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Piroxicam Therapy and *CYP2C9* Genotype

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Introduction

Piroxicam (brand name Feldene) is a nonsteroidal anti-inflammatory drug (NSAID) used to treat osteoarthritis and rheumatoid arthritis. Piroxicam provides pain relief and reduces inflammation.

Piroxicam is primarily metabolized by CYP2C9. Individuals who lack CYP2C9 activity ("CYP2C9 poor metabolizers") have an increased exposure to piroxicam, and an increased risk of side effects.

Like all NSAIDs, piroxicam increases the risk of serious cardiovascular events, including myocardial infarction and stroke, and serious gastrointestinal (GI) adverse events such as bleeding, ulceration, and perforation.

The standard dose of piroxicam for osteoarthritis and rheumatoid arthritis in adults is 20 mg once daily. But for all patients, the lowest effective dose of piroxicam should be used for the shortest length of time, consistent with the treatment goals of each individual (1).

The FDA-approved drug label for piroxicam states that a dose reduction should be considered in "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 and phenytoin)". Dose reductions should be considered because these patients may have abnormally high plasma levels of piroxicam caused by reduced metabolic clearance. However, specific dose reductions based on CYP2C9 phenotype are not provided (Table 1) (1).

As for all NSAIDs, piroxicam is contraindicated in patients with a known hypersensitivity, a history of asthma, urticaria, or other allergic-type reactions after taking aspirin or another NSAID, and following coronary artery bypass graft (CABG) surgery. Piroxicam should also be avoided by pregnant women starting at 30 weeks gestation.

Table 1. The FDA (2018) Drug Label for Piroxicam. Recommendations for CYP2C9 Phenotype. Pharmacogenomics.

Phenotype	Recommendations
CYP2C19 poor metabolizers	In 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 and phenytoin) consider dose reduction as they may have abnormally high plasma levels due to reduced metabolic clearance.

This table is adapted from (1).

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Drug Class: NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat inflammation, fever, and pain. They are one of the most commonly used classes of medicine. Worldwide, it is estimated that more than 30 million people receive NSAIDs daily (2).

Currently, more than 20 NSAIDs are licensed for use. Several NSAIDs (e.g., aspirin, ibuprofen, and naproxen) are available over-the-counter, but stronger doses and other types of NSAIDs, such as celecoxib and piroxicam, are only available via prescription.

The main action of NSAIDs is to inhibit cyclooxygenase (COX). Cyclooxygenase is the central enzyme in the synthesis of prostaglandins, prostacyclin, and thromboxanes from arachidonic acid. Prostaglandins can be protective (e.g., protect the gastric mucosal lining and aid platelet aggregation) or inflammatory (e.g., recruiting inflammatory white blood cells).

There are 2 main isoforms of COX, and the safety, and effectiveness of NSAIDs may be influenced by the degree they inhibit the 2 different forms. Cyclooxygenase-1 (COX-1) is a "housekeeping enzyme" which is expressed in most tissues. It protects the GI tract and induces platelet aggregation in response to injury. In contrast, COX-2 is often undetectable in tissues. However, the expression of COX-2 is increased during inflammation.

Most NSAIDs are non-selective COX inhibitors that inhibit both COX-1 and COX-2. There are exceptions, such as celecoxib, which is a selective COX-2 inhibitor that appears to be associated with less adverse GI events. However, GI adverse events still occur.

Approximately 25% of the exposed US population has experienced NSAID-related side effects that required medical care (3). All NSAIDs carry a boxed warning regarding the risk of serious GI and cardiovascular adverse events; e.g.,

"NSAIDs cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.

NSAIDs 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. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events" (1).

Drug: Piroxicam

Piroxicam is an NSAID used for the relief of osteoarthritis and rheumatoid arthritis. The recommended dose in adults is 20 mg daily, and although therapeutic effects are seen early, it takes up to 12 days for steady-state levels to be reached. Therefore, the effect of therapy should not be assessed for the first 2 weeks.

