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Flurbiprofen Therapy and *CYP2C9* Genotype

Laura Dean, MD[1]

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Introduction

Flurbiprofen (brand name Ansaid) is a nonsteroidal anti-inflammatory drug (NSAID). Tablets and skin patches are used in the management of osteoarthritis and rheumatoid arthritis. Flurbiprofen provides pain relief and reduces inflammation. Flurbiprofen eye drops (brand name Ocufen) may also be used to prevent miosis (excessive constriction of the pupil) during eye operations; e.g., cataract surgery.

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

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

The recommended starting dose of flurbiprofen tablets in adults is 200–300 mg per day, divided for administration 2, 3, or 4 times a day. But for all patients, the lowest effective dose of flurbiprofen should be used for the shortest length of time, consistent with the treatment goals of each individual.

The FDA-approved drug label for flurbiprofen states that the dose of flurbiprofen should be reduced 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)" (Table 1). This dose reduction is to avoid the abnormally high plasma levels of flurbiprofen in these patients caused by reduced metabolic clearance. However, specific dose reductions based on *CYP2C9* phenotype are not provided (1).

As for all NSAIDs, flurbiprofen 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 for coronary artery bypass graft (CABG) surgery. Flurbiprofen should also be avoided by pregnant women starting at 30 weeks gestation (1).

Table 1. The FDA (2017) Drug Label for Flurbiprofen. Poor Metabolizers of CYP2C9 Substrates.

Phenotype	Recommendations
CYP2C9 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), reduce the dose of flurbiprofen to avoid abnormally high plasma levels due to reduced metabolic clearance.

This table is adapted from (1).

Author Affiliation: 1 NCBI; Email: mgs@ncbi.nlm.nih.gov.

Drug Class: NSAIDs

NSAIDs are widely used to treat inflammation, fever, and pain. They are one of the most commonly used class of drugs. 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 higher doses and other types of NSAIDs, such as celecoxib, piroxicam, and flurbiprofen, 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. COX-1 is a "housekeeping enzyme" that 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 fewer adverse GI events. However, GI adverse events still occur.

Approximately 25% of the exposed population in the US 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: Flurbiprofen

Flurbiprofen is an NSAID used for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis. It may also be used for soft tissue injuries, such as bursitis and tendinitis.

The recommended starting dose of flurbiprofen tablets in adults is 200–300 mg per day, divided into doses to be taken 2, 3, or 4 times a day. The largest recommended single dose in a multiple-dose daily regimen is 100 mg (1).

Because of the adverse events associated with any type of NSAID, the lowest effective dose of flurbiprofen should be used, for the shortest duration. And, as for all NSAIDs, flurbiprofen 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. Flurbiprofen is also contraindicated to treat pain in the days following CABG surgery –– this is because NSAIDs increase the risk of myocardial infarction and stroke after surgery. Flurbiprofen should be avoided by pregnant women starting at 30 weeks gestation –– this is because NSAID use in the third trimester causes an increased risk of premature closure of the fetal ductus arteriosus. There are no well-controlled studies of flurbiprofen in pregnant women, but in animal studies, flurbiprofen was lethal to the embryos of pregnant rats and rabbits. Flurbiprofens' safety, efficacy, and pharmacokinetics have not established for pediatric patients.

Flurbiprofen can be taken orally (tablets) or topically (via a skin patch or cream) for the treatment of osteoarthritis and rheumatoid arthritis. Flurbiprofen is also available as an ophthalmic solution (eye drops) –– it is used before eye surgery to prevent miosis (excessive constriction of the pupil), which can occur in surgical procedures such as cataract surgery.

CYP2C9 is the main enzyme involved in the metabolism of flurbiprofen to its inactive metabolite: 4'-hydroxyflurbiprofen. Both flurbiprofen and its metabolite are eliminated as acyl glucuronides. Individuals who have decreased CYP2C9 activity, such as CYP2C9 intermediate and poor metabolizers, have a higher exposure to flurbiprofen (1, 4, 5).

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 (6).

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 as having normal enzyme activity (7). 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 carrying 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 carrying 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 populations, please see (7) for individual population frequencies.
[b] The enzyme activity in this grouping varies widely. Please see (7) for activity ranges.
This table is adapted from (7). Note: The nomenclature used in this table reflects the standardized pharmacogenetic terms proposed by the Clinical Pharmacogenetics Implementation Consortium (CPIC) (8).

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 (9-11).

