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NLM Citation: Dean L. Carvedilol Therapy and *CYP2D6* Genotype. 2018 Aug 1. In: Pratt VM, McLeod HL, Rubinstein WS, et al., editors. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Carvedilol Therapy and *CYP2D6* Genotype

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Created: August 1, 2018.

Introduction

Carvedilol (brand name Coreg) is used to treat heart failure and high blood pressure (hypertension). It is also used in patients who developed left ventricular dysfunction after having a heart attack (myocardial infarction, MI). In patients with cardiovascular disease, carvedilol is associated with improvements in quality of life, hospitalization rates, and survival.

Carvedilol is a non-selective beta blocker (beta 1 and beta 2) and an alpha 1 blocker. It reduces the energy demands on the heart by blocking cardiac beta receptors, which decreases the heart rate and the force of heart contractions. Carvedilol lowers blood pressure by blocking alpha receptors on blood vessels, which relaxes and dilates blood vessels.

CYP2D6 is one of the primary enzymes involved in activating and metabolizing carvedilol. Approximately 8% of Caucasians and 2% of most other populations have absent CYP2D6 activity and are predicted to be "CYP2D6 poor metabolizers."

The FDA-approved drug label for carvedilol states that plasma concentrations of carvedilol may be higher in CYP2D6 poor metabolizers compared to normal metabolizers, but does not discuss altering carvedilol dosing based on a patient's *CYP2D6* genotype (1). However, the label does state the dose of carvedilol should be individualized, and the dose should be monitored as it is gradually increased (up-titrated), based on tolerability and clinical response (Table 1).

The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) recommend that no action is needed for carvedilol and *CYP2D6* genotype. For CYP2D6 poor metabolizers, DPWG states that the plasma concentration of carvedilol can be elevated, but this does not result in an increase in side effects (Table 2) (2).

Table 1. FDA (2017) Drug Label for Carvedilol. Therapeutic recommendations based on *CYP2D6* Genotype.

Phenotype	Carvedilol
CYP2D6 poor metabolizers	Retrospective analysis of side effects in clinical trials showed that poor CYP2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the α-blocking R(+) enantiomer.

Please see Therapeutic Recommendations based on Genotype for more information from FDA. This table is adapted from (1).

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Table 2. DPWG (2016) Recommendations for Carvedilol and *CYP2D6*

Phenotype	Recommendations
CYP2D6 poor metabolizers	No action is required for this gene-drug interaction. The plasma concentration of carvedilol can be elevated. This does not, however, result in an increase in side effects.
CYP2D6 intermediate metabolizers	No action is required for this gene-drug interaction. The plasma concentration of carvedilol can be elevated. This does not, however, result in an increase in side effects.
CYP2D6 ultrarapid metabolizers	No action is required for this gene-drug interaction. The plasma concentration of carvedilol can be reduced. This does not, however, result in a decrease in the effectiveness.

Please see Therapeutic Recommendations based on Genotype for more information from DPWG. This table is adapted from (2).

Drug: Carvedilol

Carvedilol is widely considered to be the standard of care for patients with heart failure, particularly for patients who also have hypertension. Carvedilol is used to treat mild to severe congestive heart failure, as well as hypertension, and left ventricular dysfunction in patients who recently had an MI, but are otherwise stable.

Carvedilol is a non-selective beta blocker (blocks beta 1 and beta 2 receptors) and an alpha 1 blocker. By blocking beta receptors found in the heart, carvedilol reduces the heart rate and decreases the force of heart contractions. By blocking the alpha 1 receptors found on blood vessels, carvedilol relaxes and dilates the blood vessels, which lowers blood pressure.

In the treatment of heart failure, beta blockers such as carvedilol are thought to protect the heart from increased catecholamine stimulation (catecholamines include adrenaline and noradrenaline). In the short term, adrenergic activation can help the heart maintain cardiac performance, but over time, continued activation can be detrimental. Harmful effects include a persistently increased heart rate, down-regulation and impaired functioning of the beta receptors, and myocyte hypertrophy and death—which leads to adverse re-modelling of heart tissue.

Carvedilol exerts its therapeutic effects by protecting the failing heart from harmful adrenergic stimulation. Carvedilol reduces the heart rate, improves left ventricular function, and reduces vasoconstriction. Several large trials (e.g., MOCHA, PRECISE, COPERNICUS) have reported that carvedilol reduces all-cause mortality and decreases hospitalization in patients with heart failure (3-6).

The dose of carvedilol must be individualized and monitored during up-titration. Gradual up-titration should reduce the risk of syncope (fainting) or excessive hypotension (low blood pressure). The FDA drug label recommends carvedilol to be started at 6.25 mg twice daily, which can be increased after 3 to 10 days, based on tolerability, to 12.5 mg twice daily. The dose may then be increased to the target dose of 25 mg twice daily, although patients should be maintained on a lower dose if higher doses are not tolerated. In addition, a lower starting dose may be used (3.125 mg twice daily), and the rate of up-titration may be slowed if clinically indicated (e.g., due to low blood pressure or heart rate, or fluid retention) (1).

Carvedilol is a mixture of equal amounts of left-handed *S*(-) and right-handed *R*(+) enantiomers (a "racemic mixture"). Enantiomers are molecules that are mirror images of each other, but are not superimposable on one another. The nonselective beta-adrenoreceptor blocking activity of carvedilol is present in the *S*(-) enantiomer; and the α1-adrenergic blocking activity is present in both *R*(+) and *S*(-) enantiomers at equal potency.

