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Carisoprodol Therapy and *CYP2C19* Genotype

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Introduction

Carisoprodol is a centrally acting muscle relaxant used to relieve acute back pain. Due to the risk of dependence and abuse, carisoprodol should only be used for treatment periods of up to two or three weeks. Carisoprodolol is a Schedule IV controlled substance and carisoprodol overdose can lead to CNS respiratory depression, seizures, and death.

Carisoprodol is metabolized by CYP2C19 to meprobamate, a sedative used to treat anxiety disorders. In individuals who have little or no CYP2C19 activity ("CYP2C19 poor metabolizers"), standard doses of carisoprodol can lead to a 4-fold increase in exposure to carisoprodol and a concomitant 50% reduced exposure to meprobamate compared to normal metabolizers. Approximately 3–5% of Caucasians and Africans, and 15–20% of Asians, are CYP2C19 poor metabolizers (1).

The FDA-approved drug label for carisoprodol states that caution should be used when administering carisoprodol to patients with reduced CYP2C19 activity and when co-administering drugs that inhibit or induce CYP2C19 (1). There are no data on the use of carisoprodol in pregnancy, and the efficacy, safety, and pharmacokinetics of carisoprodol have not been established in pediatric patients (less than 16 years of age).

Drug: Carisoprodol

Carisoprodol is a centrally acting muscle relaxant used to treat acute musculoskeletal pain. It is often used to treat acute low back pain, providing pain relief and helping patients mobilize. However, its clinical use is limited by the risk of abuse (it is a Schedule IV controlled substance) and its toxic effects in overdose, which may be fatal.

The mechanism of action of carisoprodol is not well understood, but it is an indirect agonist of the $GABA_A$ receptor associated with altered neuronal communication at the reticular formation in the brainstem and at the spinal cord. In addition to its skeletal muscle relaxing effects, carisoprodol also has weak anticholinergic, antipyretic, and analgesic properties. Adverse effects include sedation, tachycardia, shortness of breath, and dizziness (2, 3).

Carisoprodol is metabolized by CYP2C19 into meprobamate—an active metabolite that has similar potency to carisoprodol. Meprobamate is used to treat anxiety. Again, its mechanism of action is not well understood, but it has barbiturate-like properties and is toxic in overdose (4).

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Individuals who have reduced or absent activity of CYP2C19 have higher plasma levels of carisoprodol, and a higher ratio of carisoprodol:meprobamate, compared to individuals who have normal levels of CYP2C19 activity. Carisoprodol's narrow therapeutic index implies there may be increased risk of toxicity in CYP2C19 poor metabolizers. However, data are limited. Small studies have found no evidence to support an association between *CYP2C19* genotype status and the mortality risk of carisoprodol or adverse effects after a single dose of carisoprodol (4-6).

The FDA-approved drug label for carisoprodol states that caution should be used when administering carisoprodol to patients with reduced CYP2C19 activity. The label also states that the co-administration of CYP2C19 inhibitors, such as omeprazole or fluvoxamine, could result in increased exposure of carisoprodol and decreased exposure of meprobamate, and the co-administration of CYP2C19 inducers, such as rifampin or St. John's Wort, could result in decreased exposure of carisoprodol and increased exposure of meprobamate. Low dose aspirin also showed induction effect on CYP2C19. The label states that the full pharmacological impact of these potential alterations of exposures in terms of either efficacy or safety of carisoprodol is unknown (1).

Gene: *CYP2C19*

The CYP2C19 enzyme contributes to the metabolism of a range of clinically important drugs, such as several proton pump inhibitors, clopidogrel, benzodiazepines, and several tricyclic antidepressants, including imipramine.

The *CYP2C19* gene is highly polymorphic—35 variant star (*) alleles are catalogued at the Pharmacogene Variation Consortium database: https://www.pharmvar.org/.

The *CYP2C19*1* wild-type allele is associated with normal enzyme activity and the "normal metabolizer" phenotype, whereas the *CYP2C19*17* allele is associated with increased enzyme activity and the "rapid" and "ultrarapid" metabolizer phenotypes (7).

The most common loss-of-function variant is *CYP2C19*2*, which contains a c.681G>A variant in exon 5 that results in an aberrant splice site. This leads to the production of a truncated and non-functioning protein. The *CYP2C19*2* allele frequencies are ~15% in Caucasians and Africans, and ~29–35% in Asians (7, 8).

