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Omeprazole Therapy and *CYP2C19* Genotype

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Introduction

Omeprazole blocks the secretion of gastric acid and belongs to the drug class of proton pump inhibitors. It is used to treat gastroesophageal reflux disease (GERD), gastric ulcers, duodenal ulcers, erosive esophagitis, and other acid-related disorders. It is also used in the treatment of hypersecretory conditions, such as Zollinger-Ellison syndrome, and is used in combination with antibiotics to eradicate *Helicobacter pylori (H. pylori)* infection (1).

CYP2C19 is the principal enzyme that metabolizes omeprazole to inactive metabolites. Approximately 3% of Caucasians and 15 to 20% of Asians have reduced or absent CYP2C19 enzyme activity ("poor metabolizers"). In these individuals, standard doses of omeprazole may lead to higher exposure to the drug and improved treatment outcomes (2). In contrast, individuals with increased CYP2C19 activity ("ultrarapid metabolizers") may have an insufficient response to treatment as the active drug is inactivated at a faster rate.

The FDA-approved drug label for omeprazole states that a dose reduction should be considered in the Asian population, particularly for the maintenance of healing of erosive esophagitis (1). The Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) has published dose alterations based on *CYP2C19* genotype. For *CYP2C19* poor metabolizers, they do not recommend altering the dose; however for ultrarapid metabolizers, they recommend being extra alert to an insufficient response to treatment. For the eradication of *H. pylori* in ultrarapid metabolizers, they recommend increasing the dose of omeprazole by 100–200%, and to consider the same dose increase for other conditions (see Table 1) (3, 4).

Table 1. *CYP2C19* phenotypes and the therapeutic recommendations for omeprazole therapy, adapted from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP).

Phenotype	Phenotype details	Examples of diplotypes	Therapeutic (dose) recommendations for omeprazole
Ultrarapid metabolizer	Normal or increased CYP2C19 activity	**17/*17*	Be extra alert to insufficient response. For the eradication of *H. pylori*, increase dose by 100–200%. For other conditions, consider dose increase by 100–200%.
Extensive metabolizer	Normal CYP2C19 activity	**1/*1*	No recommendations

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Table 1. continued from previous page.

Phenotype	Phenotype details	Examples of diplotypes	Therapeutic (dose) recommendations for omeprazole
Intermediate metabolizer	Decreased CYP2C19 activity	**1/*2* **1/*3* **2/*17* **3/*17*	No recommendations
Poor metabolizer	Markedly reduced or absent CYP2C19 activity	**2/*2* **2/*3* **3/*3*	No recommendations

Good quality evidence supports the dose recommendations for poor and intermediate metabolizers; moderate quality evidence supports the dose recommendations for ultrarapid metabolizers.
Table is adapted from Swen J.J., Nijenhuis M., de Boer A., Grandia L. et al. Pharmacogenetics: from bench to byte - an update of guidelines. Clinical pharmacology and therapeutics. 2011;89(5):662–73 (3).

Drug class: Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are inhibitors of gastric acid secretion that are used in the treatment of stomach-acid related disorders. PPIs are also used to prevent and treat ulcers associated with nonsteroidal anti-inflammatory drugs (NSAIDs), and can be used in combination with antibiotics to eradicate *H. pylori* infection.

Six PPIs are currently FDA-approved for clinical use: esomeprazole, dexlansoprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. All PPIs are similarly potent at inhibiting gastric acid secretion and are thought to be similarly efficacious (5, 6).

PPIs are metabolized and inactivated by a number of CYP enzymes, including CYP2C19, which has a principal role in the metabolism of omeprazole. The increased function *CYP2C19*17* variant allele may enhance PPI clearance (7) resulting in less active PPI available to inhibit gastric acid secretion. In contrast, the *CYP2C19*2* loss-of-function allele is associated with decreased PPI clearance, resulting in more active PPI available and enhanced treatment. For several PPIs, including omeprazole and lansoprazole, higher drug levels in patients with low or absent CYP2C19 activity have been associated with increased drug efficacy and improved treatment outcomes (2, 8).

Drug: Omeprazole

Omeprazole was the first PPI to be introduced to the US market in 1989. Today, omeprazole is one of the PPIs that are available both as prescription and over-the-counter (OTC) medications.

In adults, omeprazole is used in the treatment of ulcers (gastric and duodenal), GERD, and to maintain healing of erosive esophagitis. Omeprazole is also used in the long-term treatment of hypersecretory conditions such as Zollinger-Ellison syndrome, multiple endocrine adenomas, and systemic mastocytosis. In children, omeprazole is used in the treatment of GERD and erosive esophagitis (1).