Even though carvedilol plasma levels are about 50% higher in the elderly compared with young subjects, no overall differences in the safety or effectiveness were observed between these two populations except for higher incidence of dizziness in hypertensive subjects (incidence 8.8% in the elderly versus 6% in younger subjects) (1).

Carvedilol is contraindicated in patients with severe hepatic (liver) impairment because patients with severe liver impairment (i.e., cirrhosis) exhibit a 4- to 7-fold increase in carvedilol plasma levels when compared with healthy subjects (1).

Gene: *CYP2D6*

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. The CYP450 genes are highly polymorphic and can result in no, decreased, normal, or increased enzyme activity.

CYP2D6 and CYP2C9 are the primary enzymes involved in the activation and metabolism of carvedilol. Other enzymes involved to a lesser extent include CYP3A4, CYP2C19, CYP1A2, and CYP2E1. The pharmacokinetics of carvedilol are known to be influenced by genetic variation in *CYP2D6*—data do not exist for *CYP2C9*.

Individuals who have two non-functional copies of the *CYP2D6* gene are predicted to be "CYP2D6 poor metabolizers". Plasma concentrations of *R*(+)- carvedilol are 2–3 times higher in poor metabolizers, and levels of *S*(-)-carvedilol are increased by approximately 20% to 25%, compared to normal metabolizers with normal CYP2D6 activity (1).

Retrospective analysis of side effects in clinical trials showed that individuals who are CYP2D6 poor metabolizers had a higher rate of dizziness during up-titration. This is thought to result from vasodilating effects of the 2–3 times higher concentrations of the α-blocking *R*(+) enantiomer (1).

Variation in *CYP2D6* does not appear to be associated with a change in the response to carvedilol therapy. This may be because other CYP450 enzymes can convert carvedilol to its active metabolite. One small study (n=93) reported that there were no significant differences of carvedilol dose as well as the number of adverse drug reactions among patients with different *CYP2D6* genotypes (7). Another small study (n=110) found that there were significant *CYP2D6* allele-specific differences in carvedilol pharmacokinetics, but *CYP2D6* genotype had no effect on heart rate, blood pressure or adverse effects (8).

The *CYP2D6* genotype may be associated with carvedilol dosage, however. Two small studies reported that higher maintenance doses of carvedilol were tolerated by carriers of non-functional *CYP2D6* alleles (n=65) (9), and by CYP2D6 poor metabolizers (n=93) (10).

Genetic Testing

The NIH's Genetic Testing Registry (GTR) displays genetic tests that are currently available for carvedilol response and the *CYP2D6* gene. According to the FDA, the pharmacokinetics of carvedilol do not appear to be different in patients with decreased or absent CYP2D6 activity. Therefore, genetic testing prior to the use of carvedilol is not recommended.

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.

[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. Certain terms, genes and genetic variants*

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

The primary P450 enzymes responsible for the metabolism of both *R*(+) and *S*(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and 5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary importance in the O-methylation pathway of *S*(-)-carvedilol.

[…]

Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of *R*(+)-carvedilol compared with extensive metabolizers. In contrast, plasma levels of *S*(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than *R*(+)-carvedilol. The pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of *S*-mephenytoin (patients deficient in cytochrome P450 2C19).

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

2016 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

CYP2D6 PM: CARVEDILOL

Pharmacist text

NO action is required for this gene-drug interaction.

The plasma concentration of carvedilol can be elevated. This does not, however, result in an increase in side effects.

Background information

Carvedilol is primarily converted by CYP2D6 to 4'-hydroxycarvedilol and 5'-hydroxycarvedilol. Data from pre-clinical studies suggest that these metabolites are active.

Carvedilol is also converted by other CYP450 enzymes to the active metabolite desmethylcarvedilol.

CYP2D6 IM: CARVEDILOL

Pharmacist text

NO action is required for this gene-drug interaction.

The plasma concentration of carvedilol can be elevated. This does not, however, result in an increase in side effects.

Background information

Carvedilol is primarily converted by CYP2D6 to 4'-hydroxycarvedilol and 5'-hydroxycarvedilol. Data from pre-clinical studies suggest that these metabolites are active.

Carvedilol is also converted by other CYP450 enzymes to the active metabolite desmethylcarvedilol.

CYP2D6 UM: CARVEDILOL

Pharmacist text

NO action is required for this gene-drug interaction.

The plasma concentration of carvedilol can be reduced. This does not, however, result in a decrease in the effectiveness.

Background information

Carvedilol is primarily converted by CYP2D6 to 4'-hydroxycarvedilol and 5'-hydroxycarvedilol. Data from pre-clinical studies suggest that these metabolites are active.

Carvedilol is also converted by other CYP450 enzymes to the active metabolite desmethylcarvedilol.

Please review the complete therapeutic recommendations that are located here: (2)

Acknowledgments

The author would like to thank Saeed Alzghari, MS, MBA, PharmD, BCPS Director of Clinical Pharmacy, Gulfstream Genomics; Bernard Esquivel MD, PhD, Personalized Medicine Latin American Association – President; and Inge Holsappel, Pharmacist, Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP), Netherlands, for reviewing this summary.

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