table 1 outlines selected genotypes associated with each category of metabolizers. Particular emphasis should be assigned to poor metabolizers because they exhibit a decreased ability to metabolize the enzymes' substrates (Genetics Home Reference, 2013). Poor metabolizers usually occur as a result of having two loss-of-function alleles. One of the most serious consequences of being a poor metabolizer is the possibility of ineffective drug therapy (Cavallari, Jeong, & Bress, 2011). In regard to specific populations, about 7%–10% of

Caucasians, 2% of African Americans, and 1% of the Asian population have CYP2D6 polymorphisms associated with being poor metabolizers (Desmarias & Looper, 2009).

The cytochrome P450 protein metabolizes about 25% of commonly prescribed medications (including several categories of beta blockers, antidepressants, antipsychotics, and antiarrhythmics, dextromethorphan, codeine, and tamoxifen) and can result in over- or under-response to these medications. This response issue is important particularly for women diagnosed with breast cancer because about 70% will have estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive tumors (Stearns & Rae, 2008). Tamoxifen, a selective ER modulator, is commonly prescribed as chemoprevention to reduce the risk of breast cancer occurrence in women with a high risk for developing breast cancer, and as treatment for ER/PR-positive breast cancer because of its ability to block estrogen from binding to the ER (Stearns & Rae, 2008). Because tamoxifen is a mainstay of therapy for many patients with breast cancer, understanding the factors that could

diminish its effectiveness is important. Tamoxifen is known as a pro-drug, and weakly binds to ER. Conversion from tamoxifen to endoxifen is required for the drug to become biologically active; this occurs through biotransformation, activated by phase 1 and 2 liver enzymes and involves several cytochrome P450 enzymes (Stearns & Rae, 2008). Endoxifen has a 30–100 fold greater affinity for ERs compared to tamoxifen (Regan et al., 2012). Endoxifen levels are directly correlated to the number of defective CYP2D6 alleles, and the CYP2D6 genotype of the patient explains a significant percentage of variability in plasma endoxifen concentrations (Cavallari, 2011). Patients with genetic variants in CYP2D6 have lower plasma concentrations of endoxifen, the active metabolite of tamoxifen (Stearns & Rae, 2008). This finding is important because the ability to optimally metabolize tamoxifen is thought to be associated with outcomes in breast cancer treatment (Cavallari et al., 2011). In a study of 1,370 ER-positive patients with breast cancer, Madlensky et al. (2011) reported that recurrence rates in patients with ER-positive breast cancer treated with tamoxifen were

Table 1. CYP2D6 Genotype and Metabolizer Category

Category	Activity	Genotype
Poor	None	Two null alleles (CYP2D6 *3, *4, *5, *6, *11)
Intermediate	Reduced	One null allele (CYP2D6 *3, *4, *5, *6, *11)
Extensive	Normal	Two "wild-type"/normal alleles (CYP2D6 *1, *2, *35)
Ultrarapid	Excess	*1xN, *2xN, *35xN, *41xN

Note. From "Pharmacogenetics and Breast Cancer Endocrine Therapy: CYP2D6 as a Predictive Factor for Tamoxifen Metabolism and Drug Response," by V. Stearns and J. Rae, 2008, *Expert Reviews in Molecular Medicine, 10*(e34), p. 4. Copyright 2008 by Cambridge University Press. Adapted with permission.

notably higher in patients with two loss-of-function alleles (poor metabolizers) when compared to those with normal enzyme activity. Other research revealed conflicting results. Regan et al. (2012) looked at CYP2D6 genotype and tamoxifen response in postmenopausal women diagnosed with hormone receptor-positive breast cancer and found that "CYP2D6 phenotypes of reduced enzyme activity were not associated with worse disease control" (Regan et al., 2012, p. 441). As reported by Goetz et al. (2011), alterations in CYP2D6 metabolism were not associated with tamoxifen (or raloxifene) efficacy in the National Surgical Adjuvant Breast and Bowel Project P1 and P2 (STAR) trials (trials in which tamoxifen was used for breast cancer prevention). More research and additional study are needed in this area.

Medications

In addition to issues of metabolism, many medications inhibit the CYP2D6 enzyme, which can lead to lower plasma concentrations of endoxifen (Stearns & Rae, 2008). Of particular interest is the concomitant use of tamoxifen with certain classes of antidepressants, of which several are strong inhibitors of CYP2D6. Antidepressants are the most commonly prescribed class of medication in the United States, and an estimated 20%–30% of patients taking tamoxifen also are taking antidepressants (Desmarais & Looper, 2009). Antidepressants frequently are prescribed along with tamoxifen to reduce the occurrence of hot flashes. Medications known to strongly inhibit CYP2D6 include paroxitene, fluoxetine, bupropion, and quinidine-moderate inhibitors of CYP2D6 such as duloxetine, thioridazine, amiodarone, diphenhydramine, and cimetidine (Stearns & Rae, 2008). Of all the classes of antidepressants, venlaxafine and citalopram appear to be the weakest inhibitors of CYP2D6 and are preferential treatment choices for depression and reduction of hot flashes in those taking tamoxifen (National Comprehensive Cancer Network [NCCN], 2013; Stearns & Rae, 2008). The concomitant use of tamoxifen with medications that are strong inhibitors of CYP2D6 is so significant that it is deemed equivalent to having two loss-of-function (null) alleles (Stearns & Rae, 2008), essentially turning those who are genotypically extensive metabolizers into poor metabolizers (Desmarias & Looper, 2011).

In 2006, the U.S. Food and Drug Administration Endocrinology and Metabolic Drugs Advisory Committee made the recommendation that tamoxifen prescribing information be updated to include information on CYP2D6 and the potential for clinical outcomes to be affected in association with this genotype (Desmarias & Looper, 2009). However, CYP2D6 genotyping has not been endorsed for routine use by other prominent organizations, such as the American Society of Clinical Oncology or NCCN, because of the lack of supportive evidence (Kaplan & Mahon, 2013).

Conclusion

The role of CYP2D6 is important in drug metabolism and potential drug interactions. Additional evaluation and research on this topic is necessary to improve understanding and guide evidence-based practice decisions with the ultimate goal of improving patient outcomes.

Edith Caroline Smith, MSN, CNM, WHNP-C, is a nurse practitioner and regional medical specialist at Myriad Genetics in Salt Lake City, UT. No financial relationships to disclose. Smith can be reached at edsmith @myriad.com, with copy to editor at ONFEditor@ons.org.

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