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Celecoxib Therapy and *CYP2C9* Genotype

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Introduction

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that is used in the management of osteoarthritis, rheumatoid arthritis, menstrual symptoms, and acute pain. Most NSAIDs inhibit both types of cyclooxygenase, COX-1 and COX-2. These enzymes catalyze pathways that play a key role in the generation of the inflammatory response; however, celecoxib, selectively inhibits COX-2.

The *CYP2C9* gene encodes an enzyme involved in the metabolism of many drugs, and is one of the main enzymes that metabolizes and inactivates celecoxib. Two common variants, *CYP2C9*2* and *CYP2C9*3*, are associated with significantly reduced CYP2C9 enzyme activity. Individuals who carry two copies of these variants (or other loss-of-function variant *CYP2C9* alleles) are considered CYP2C9 "poor metabolizers" and may be exposed to high drug levels after standard celecoxib doses.

The FDA-approved drug label for celecoxib states: "patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose in poor metabolizers (i.e., *CYP2C9*3/*3*). Consider using alternative management in juvenile rheumatoid arthritis (JRA) patients who are poor metabolizers" (1).

Drug: Celecoxib

Celecoxib is a NSAID that is used to treat osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, painful menstruation, and acute pain (1). It is also used to reduce the number of colon and rectum polyps in patients with familial adenomatous polyposis.

Worldwide, it is estimated that more than 30 million people receive NSAIDs daily (2). They are one of the most commonly used classes of medicine. Several NSAIDs (aspirin, ibuprofen, and naproxen) are available over-the-counter, but stronger doses and other types of NSAIDs, such as celecoxib, are only available via prescription. It is thought that approximately 25% of the population has experienced NSAID-related side effects that require medical care (3).

Most NSAIDs are non-selective COX inhibitors that reduce the production of pro-inflammatory prostaglandins by inhibiting both COX-1 and COX-2. COX is the central enzyme in the synthesis of prostaglandins and thromboxane A_2 from arachidonic acid. Prostaglandins can be protective (e.g., protect the gastric mucosal lining and aids platelet aggregation) or inflammatory (e.g., recruiting inflammatory white blood cells).

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Celecoxib is a selective COX-2 inhibitor, which promotes the production of the gastric mucosal lining. Although celecoxib may be more gastroprotective than non-selective NSAIDs (4-7), the use of celecoxib still increases the risks of gastrointestinal adverse events. The FDA-approved label for celecoxib includes the warning that:

NSAIDs, including CELECOXIB, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms (1).

In the US, acute gastrointestinal bleeding associated with the use of NSAIDs may cause more than 30,000 hospitalizations per year (8). Several risk factors for NSAID-related bleeding have been identified, including old age, a history of peptic ulcer disease, high dosages of NSAIDs, concomitant use of different NSAIDs (9), and *CYP2C9* genotype.

Gene: *CYP2C9*

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs in the liver. The CYP450 genes are very polymorphic and can result in reduced, absent, or increased enzyme activity. CYP2C9 metabolizes approximately 15% of clinically used drugs, and atypical metabolic activity caused by genetic variants in the *CYP2C9* gene can play a major role in adverse drug reactions (10, 11).

At least 16 different NSAIDS are metabolized, in part, by CYP2C9 (12). Celecoxib is extensively metabolized by CYP2C9, with minor contributions from CYP3A4, CYP2C8 and CYP2C19 (3).

*CYP2C9*1* is the wild-type allele and is associated with normal enzyme activity and the normal metabolizer phenotype. Two common variants, *CYP2C9*2* (p.Arg144Cys) and *CYP2C9*3* (p.Ile359Leu), are associated with significantly reduced enzyme activity. Carriers of these variants have altered pharmacokinetics of several NSAIDs: celecoxib, flurbiprofen, ibuprofen, and tenoxicam (12, 13). This could potentially lead to dose recommendations based upon *CYP2C9* genotype, and be used to identify individuals who are at increased risk of adverse events. However, pharmacogenetic testing has been limited to retrospective studies to identify the causes of an atypical response to NSAID (11).

Studies have found that *CYP2C9*3* is associated with an increased risk of bleeding associated with NSAID use (9, 14). In contrast, *CYP2C9*3* was found to be beneficial in a trial where celecoxib was given to prevent colorectal adenomas. High dose celecoxib had greater efficacy in preventing new adenomas than low-dose celecoxib, but only among individuals who were carriers of *CYP2C9*3* (15, 16).

The frequencies of variant *CYP2C9* alleles vary between different ethnic groups (17-19). The **2* allele is more common in Caucasian and Middle Eastern populations (10-20%), than in Asian or African populations (0-6%) (19-21). The **3* allele is less common (<10% in most populations) and extremely rare in African populations (19, 22).

The influence of other variant alleles, such as *CYP2C9*8* and *CYP2C9*11*, on celecoxib levels in the plasma has not yet been evaluated.

Genetic Testing

Clinical genotyping tests are available for several *CYP2C9* alleles, and a list of tests is available at the Genetic Testing Registry (GTR) of the National Institutes of Health: http://www.ncbi.nlm.nih.gov/gtr/tests/?term=1559[geneid].

The variants that are most commonly tested for are *CYP2C9*2* and *CYP2C9*3*. Test results are typically reported as a diplotype (e.g., *CYP2C9 *3/*3*), and may also include an interpretation of the patient's predicted metabolizer phenotype: ultrarapid, normal (extensive), intermediate, or poor.

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2015 Statement from the US Food and Drug Administration (FDA): Poor Metabolizers of CYP2C9 Substrates: Patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose in poor metabolizers (i.e., *CYP2C9*3/*3*). Consider using alternative management in junior rheumatoid arthritis (JRA) patients who are poor metabolizers.

Please review the complete therapeutic recommendations that are located here: (1).

Nomenclature

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C9*2*	430C>T Arg144Cys	NM_000771.3:c.430C>T	NP_000762.2:p.Arg144Cys	rs1799853
*CYP2C9*3*	1075A>C Ile359Leu	NM_000771.3:c.1075A>C	NP_000762.2:p.Ile359Leu	rs1057910

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

Nomenclature for Cytochrome P450 enzymes is available from the Human Cytochrome P450 (CYP) Allele Nomenclature Database: http://www.cypalleles.ki.se/

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[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

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