Because of the adverse events associated with any type of NSAID, the lowest effective dose of piroxicam should be used for the shortest duration. And, as for all NSAIDs, piroxicam is contraindicated in patients with a known hypersensitivity, or a history of asthma, urticaria, or other allergic-type reactions after taking aspirin or another NSAID. Piroxicam is also contraindicated to treat pain in the days following CABG surgery (NSAIDs cause an increased risk of myocardial infarction and stroke post-operatively), and piroxicam should be avoided by pregnant women starting at 30 weeks gestation (NSAID use in the third trimester causes an increased risk of premature closure of the fetal ductus arteriosus).

A subset of NSAIDs, known as oxicams, are highly potent and share a similar structure with a new binding fold that is different to typical NSAIDs. Piroxicam was the first oxicam to be licensed, other oxicams include isoxicam, meloxicam, tenoxicam, and lornoxicam (4, 5).

One study found that oxicams (piroxicam and tenoxicam) had a higher risk of Stevens -Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN) (relative risk [RR] of 34) than diclofenac (RR 4.1) and ibuprofen (RR 5.3). However, the absolute risk of SJS or TEN during piroxicam is still thought to be low –– the incidence of SJS or TEN during the first 8 weeks of piroxicam or tenoxicam therapy is one per 100,000 patients (6).

CYP2C9 is the main enzyme involved in the metabolism of piroxicam to its major inactive metabolite: 5′-hydroxy-piroxicam. Individuals with low CYP2C9 activity ("CYP2C9 poor metabolizers") have a higher exposure to piroxicam (1).

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 (7).

The *CYP2C9* gene is highly polymorphic, with approximately 60 known alleles. *CYP2C9*1* is considered the wild-type allele when no variants are detected, and is categorized by normal enzyme activity (8). Individuals who have 2 normal-function alleles (e.g., *CYP2C9 *1/*1*) are classified as "normal metabolizers" (Table 2).

Table 2. Assignment of likely *CYP2C9* Phenotype based on Genotype (CPIC, 2014)

Likely phenotype[a]	Genotype	Examples of diplotypes
Ultrarapid metabolizer (increased activity) (frequency unknown)	Unknown – currently there are no known increased activity alleles	Unknown
Normal metabolizer (normal activity) (approximately 91% of individuals)	An individual with 2 normal-function alleles	*1/*1
Intermediate metabolizer (heterozygote or intermediate activity) (approximately 8% of individuals)[b]	An individual with one normal-function allele plus one decreased-function allele	*1/*3, *1/*2
Poor metabolizer (homozygous variant, low or deficient activity) (approximately 1% of individuals)	An individual with 2 decreased function alleles	*2/*2, *3/*3, *2/*3

Note: There are no known cases of CYP2C9 ultrarapid metabolizers
[a] Global frequencies are approximate. Because haplotype frequencies vary considerably among popualations, please see (8) for individual population frequencies.
[b] The enzyme activity in this grouping varies widely. Please see (8) for activity ranges.
This table is adapted from (8). Note: The nomenclature used in this table reflects the standardized pharmacogenetic terms proposed by CPIC (9).

Two allelic variants associated with reduced enzyme activity are *CYP2C9*2* and **3*. The **2* allele is more common in Caucasian (10-20%), than Asian (1-3%) or African (0-6%) populations. The **3* allele is less common (<10% in most populations) and is extremely rare in African populations. In African-Americans, the *CYP2C9*5*, **6*, **8* and **11* alleles are more common (10-12).

