Omeprazole Therapy and *CYP2C19* Genotype

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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 and duodenal ulcers. It is also used to eradicate *H. pylori* infection and maintain healing in erosive esophagitis.

CYP2C19 is the principal enzyme that metabolizes omeprazole to inactive metabolites. In individuals who have reduced or absent CYP2C19 enzyme activity, the recommended doses of omeprazole may lead to higher exposure to the drug and increased clinical efficacy. In contrast, individuals with increased CYP2C19 activity ("ultrarapid metabolizers") may be exposed to lower levels of omeprazole.

Currently, the FDA does not provide recommendations about the use of *CYP2C19* genetic testing for omeprazole treatment ([1]). However, the Dutch Pharmacogenetics Working Group recommends dose alterations based on *CYP2C19* genotype. For the eradication of *H. pylori* in ultrarapid metabolizers, they recommend a 100–200% increase of omeprazole dose. The same dose increase should also be considered for the treatment of other conditions (see Table 1) ([2, 3]).

Table 1.

CYP2C19 phenotypes and the therapeutic recommendations for omeprazole therapy

Phenotype	Phenotype details	Examples of diplotypes	Therapeutic 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*	Dose recommended by drug label
Intermediate metabolizer	Decreased CYP2C19 activity	**1/*2* **1/*3* **2/*17* **3/*17*	Dose recommended by drug label
Poor metabolizer	Markedly reduced or absent CYP2C19 activity	**2/*2* **2/*3* **3/*3*	Dose recommended by drug label

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: Omeprazole

Omeprazole, like all proton pump inhibitors, blocks gastric acid secretion in a dose-dependent manner. It acts by inhibiting the H^+/K^+-ATPase ("proton pumps") in gastric parietal cells ([4]).

Omeprazole is metabolized in the liver by the cytochrome P450 system. Most of the drug is metabolized by the CYP2C19 enzyme, which forms hydroxy and desmethyl metabolites, which have no effect on gastric acid secretion. Omeprazole is also metabolized by CYP3A4 ([5]).

For many proton pump inhibitors, the activity of CYP2C19 influences the level of drug exposure, drug response (higher pH), and clinical outcome (eradication of *H. pylori*, healing rates of peptic ulcers, and GERD) ([6]). Individuals with reduced CYP2C19 enzyme activity may experience twice the drug exposure compared to individuals with normal enzyme function ([1]), which can have a positive clinical effect ([7, 8]). Patients with increased CYP2C19 activity may require an increased dose of omeprazole to compensate for the increased rate of drug metabolism.

Gene: *CYP2C19*

The cytochrome P450 superfamily (CYP) is a large and diverse group of enzymes, which together form the major system for metabolizing drugs. The CYP genes are often polymorphic and can result in either reduced or absent drug metabolism, or conversely, increased drug metabolism.

CYP2C19 is involved in the metabolism of many drugs, and the *CYP2C19* gene is highly polymorphic with more than 25 currently known variants. *CYP2C19*1* is the wild-type allele and is associated with normal enzyme activity. Individuals who are homozygous for the **1* allele are known as "extensive metabolizers" ([9]).

The most common loss-of-function variant is *CYP2C19*2* (c.681G>A), which has allele frequencies of ~15% in Caucasians and Africans, and 29–35% in Asians ([5]). It is inherited as an autosomal co-dominant trait ([10]). "Intermediate metabolizers" carry one copy of an allele that encodes reduced or absent function (e.g. **1/*2*), whereas "poor metabolizers" are homozygous for two loss-of-function alleles (e.g. **2/*2*).

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% in different populations ([10]). 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 proton pump inhibitors and treatment outcomes ([7, 11, 12]).

Genetic Testing

Genetic testing is available for several *CYP2C19* variant alleles, including the **17* allele ([7]). Currently, the FDA does not provide recommendations about the use of *CYP2C19* genetic testing for omeprazole treatment ([1])

Therapeutic Recommendations based on Genotype

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

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	Variant	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*17*	-806C>T	NM_000769.1:c.-806C>T	Not applicable—variant occurs in a (non-coding) promoter 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

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Tests in GTR by Condition

Omeprazole response

Tests in GTR by Gene

CYP2C19 gene