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,

Ultra-Rapid Metabolizer
- Three or more *CYP2D6* gene copies
- Rapid conversion to morphine metabolite
- Higher drug concentrations
- Potential for more serious adverse drug reactions

Extensive Metabolizer
- Two normal, wild-type alleles, or a combination of a wild-type allele with a reduced-function or nonfunctional allele
- Normal conversion to morphine metabolite
- Likely to have a therapeutic effect

Intermediate Metabolizer
- One reduced-function and one nonfunctional allele
- Reduced conversion to morphine metabolite
- Likely to have a reduced therapeutic effect

Poor Metabolizer
- Two nonfunctional alleles
- No enzyme activity
- Unlikely to have a therapeutic effect
- Increased plasma drug concentration but no active metabolites
- May result in adverse drug reactions

Figure 1. *CYP2D6* Enzyme Metabolizer Categories by Genotype

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

significant variability exists in the ultra-rapid metabolizer *CYP2D6* genotype by ethnicity and selected studies. As shown in Table 1, the prevalence of ultra-rapid metabolizers ranges from 1%–28% for specific populations (FDA, 2010).

Practice Pointers

Codeine is a commonly prescribed analgesic, either as a single-ingredient product or in combination with acetaminophen and aspirin. Many cough and cold prescription medications contain codeine (FDA, 2013a). Visit www.nlm.nih.gov/medlineplus/druginfo/meds/a682065.html#brand-name-2 for a list of at least 65 brand names of combination medications that contain codeine.

Nurses need to understand the variability in *CYP2D6* genotyping, codeine metabolism, and the critical importance of observing for toxicities even when codeine is prescribed with normal dosages. The following practice pointers are important for RNs and advanced practice nurses.

- Consider ethnicity when ordering codeine medications or when assessing for codeine side effects or adverse events. Ultra-rapid metabolizers are more common in selected populations (e.g., North African) and have a high risk of toxicity from the rapid conversion of codeine to morphine. Be alert for morphine toxicities (e.g., sedation, nausea) (Sheffield & Phillimore, 2009).
- Refrain from judging patients who are not responding to standard codeine analgesics. Offer alternative analgesics. Poor and intermediate metabolizers may have reduced or no pain relief from codeine but may have side effects from high plasma concentrations (Sheffield & Phillimore, 2009). Consider morphine or nonopioid analgesics as an alternative (Crews et al., 2012).
- Be aware that some patients who are poor metabolizers may be reluctant to report a lack of pain relief after receiving codeine (Kelly, 2007). Assess analgesic responses carefully.
- Teach patients and their families about genetics and the variable analgesic responses (poor metabolizers and ultra-rapid metabolizers) to codeine medications.
- Remember that genotypes do not change, so patients who exhibit poor response to a codeine or codeine-derivative medication will not experience pain relief with additional administration (Kelly, 2007).
- Avoid prescribing tramadol for patients who may be poor or ultra-rapid metabolizers, as tramadol has chemical structure similar to codeine (Crews et al., 2012).
- Be aware that nursing mothers who are ultra-rapid metabolizers may have dangerously high serum morphine levels in their breast milk (Crews et al., 2012; FDA, 2010).
- Teach parents and caregivers that some infants and children are ultra-rapid metabolizers of codeine and can have serious toxicities over a relatively short period of time (FDA, 2008). Parents and caregivers should be taught to be alert for unusual sleepiness, disorientation, or difficulty breathing (FDA, 2013a).
- Be aware that the FDA (2013b) issued a drug safety communication that includes a boxed warning and strong recommendation against using any codeine-containing medications postoperatively for pain management in children who have had a tonsillectomy and/or adenoidectomy.

The FDA (2013b) provides consumer warning information about the use of codeine after a tonsillectomy or adenoidectomy and consumer updates for nursing mothers taking codeine (FDA, 2013c). The Flesch-Kincaid grade level readability test scores for these materials are 11.6 and 11.2, respectively. Because those reading levels are higher than the recommended eighth-grade level readability scores, nurses need to assess whether these materials are suitable for their patient populations.

Table 1. Approximate Number of Ultra-Rapid Metabolizers of Codeine in Different Populations

Population	Ultra-Rapid Metabolizers (per 100 people)
Caucasians	1–10
African Americans	3
Chinese or Japanese	1
Hispanics	1
North Africans, Ethiopians, or Saudi Arabians	16–28

Note. Table courtesy of the U.S. Food and Drug Administration, 2010.

CYP2D6 Genotype Testing

CYP2D6 genetic testing (genotyping) is not currently offered on a routine basis, although a number of academic and clinical laboratories provide the testing. A pharmacogenomics knowledge resource Web site, PharmGKB (www.pharmgkb.org/views/viewGeneticTests.action), provides a partial listing of laboratories that perform CYP2D6 genotyping. If genotyping information is known, Clinical Pharmacogenetics Implementation Consortium guidelines for codeine dosing (PharmGKB, 2012) are available.

Conclusion

Nurses need to understand that patients' responses to codeine are variable depending on genotype and metabolizer categories. Most patients will experience a therapeutic effect. However, some will notice no effect and others may have serious life-threatening toxicities. Nurses should be alert for variable responses, assess for toxicities, and adjust the patient plan of care accordingly. Pharmacogenomics is a rapidly evolving field with the promise that all patients can receive the right drug at the right dosage with maximum safety and efficacy.

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Digital Object Identifier: 10.1188/13.ONF.322-324

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Genetics & Genomics

This feature aims to educate oncology nurses about the emerging role of genetics and genomics in cancer care. Possible submissions include, but are not limited to, application of genetics and genomics in clinical practice, screening and surveillance, case studies to present new ideas or challenge current notions, and ethical issues. Manuscripts should clearly link the content to the impact on cancer care. Manuscripts should be 1,000–1,500 words, exclusive of tables and figures, and accompanied by a cover letter requesting consideration for this feature. For more information, contact Associate Editor Lisa B. Aiello-Laws, RN, MSN, AOCNS®, APN-C, at lba34@drexel.edu.