Linking Gene Variation with Treatment Response

Studies have shown that CYP2C9 poor metabolizers have increased exposure and reduced clearance when taking standard doses of piroxicam (1, 13). A gene-dose effect was proposed recently to explain the gradual increase in piroxicam exposure in an individual with a *CYP2C9* *3/*3 genotype compared with those with the *1/*1 and *1/*3 genotypes. And although data are lacking, overall it appears that the decreased function alleles

*CYP2C9*2*, *CYP2C9*3* are associated with an increased risk of acute GI bleeding in patients receiving NSAID therapy. The *CYP2C8* variant, *CYP2C8*3*, may also contribute to this increased risk (3, 14, 15).

A recent small study (n=102 volunteers heterozygous for *CYP2C8*3* and *CYP2C9*3*) reported that the administration of 20 mg oral piroxicam for 4 days was effective in the control of pain following molar surgery regardless of the CYP haplotype (16). However, this study was not specifically designed to address the risk of adverse events across genotype groups, and the study used a low dose for a short duration (20 mg once daily for 4 days).

In addition to increased exposure of piroxicam by decreased CYP2C9 activity in poor metabolizers, CYP2C9 may also impact cardiovascular morbidity by altering the metabolism of fatty acids, prostanoids, and steroid hormones, especially in poor metabolizers of CYP2C9 (7).

Genetic Testing

Clinical genotyping tests are available for several *CYP2C9* alleles. The NIH Genetic Testing Registry (GTR) displays genetic tests that are currently available for the *CYP2C9* gene.

The *CYP2C9* variants that are routinely tested for include *CYP2C9*2* and **3*. Usually, the results are reported as a diplotype, such as *CYP2C9 *1/*1*, and may also include an interpretation of the patient's predicted metabolizer phenotype (normal, intermediate, or poor). Table 2 summarizes common CYP2C9 phenotypes.

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.

2018 Statement from the US Food and Drug Administration (FDA)

Higher systemic exposure of piroxicam has been noted in subjects with *CYP2C9* polymorphisms compared to normal metabolizer type subjects.

[...]

CYP2C9 activity is reduced in individuals with genetic polymorphisms, such as the *CYP2C9*2* and *CYP2C9*3* polymorphisms. Limited data from two published reports showed that subjects with heterozygous *CYP2C9*1/*2* (n=9), heterozygous *CYP2C9*1/*3* (n=9), and homozygous *CYP2C9*3/*3* (n=1) genotypes showed 1.7-, 1.7-, and 5.3-fold higher piroxicam systemic levels, respectively, than the subjects with *CYP2C9*1/*1* (n=17, normal metabolizer genotype) following administration of a single oral dose. The mean elimination half-life values of piroxicam for subjects with *CYP2C9*1/*3* (n=9) and *CYP2C9*3/*3* (n=1) genotypes were 1.7- and 8.8-fold higher than subjects with *CYP2C9*1/*1* (n=17). It is estimated that the frequency of the homozygous **3/*3* genotype is 0% to 1% in the population at large; however, frequencies as high as 5.7% have been reported in certain ethnic groups.

Poor Metabolizers of CYP2C9 Substrates: In 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 and phenytoin) consider dose reduction as they may have abnormally high plasma levels due to reduced metabolic clearance.

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

[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.

Nomenclature for selected *CYP2C9* alleles

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
*CYP2C9*5*	1080C>G Asp360Glu	NM_000771.3:c.1080C>G	NP_000762.2:p.Asp360Glu	rs28371686
*CYP2C9*6*	818delA Lys273Argfs	NM_000771.3:c.817delA	NP_000762.2:p.Lys273Argfs	rs9332131
*CYP2C9*8*	449G>A Arg150His	NM_000771.3:c.449G>A	NP_000762.2:p.Arg150His	rs7900194
*CYP2C9*11*	1003C>T Arg335Trp	NM_000771.3:c.1003C>T	NP_000762.2:p.Arg335Trp	rs28371685

Note: the normal "wild-type" allele is *CYP2C9*1* and is reported when no variant is detected.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (17).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
Nomenclature for cytochrome P450 enzymes is available from Pharmacogene Variation (PharmVar) Consortium.

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