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Metoprolol Therapy and *CYP2D6* Genotype

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Introduction

Metoprolol is a beta blocker used in the treatment of hypertension, angina, and heart failure. Metoprolol selectively blocks beta$_1$ adrenoreceptors mainly expressed in cardiac tissue. Blockade of these receptors reduces the heart rate and decreases the force of heart contractions.

Metoprolol is primarily metabolized by the CYP2D6 enzyme. Approximately 8% of Caucasians and 2% of most other populations have absent CYP2D6 activity and are known as "*CYP2D6* poor metabolizers." In addition, a number of drugs inhibit CYP2D6 activity, such as quinidine, fluoxetine, paroxetine, and propafenone.

The FDA-approved drug label for metoprolol states that *CYP2D6* poor metabolizers, and normal metabolizers who concomitantly take drugs that inhibit CYP2D6, will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity (1).

The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) has published metoprolol dosing recommendations based on *CYP2D6* genotype. For individuals who have a *CYP2D6* gene variation that reduces the conversion of metoprolol to inactive metabolites, DPWG states that the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia. For CYP2D6 poor metabolizers, if a gradual reduction in heart rate is desired, or in the event of symptomatic bradycardia, DPWG recommends increasing the dose of metoprolol in smaller steps and/or prescribing no more than 25% of the standard dose. For other cases, no action is required (2).

Please note: Beta blockers such as metoprolol have been demonstrated in several large trials to be safe and effective for treatment of patients with cardiovascular disease. As a mainstay of therapy associated with improvements in quality of life, hospitalization rates, and survival (3, 4), clinical care pathways that might lead to underutilization of beta blockers require scrutiny. FDA points out that CYP2D6 poor metabolizers will have decreased cardioselectivity for metoprolol due to increased metoprolol blood levels. Yet, it is common clinical practice to adjust the dose of metoprolol according to the patient's heart rate. FDA does not specifically comment on the role of genetic testing for initiating therapy.

Drug: Metoprolol

Metoprolol is a commonly prescribed drug that belongs to the drug class of beta-adrenoreceptor antagonists, also known as "beta blockers." Metoprolol is indicated to treat hypertension, angina, and heart failure (stable, symptomatic (NYHA Class II or III) heart failure). Metoprolol selectively blocks the beta$_1$ adrenoreceptor (1).

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There are two main types of adrenoreceptors, alpha and beta, each of which have numbered subtypes. The beta adrenoreceptors have three subtypes, $beta_1$, $beta_2$, and $beta_3$. All three subtypes are coupled to the G_s protein, which in turn activates adenylate cyclase enzyme, which catalyzes the production of cyclic AMP (cAMP).

The binding of an agonist, such as the catecholamines adrenaline and noradrenaline, to beta receptors leads to a rise in the intracellular concentration of cAMP, which triggers signaling pathways. Stimulation of the $beta_1$ receptor, which is predominantly expressed in cardiac tissue, leads to an increase in heart rate and an increase in the contractility of the atria and ventricles. It also leads to the increased secretion of hormones from other tissues —renin (from the kidneys), ghrelin (from the stomach), and amylase (from the salivary glands).

In the treatment of heart failure, beta blockers such as extended-release metoprolol are thought to protect the heart from increased catecholamine stimulation. 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 remodeling of heart tissue (5, 6).

Metoprolol exerts its therapeutic effects by reducing the impact of catecholamine stimulation. Metoprolol reduces the heart rate, improves contractile function by stimulating the upregulation of beta-1 receptors, reduces vasoconstriction, and possibly also reduces the risk of arrhythmias (3, 5, 7, 8).

Metoprolol is a racemic mixture of R- and S-enantiomers (an equal amount of left- and right-handed enantiomers, which are molecules that are mirror images of each other, but are not superimposable on one another).

Metoprolol is primarily metabolized by CYP2D6, an enzyme which is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. Individuals who lack CYP2D6 activity will have higher plasma concentrations of metoprolol, almost 5-fold higher, and may be at an increased risk of side effects (9-12).

In addition, at higher plasma concentrations, metoprolol is less cardio-selective. Metoprolol can inhibit $beta_2$ receptors, which are mainly located in the bronchial and vascular musculature.

Genetic variants of the *CYP2D6* gene have been found to influence the ratio of enantiomers, the dose and dose titration of metoprolol, and to influence heart rate—CYP2D6 poor metabolizers have an increased risk of bradycardia (13-16). However, *CYP2D6* does not appear to influence the efficacy of metoprolol when used to treat hypertension (17).

Variants within the $beta_1$ receptor have also been found to influence the treatment response to specific beta blockers. The most commonly studied is a reduced function variant, Arg389Gly, which leads to reduced levels of cAMP and diminished $beta_1$ receptor signaling cascades (18). Individuals who are homozygous Arg389 carriers may have a more favorable response to metoprolol treatment than individuals who are homozygous for Gly389 (18), (19), (20), (21).

