Pharmacogenomics: Why Standard Codeine Doses Can Have Serious Toxicities or No Therapeutic Effect

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Three children died in August 2012 after receiving usual doses of codeine for postoperative pain following a tonsillectomy and/or adenoidectomy (U.S. Food and Drug Administration [FDA], 2013a). Those incidents, combined with a case report of a breast-feeding infant who died in 2005 of an apparent overdose after the mother received a standard dose of codeine for episiotomy pain (Health Sciences Authority, 2009; Koren, Cairns, Chitayat, Gaedigk, & Leeder, 2006), heighten the need to understand the pharmacogenomics of codeine metabolism.

Drug Metabolism and Genotyping

Healthcare providers have long noted variability in how individuals respond to medications (Howe & Eggert, 2007). “One size does not fit all” characterizes the complexity of medication administration. Some variations are explained by body mass index, age, kidney and liver function, comorbidities, and lifestyle influences. Other variations are a result of pharmacogenomics, defined as “the study of how an individual’s genetic inheritance affects the body’s response to drugs” (U.S. Department of Energy Human Genome Programs, 2011, “What is Pharmacogenomics,” para. 1).

The pain medication codeine is an example of how genetics influences metabolism. Codeine is a pro-drug (i.e., active only after converted to its active metabolite, morphine) (Sheffield & Phillimore, 2009). Drug activation occurs when the CYP2D6 gene produces a hepatic drug-metabolizing enzyme, CYP2D6, one of about 30 drug-metabolizing enzymes that are part of the cytochrome P450 system (U.S. Department of Energy Human Genome Programs, 2011). The CYP2D6 enzyme is responsible for codeine metabolism as well as the metabolism of about 25% of all drugs in clinical use (Sheffield & Phillimore, 2009). The gene nomenclature, CYP2D6, can be explained as follows: CYP is an abbreviation for the cytochrome P450 enzyme system, and 2D6 indicates the family, subfamily, and specific polypeptide for the gene (Genetics Home Reference, 2013a).

An individual inherits two alleles (versions) of the CYP2D6 gene, one from each parent. Occasionally, an individual can have additional copies (duplicate genes) for a specific gene. Those individuals generally are classified as ultra-rapid metabolizers and are at increased risk for serious drug reactions. The process where duplicate genes are formed, known as gene amplification, is “a selective increase in the number of copies of a gene coding for a specific protein without a proportional increase in other genes” (Genetics Home Reference, 2013b, “Gene amplification,” para. 1).

The CYP2D6 gene is polymorphic, meaning many versions (alleles) exist for the gene. Alleles are characterized as (a) normal function, also called wild type; (b) reduced function; or (c) nonfunctional (Crews et al., 2012). An individual’s genotype is represented by the two inherited alleles.

Different CYP2D6 genotypes account for the variability in CYP2D6 enzyme activity and subsequent clinical responses to codeine administration (see Figure 1). The combination of the two inherited alleles determines the phenotypic drug metabolism category (Crews et al., 2012; Sheffield & Phillimore, 2009).

Ethnicity Affects Drug Metabolism

Based on frequency data from Caucasian populations, most individuals (77%–92%) are extensive, wild-type metabolizers; 2%–11% are intermediate metabolizers; 5%–10% are poor metabolizers; and 1%–2% are ultra-rapid metabolizers (Crews et al., 2012). However,

Figure 1. CYP2D6 Enzyme Metabolizer Categories by Genotype

Note. Based on information from Crews et al., 2012; Sheffield & Phillimore, 2009.