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Propafenone Therapy and *CYP2D6* Genotype

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Introduction

Propafenone is an antiarrhythmic medication. It is used to prevent the reoccurrence of atrial fibrillation in patients with episodic atrial fibrillation who do not have underlying structural heart disease (propafenone may provoke proarrhythmic events in patients with structural heart disease).

Propafenone belongs to class IC of antiarrhythmic agents and acts on cardiac sodium channels to inhibit action potentials. In general, because of the lack of evidence that antiarrhythmic agents improve survival, they should only be used to treat arrhythmias that are thought to be life-threatening.

Propafenone is metabolized by CYP2D6, CYP3A4, and CYP1A2 enzymes. Approximately 6% of Caucasians in the US lack CYP2D6 activity, and are known as "CYP2D6 poor metabolizers" (Table 1) (1). Standard doses of propafenone will lead to higher plasma drug concentrations in poor metabolizers, compared to normal metabolizers. In addition, drugs that inhibit CYP2D6, CYP3A4, and CYP1A2 may also increase propafenone levels, which may lead to cardiac arrhythmia episodes.

The FDA-approved drug label for propafenone states that the recommended dosing regimen of propafenone is the same for all patients (CYP2D6 poor metabolizers and normal metabolizers). However, the label also cautions that the simultaneous use of propafenone with both a CYP2D6 inhibitor (or in patients with CYP2D6 deficiency) and a CYP3A4 inhibitor should be avoided, because of the increased risk of causing arrhythmias and other adverse events (1).

A guideline from The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Pharmacists Association (KNMP) provides dosing recommendations for propafenone, based on *CYP2D6* genotype. For CYP2D6 poor metabolizers, the guideline recommends reducing the initial dose of propafenone by 70%, ECG monitoring, and monitoring plasma concentrations. For intermediate and ultrarapid metabolizers, the guideline states there is insufficient data to allow for a calculation of dose adjustment. Therefore, it is recommended to adjust the dose in response to plasma concentration and to monitor with ECG, or select an alternative drug (e.g., sotalol, disopyramide, quinidine, amiodarone) (2, 3) (Table 2).

Drug class: Antiarrhythmics

Antiarrhythmic agents suppress abnormal heart rhythms (cardiac arrhythmias), which can originate from the atria (e.g., atrial fibrillation, atrial flutter) or the ventricles (e.g., ventricular tachycardia, ventricular fibrillation).

There are five main classes of antiarrhythmic agents, based on their primary site of action:

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- Class I: block sodium (Na+) channels e.g., quinidine (class IA), lidocaine (class IB), propafenone (class IC)
- Class II: block beta adrenoreceptors e.g., carvedilol, metoprolol, propranolol
- Class III: block potassium (K+) channels e.g., amiodarone, sotalol
- Class IV: block calcium (Ca2+) channels e.g., verapamil, diltiazem
- Class V: work by other or unknown mechanisms e.g., adenosine, digoxin

Drug: Propafenone

Propafenone is an antiarrhythmic used to prevent the recurrence of atrial fibrillation in patients who have episodic atrial fibrillation and no underlying structural heart disease. Propafenone is also used in the management of paroxysmal supraventricular tachycardia and atrial flutter (1).

Because there are no well-controlled studies in pregnant women, the FDA-approved drug label states that propafenone should only be used during pregnancy if the benefit justifies the potential risk to the fetus. The label also states that the safety and effectiveness of propafenone in pediatric patients have not been established.

Atrial fibrillation is the most common type of harmful cardiac arrhythmias. It is more common in men than women, and the risk of developing atrial fibrillation increases with age. Atrial fibrillation may be paroxysmal (intermittent), persistent (persists for at least 7 days), long-standing (more than 12 months), or permanent.

The symptoms of atrial fibrillation range from no symptoms, to feeling dizzy, short of breath, and experiencing palpitations. The pulse feels irregular, and an ECG will show an absence of P waves and an irregular QRS complex. Atrial fibrillation can lead to reduced cardiac output, increase the risk of thrombosis and stroke, and affected patients may be at an increased risk for mortality (4). Management typically includes antithrombotic therapy and rhythm control.

Propafenone is a class IC *antiarrhythmic* agent. All class I agents have a "membrane stabilizing effect"—by reducing the fast influx of sodium ions into the cardiac muscle cells, they inhibit the propagation of action potentials. Propafenone also has some Class II activity—it can act as a beta blocker. Side effects of this action include bradycardia and bronchospasm (5, 6).

The class IC agents encainide and flecainide have been associated with increasing the risk of cardiac arrest or death, compared to placebo. Consequently all class IC agents, including propafenone, are considered to have a significant risk of provoking proarrhythmic events in patients with structural heart disease. Therefore, propafenone should not be used in patients with underlying structural heart disease. Its use is contraindicated in a number of conditions, including heart failure, conduction disorders, bradycardia, and recent myocardial infarction (within the last 3 months) (1, 7, 8, 9).

Propafenone is metabolized into two active metabolites: 5-hydroxypropafenone, which is formed by CYP2D6, and norpropafenone, which is formed by both CYP3A4 and CYP1A2. Multiple studies have found that genetic variants in the *CYP2D6* gene influence the plasma drug levels of propafenone (10, 11, 12, 13).