The Cytochrome P450 Superfamily

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 very polymorphic and can result in reduced, absent, or increased enzyme activity.

Gene: *CYP2D6*

CYP2D6 is highly polymorphic, with over 100 star (*) alleles described (22) . *CYP2D6*1* is the reference (or wild-type) allele encoding enzyme with normal activity. The *CYP2D6*2*, **33*, and **35* alleles are also considered to confer normal activity (Table 1).

Table 1. Activity status of selected *CYP2D6* alleles

Allele type	*CYP2D6* Alleles
Normal function	**1, *2, *33, *35*
Decreased function	**9, *10, *17, *29, *36, *41*
No function	**3-*8, *11-*16, *19-*21, *38, *40, *42*

For a detailed list of *CYP2D6* alleles, please see (22).

Individuals who have more than two normal function copies of the *CYP2D6* gene are "ultrarapid metabolizers," whereas individuals who carry two normal or one normal and one decreased function allele are classified as "normal metabolizers."

Individuals with one normal and one no function allele or two decreased function alleles are categorized as "normal metabolizers" by recent nomenclature guidelines (23), but have also been categorized as "intermediate metabolizers" in the literature. Subjects with one decreased and one no function allele are predicted to be intermediate metabolizers and those with two no function alleles, poor metabolizers.

The most common no function alleles include *CYP2D6*3*, **4*, **5*, and **6* (22, 24-26), and the most common decreased function alleles include *CYP2D6*9, *10, *17, *29* and **41* (27-31) (Table 1).

There are large inter-ethnic differences in the frequency of these alleles. For example, *CYP2D6*4* is the most common no function allele in Caucasians, but is less abundant in subjects with African ancestry, and is rare in Asians. In contrast, the decreased function allele *CYP2D6*10* is the most common allele in Asians, and *CYP2D6*17* is almost exclusively found in individuals with African ancestry (32).

Consequently, the phenotype frequencies also vary substantially among the major ethnicities and may vary among populations. Approximately 6-8% of European Caucasians and their descendants are poor metabolizers, mainly due to the prevalent no function *CYP2D6*4* and **5* alleles (24, 25).

Genetic Testing

The NIH's Genetic Testing Registry provides examples of the genetic tests that are currently available for metoprolol response and the CYP2D6 gene.

Results are typically reported as a diplotype, such as *CYP2D6 *1/*1*. A result for copy number, if available, is also important when interpreting *CYP2D6* results (26).

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): Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Poor metabolizers and extensive metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity.

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

[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.

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

CYP2D6 Poor Metabolizers:

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

If a gradual reduction in heart rate is desired, or in the event of symptomatic bradycardia:

1 Increase the dose in smaller steps and/or prescribe no more than 25% of the standard dose

Other cases:

1 No action required

CYP2D6 Intermediate Metabolizers:

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

If a gradual reduction in heart rate is desired, or in the event of symptomatic bradycardia:

1 Increase the dose in smaller steps and/or prescribe no more than 50% of the standard dose

Other cases:

1 No action required

CYP2D6 Ultrarapid Metabolizers:

The gene variation increases the conversion of metoprolol to inactive metabolites. This can increase the dose requirement. However, with a target dose of 200 mg/day, there was no effect on the blood pressure and hardly any effect on the reduction of the heart rate.

Recommendation:

1. Use the maximum dose for the relevant indication as a target dose
2. If the effectiveness is still insufficient: increase the dose based on effectiveness and side effects to 2.5 times the standard dose or select an alternative

Possible alternatives include:

- Heart failure: bisoprolol or carvedilol. Bisoprolol: advantage: not metabolised by CYP2D6; disadvantage: elimination depends on the kidney function. Carvedilol: advantage: elimination does not depend on the kidney function; disadvantage: is metabolised (to a lesser extent than metoprolol) by CYP2D6.
- Other indications: atenolol or bisoprolol. Neither is metabolised by CYP2D6.

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

Nomenclature of selected *CYP2D6* alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.5:c.506-1G>A	Variant occurs in a non-coding region (splice variant causes a frameshift)	rs3892097
*CYP2D6*5*	Variant results in a whole gene deletion			
*CYP2D6*6*	1707 del T Trp152Gly CYP2D6T	NM_000106.5:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T (Pro34Ser)	NM_000106.5:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
*CYP2D6*17*	1023C>T[1] (Thr107Ile)	NM_000106.5:c.320C>T	NP_000097.3:p.Thr107Ile	rs28371706
	2850C>T[2] (Cys296Arg)	NM_000106.5:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
*CYP2D6*41*	2850C>T[2] (Cys296Arg)	NM_000106.5:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	2988G>A	NM_000106.5:c.985+39G>A	Variant occurs in a non-coding region (impacts slicing).	rs28371725

[1] In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.
[2] In the literature, 2850C>T is also referred to as 2938C>T.

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: https://www.pharmvar.org/

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