The human stomach contains approximately one billion parietal cells that secrete hydrochloric acid (HCl) into the gastric lumen. Gastric acid aids digestion by hydrolyzing dietary protein and facilitating the absorption of calcium, iron, and vitamin B. Gastric acid also helps maintain a sterile environment by suppressing the growth of bacteria (9).

Hydrogen ions (H+) are actively secreted in to the gastric lumen in exchange for potassium ions (K+) via an H^+/K^+-ATPase, which is also known as a "proton pump". Located on the surface of gastric parietal cells, the proton pump controls the last step in acid secretion, and by targeting this step, omeprazole and the other PPIs are able to potently inhibit gastric acid secretion.

Omeprazole is metabolized and inactivated in the liver by the cytochrome P450 system. CYP2C19 is the principal enzyme involved, although other enzymes such as CYP3A4 may also contribute. Omeprazole is metabolized to hydroxy and desmethyl metabolites, which have no effect on gastric acid secretion (10).

Individuals with reduced CYP2C19 enzyme activity may experience twice the exposure to omeprazole compared to individuals with normal enzyme function. This reduced enzyme activity has a positive effect on clinical outcomes, and because PPIs are generally regarded as safe drugs, especially in the short-term (less than 6 months), this can have a beneficial effect without an increased risk of omeprazole toxicity (11, 12).

One study reported that when using omeprazole as part of the treatment to eradicate *H. pylori*, success was achieved in all patients who had little or no CYP2C19 activity, but in only 29% of patients who had "normal" CYP2C19 activity. Similar results were found in another study that evaluated lansoprazole in the treatment of GERD: the cure rate was 85% for patients with little or no CYP2C19 activity, compared to 16% for patients with normal CYP219 activity (13-15).

The FDA-approved drug label for omeprazole does not comment on dose adjustments based on CYP2C19 status. However, guidelines from KNMP recommend that patients with increased CYP2C19 activity ("ultrarapid metabolizers") should receive an increased dose of omeprazole for the eradication of *H. pylori*, and that an increased dose should be considered for other indications (Table 1).

The long-term use of PPIs has been associated with several adverse effects. Daily treatment with any PPI for longer than three years may lead to malabsorption of vitamin B12, caused by hypochlorhydria. Because prolonged hypochlorhydria also increases the risk of *Clostridium difficile* infection, and may increase the risk for osteoporosis-related fractures, the FDA recommends that patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated (1).

Gene: *CYP2C19*

The cytochrome P450 superfamily (CYP) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The CYP genes are very polymorphic and can result in reduced, absent, or increased drug metabolism.

The CYP2C19 enzyme contributes to the metabolism of a range of clinically important drugs, such as antidepressants, benzodiazepines, and some of the PPIs, including omeprazole.

CYP2C19 is highly polymorphic, as 35 variant star (*) alleles are currently 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 "extensive metabolizer" phenotype (16).

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 (17). "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*).

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* (17, 18).

In contrast to non-functional alleles, the *CYP2C19*17* allele (c.-806C>T) is associated with increased enzyme activity. Allele frequencies range from 3 to 21% across different populations (19). Individuals who are homozygous for the **17* allele are known as "ultrarapid metabolizers", and it is this patient group who may

benefit from an increased dose of omeprazole. However, not all studies have identified a significant effect of *CYP2C19*17* on the metabolism of PPIs and treatment outcomes (15, 20, 21).

Genetic Testing

Currently, the FDA does not provide recommendations about the use of *CYP2C19* genetic testing for omeprazole treatment (1).

Clinical genotyping tests are available for several *CYP2C19* alleles, and a list of some test providers is available at the Genetic Testing Registry (GTR) of the National Institutes of Health: http://www.ncbi.nlm.nih.gov/gtr/tests/?term=1557[geneid].

Usually a patient's result is reported as a diplotype, such as *CYP2C19 *1/*1*, and may also include an interpretation of the patient's predicted metabolizer phenotype (ultrarapid, extensive, intermediate, or poor).

Table 1 summarizes common *CYP2C19* phenotypes with recommendations developed by the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP).

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.

2014 Statement from the US Food and Drug Administration (FDA): Asian Population: In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared with Caucasians. Dose reduction, particularly where maintenance of healing of erosive esophagitis is indicated, for Asian subjects should be considered.

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

2011 Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP): For individuals who are ultrarapid metabolizers, an increase in the dose of omeprazole by 100–200% is recommended for the eradication of *H.pylori*, and the physician should be extra alert to an insufficient response. For other conditions, the physician should remain extra alert to an insufficient response, and consider a dose increase by 100–200%.

There are no therapeutic (dose) recommendations for individuals who are either poor or intermediate metabolizers.

Please review the complete therapeutic recommendations that are located here: (3).

Nomenclature

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

[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 labelled all formulations containing the generic drug.

Table continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*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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Version History

To view an earlier version of this summary (update: 18 March 2013), please click here.

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