In patients who lack CYP2D6 activity, metabolism of propafenone is slower, so the 5-hydroxy metabolite is not formed or is formed at very slow rates. In these patients, high doses of propafenone (850mg daily) lead to plasma concentrations of propafenone that are about twice those of patients who have normal CYP2D6 activity. At lower initial doses, the difference between propafenone and 5-hydroxy metabolite concentrations is even greater (1, 14).

However, the FDA recommends that the dosing regimen of propafenone should be the same for all patients, regardless of their CYP2D6 activity levels. This is because even at high doses, the effects of high propafenone levels are mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolizers, and also because steady-state conditions are achieved after 4 to 5 days of titrating the dose in all patients. But the FDA also recommends that because of the large variation in plasma drug levels between individuals, the dose of

propafenone should be individually titrated on the basis of response and tolerance, with close attention paid to clinical and ECG evidence of toxicity (1).

The FDA-approved drug label for propafenone cautions against the simultaneous use of propafenone with both a CYP2D6 inhibitor and a CYP3A4 inhibitor. This is because the combination of CYP3A4 inhibition and either CYP2D6 inhibition or deficiency may increase propafenone exposure, which may trigger new cardiac arrhythmias and exaggerate beta adrenoreceptor blockage (1).

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 (15). *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 (15).

Individuals who have more than two normal function copies of the *CYP2D6* (*CYP2D6*xN*) 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 (16), 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 are classified as poor metabolizers.

The most common no function alleles include *CYP2D6*3*, **4*, **5*, and **6* (17, 18, 19, 20), and the most common decreased function alleles include *CYP2D6*9, *10, *17, *29* and **41* (5, 6, 18, 20, 21) (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 (22).

Consequently, the phenotype frequencies vary substantially among the major ethnicities and may vary among populations. Approximately 6-10% of European Caucasians and their descendants are poor metabolizers, mainly due to the prevalent no function *CYP2D6*4* and **5* alleles (17, 23).

Genetic Testing

The NIH's Genetic Testing Registry (GTR) lists genetic tests currently available for propafenone response and the CYP2D6 gene.

Results are typically reported as a diplotype, such as *CYP2D6 *1/*1* (wild type). A result for copy number, if available, is also important when interpreting *CYP2D6* results (19).

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): Propafenone is metabolized by CYP2D6, CYP3A4, and CYP1A2 isoenzymes. Approximately 6% of Caucasians in the US population are naturally deficient in CYP2D6 activity and other demographic groups are deficient to a somewhat lesser extent. Drugs that inhibit these CYP pathways (such as desipramine, paroxetine, ritonavir, sertraline for CYP2D6; ketoconazole, erythromycin, saquinavir, and grapefruit juice for CYP3A4; and amiodarone and tobacco smoke for CYP1A2) can be expected to cause increased plasma levels of propafenone.

Increased exposure to propafenone may lead to cardiac arrhythmias and exaggerated beta-adrenergic blocking activity. Because of its metabolism, the combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition in users of propafenone is potentially hazardous. Therefore, avoid simultaneous use of propafenone with both a CYP2D6 inhibitor and a CYP3A4 inhibitor.

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 Pharmacists Association (KNMP): For CYP2D6 poor metabolizers (PMs), defined as patients carrying two defective alleles, dose reductions are recommended for clomipramine, flecainide, haloperidol, zuclopenthixol (all 50%); doxepin, nortriptyline (both 60%); imipramine, propafenone (both 70%); and metoprolol (75%).

[…].

For CYP2D6 intermediate metabolizers (IMs), defined as patients carrying two decreased-activity alleles or one active/decreased-activity allele and one inactive allele, dose reductions ranging from 20 to 50% are advised for doxepin, amitriptyline, zuclopenthixol, imipramine, nortriptyline, and metoprolol. There were insufficient data to calculate dose adjustments for clomipramine, oxycodone, propafenone, risperidone, and venlafaxine (Table 2).

Please review the complete therapeutic recommendations that are located here: (2, 3).

Table 2. *CYP2D6* phenotypes and the therapeutic recommendations for propafenone therapy, from The Dutch Pharmacogenetics Working Group (2016)

CYP2D6 Phenotype	Recommendations for propafenone therapy
Ultrarapid metabolizer	Insufficient data to allow calculation of dose adjustment. Adjust dose in response to plasma concentration and record ECG or select alternative drug (e.g., sotalol, disopyramide, quinidine, amiodarone).

[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.

Table 2. continued from previous page.

CYP2D6 Phenotype	Recommendations for propafenone therapy
Intermediate metabolizer	Insufficient data to allow calculation of dose adjustment. Adjust dose in response to plasma concentration and record ECG or select alternative drug (e.g., sotalol, disopyramide, quinidine, amiodarone).
Poor metabolizer	Reduce dose by 70%, record ECG, monitor plasma concentration

The level of evidence for the therapeutic (dose) recommendations is 4/4 ("good quality") for poor metabolizers, and 3/4 ("moderate quality") for intermediate and ultrarapid metabolizer types. The 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 (2, 3).

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 (PharmVar) https://www.pharmvar.org/.

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