Linking Gene Variation with Treatment Response

Studies have shown that CYP2C9 intermediate or poor metabolizers have increased drug exposure when taking standard doses of flurbiprofen.

Although data are lacking that link CYP2C9 intermediate or poor metabolizers with an increased risk of the adverse effects associated with NSAID therapy, the dose, and duration of NSAID therapy do influence the risk of adverse effects, such as severe GI bleeding.

Therefore, the FDA drug label for flurbiprofen recommends reducing the dose of flurbiprofen in CYP2C9 poor metabolizers. The FDA label does not however recommend a dose reduction in CYP2C9 intermediate metabolizers, despite the observed high levels of the drug in this genotype group in other studies (1, 4, 5, 12).

Genetic Testing

Clinical genotyping tests are available for several *CYP2C9* alleles. The NIH's Genetic Testing Registry (GTR) displays genetic tests that are currently available for flurbiprofen response and 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.

2017 Statement from the US Food and Drug Administration (FDA)

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), reduce the dose of flurbiprofen to avoid abnormally high plasma levels due to reduced metabolic clearance.

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

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

[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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Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*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 (13).
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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References

1. FLURBIPROFEN- flurbiprofen tablet, film coated [package insert]; June 9, 2017. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4e5c06f1-f279-4f2f-b10d-0f70005a27e6
2. Singh G., Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. J Rheumatol Suppl. 1999 Apr;56:18–24. PubMed PMID: 10225536.
3. Agúndez J.A., Garcia-Martin E., Martinez C. Genetically based impairment in CYP2C8- and CYP2C9-dependent NSAID metabolism as a risk factor for gastrointestinal bleeding: is a combination of pharmacogenomics and metabolomics required to improve personalized medicine? Expert Opin Drug Metab Toxicol. 2009 Jun;5(6):607–20. PubMed PMID: 19422321.
4. Lee C.R., Pieper J.A., Frye R.F., Hinderliter A.L., et al. Differences in flurbiprofen pharmacokinetics between CYP2C9*1/*1, *1/*2, and *1/*3 genotypes. Eur J Clin Pharmacol. 2003 Apr;58(12):791–4. PubMed PMID: 12698304.
5. Lee Y.J., Byeon J.Y., Kim Y.H., Kim S.H., et al. Effects of CYP2C9*1/*3 genotype on the pharmacokinetics of flurbiprofen in Korean subjects. Arch Pharm Res. 2015 Jun;38(6):1232–7. PubMed PMID: 25712887.
6. Kirchheiner J., Brockmoller J. Clinical consequences of cytochrome P450 2C9 polymorphisms. Clin Pharmacol Ther. 2005 Jan;77(1):1–16. PubMed PMID: 15637526.
7. Relling M.V., McDonagh E.M., Chang T., Caudle K.E., et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of G6PD deficiency genotype. Clin Pharmacol Ther. 2014 Aug;96(2):169–74. PubMed PMID: 24787449.
8. Hicks J.K., Sangkuhl K., Swen J.J., Ellingrod V.L., et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017 Dec 20;102(1):37–44. PubMed PMID: 27997040.
9. Sistonen J., Fuselli S., Palo J.U., Chauhan N., et al. Pharmacogenetic variation at CYP2C9, CYP2C19, and CYP2D6 at global and microgeographic scales. Pharmacogenetics and genomics. 2009 Feb;19(2):170–9. PubMed PMID: 19151603.
10. Solus J.F., Arietta B.J., Harris J.R., Sexton D.P., et al. Genetic variation in eleven phase I drug metabolism genes in an ethnically diverse population. Pharmacogenomics. 2004 Oct;5(7):895–931. PubMed PMID: 15469410.
11. Lee C.R., Goldstein J.A., Pieper J.A. Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. Pharmacogenetics. 2002 Apr;12(3):251–63. PubMed PMID: 11927841.

12. Vogl S., Lutz R.W., Schonfelder G., Lutz W.K. CYP2C9 genotype vs. metabolic phenotype for individual drug dosing--a correlation analysis using flurbiprofen as probe drug. PLoS One. 2015;10(3):e0120403. PubMed PMID: 25775139.
13. Kalman L.V., Agundez J., Appell M.L., Black J.L., et al. Pharmacogenetic allele nomenclature: International workgroup recommendations for test result reporting. Clin Pharmacol Ther. 2016 Feb;99(2):172–85. PubMed PMID: 26479518.

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