Another commonly tested loss-of-function variant is *CYP2C19*3*, which contains a c.636G>A variant in exon 4 that causes a premature stop codon. The *CYP2C19*3* allele frequencies are ~2–9% in Asian populations, but rare in other racial groups. Other loss-of-function variants occur in less than 1% of the general population and include *CYP2C19*4-*8* (7, 8).

CYP2C19 intermediate metabolizers carry one copy of an allele that encodes reduced or absent function (e.g. **1/*2*), whereas "poor metabolizers" are homozygous or compound heterozygous for two loss-of-function alleles (e.g., **2/*2*, **2/*3*) (table 1).

Table 1. *CYP2C19* functional status and phenotypes

Phenotype	Genotype	Examples of diplotypes
CYP2C19 Ultrarapid metabolizer (~2–5% of patients)[a]	An individual carrying two increased function alleles.	**17/*17*
CYP2C19 Rapid metabolizer (~2–30% of patients)	An individual carrying one normal function allele and one increased function allele.	**1/*17*
CYP2C19 Normal metabolizer (~35–50% of patients)	An individual carrying two normal function alleles.	**1/*1*

Table 1. continued from previous page.

Phenotype	Genotype	Examples of diplotypes
CYP2C19 Intermediate metabolizer (~18–45% of patients)	An individual carrying one normal function allele and one no function allele or one no function allele and one increased function allele.	**1/*2* **1/*3* **2/*17*[b]
CYP2C19 Poor metabolizer (~2–15% of patients)	An individual carrying two no function alleles.	**2/*2* **2/*3* **3/*3*

[a] CYP2C19 metabolizer status frequencies are based on average multi-ethnic frequencies. See the *CYP2C19* Frequency Tables for population-specific allele and phenotype frequencies (9).
[b] The predicted metabolizer phenotype for the**2/*17* genotype is a provisional classification. The currently available evidence indicates that the *CYP2C19*17* increased function allele is unable to completely compensate for the *CYP2C19*2* no function allele.
Table is adapted from Hicks J.K., Sangkuhl K., Swen J.J., Ellingrod V.L., Müller D.J., Shimoda K., Bishop J.R., Kharasch E.D., Skaar T.C., Gaedigk A., Dunnenberger H.M., Klein T.E., Caudle K.E., and Stingl J.C. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update. 2016 Dec 20; doi: 10.1002/cpt.597. [Epub ahead of print] (9)
Note: The nomenclature used in this table reflects the standardized nomenclature for pharmacogenetic terms proposed by CPIC in a 2016 paper, "Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)" (10).

Genetic Testing

Clinical genotyping tests are available for several *CYP2C19* alleles. The NIH's Genetic Testing Registry (GTR) provides examples of the genetic tests that are currently available for carisoprodol response, CYP2C19-related poor drug metabolism, and the CYP2C19 gene.

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.

2016 Statement from the US Food and Drug Administration (FDA):

Carisoprodol Tablets are metabolized in the liver by CYP2C19 to form meprobamate. Co-administration of CYP2C19 inhibitors, such as omeprazole or fluvoxamine, with Carisoprodol Tablets could result in increased exposure of carisoprodol and decreased exposure of meprobamate. Co-administration of CYP2C19 inducers, such as rifampin or St. John's Wort, with Carisoprodol Tablets could result in decreased exposure of carisoprodol and increased exposure of meprobamate. Low dose aspirin also showed induction effect on CYP2C19.

The full pharmacological impact of these potential alterations of exposures in terms of either efficacy or safety of Carisoprodol Tablets is unknown.

[...]

Patients with Reduced CYP2C19 Activity: Carisoprodol Tablets should be used with caution in patients with reduced CYP2C19 activity. Published studies indicate that patients who are poor CYP2C19 metabolizers have a 4-fold increase in exposure to carisoprodol, and concomitant 50% reduced exposure to meprobamate compared to normal CYP2C19 metabolizers. The prevalence of poor metabolizers in Caucasians and African Americans is approximately 3-5% and in Asians is approximately 15-20%.

[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.

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

Nomenclature for selected *CYP2C19* alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C19*2*	681G>A Pro227Pro	NM_000769.1:c.681G>A	NP_000760.1:p.Pro227=	rs4244285
*CYP2C19*3*	636G>A Trp212Ter	NM_000769.1:c.636G>A	NP_000760.1:p.Trp212Ter	rs4986893
*CYP2C19*17*	-806C>T	NM_000769.2:c.-806C>T	Not applicable—variant occurs in a non-coding region	rs12248560

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 Pharmacogene Variation Consortium database: https://www.pharmvar.org/

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