

Personalized Medicine of Flecainide (The Impact of the CYP2D6 and CYP1A2 Polymorphism on Responses to Flecainide)

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<https://dx.doi.org/10.13005/bpj/2830>

(Received: 25 October 2023; accepted: 18 January 2024)

Flecainide is an antiarrhythmic drug (AAD) class IC that has a narrow therapeutic index. The enzymes CYP2D6 and CYP1A2 are thought to catalyse the metabolism of this medication. This gene's polymorphism permits metabolic adjustments and modifies the pharmacokinetic profile. The objective of this review is to elucidate the impact of CYP2D6 and CYP1A2 gene polymorphisms on the pharmacological response to flecainide within the human body. Using the search terms "flecainide and CYP2D6; "flecainide and CYP1A2," papers on PubMed and Science Direct were found for the review. When the terms "flecainide and CYP2D6" were searched for in PubMed for all publications published between 2000 and 2023, 23 results were identified; when the same terms were searched on SD (Research article & English version), 97 results were found, just 13 of which were open access. With the keyword "flecainide and CYP1A2" in PubMed, a search of all articles published from 1995 to 2023 there were 7 articles and 52 articles in SD (Research article & English version), meanwhile open access were 8 articles. We add several articles other than PubMed and SD. The kinetic profile of flecainide is influenced by CYP2D6 gene polymorphism, however the effect of CYP1A2 gene polymorphism on flecainide is unknown due to a lack of studies.

Keywords: CYP2D6; CYP1A2; Flecainide; Polymorphism.

Anti-arrhythmia drug class IC called Flecainide is used to treat specific kinds of irregular heartbeats. Pharmacogenetics is the study of how a person's response to medication is affected by genetic differences. In the case of flecainide, genetic variables may affect the drug's effectiveness, the way it is metabolized, and the likelihood of side effects. Genetic variations in some drug-metabolizing enzymes, such as the cytochrome P450 family of enzymes, may have an effect on the body's metabolism of flecainide. Variations in medication levels brought on by these enzyme polymorphisms may affect both treatment efficacy and safety.

Flecainide therapeutic class

Flecainide is a class IC AAD. Flecainide is recommended in the management of patients without structural abnormalities, such as for (a) management of newly emerging atrial fibrillation (AF) (class I recommendation, level A), (b) prevention of recurrent AF (class IIa recommendation, level B) and (c) control of heart rhythm long-term (class I recommendation, level A)^{1,2,3}

Pharmacokinetic

Flecainide acetate is slowly absorbed after oral administration; the C_{max} is reached in 3 hours (T_{max}: 1-6 hours). Flecainide has a

bioavailability of 90% to 95%.⁴ There is no first-pass hepatic metabolism of flecainide. Flecainide is taken in doses of 200–500 mg per day.⁵ This medicine is metabolized by Cytochromes CYP2D6 and CYP1A2 in the liver. research by Manuel *et al.*, in 2005 found that flecainide metabolism is influenced by CYP2D6.⁶

Flecainide taken orally has a elimination half-life ($t_{1/2}$) of around 13 hours (7–22 hours), which is unaffected by dose⁴ Most of the metabolites and flecainide are excreted in urine.^{4,5,7}

Metabolism of flecainide

Meta-O-dealkylated flecainide or the meta-O-dealkylated lactam of flecainide is the principal product of flecainide metabolism.⁶ The activity of meta-O-dealkylated flecainide is 20% that of flecainide.⁵ Both of these metabolites are typically found as conjugates of glucuronide or sulfate.⁵ The metabolism of flecainide is dependent on CYP2D6 and CYP1A2.⁸

Genetic Variability and Flecainide Response

A person's reaction to flecainide is mostly determined by hereditary variables. The

way the body breaks down flecainide can be affected by variations in genes that code for drug-metabolizing enzymes, such as cytochrome P450 enzymes.. Polymorphisms in these genes can lead to variations in drug metabolism rates, potentially resulting in different levels of drug efficacy and side effects. Some individuals may be genetically predisposed to particular arrhythmia types, which may affect how they respond to flecainide therapy. Pharmacologic can make better treatment decisions and possibly avoid administering flecainide on individuals who might not respond well by employing genetic testing to identify these predispositions

The effect of CYP2D6 and CYP1A2 gene polymorphisms on flecainide pharmacokinetics

CYP2D6 gene is located in 22q13.2 exon 9. An enzyme from the cytochrome P450 superfamily is encoded by this gene. CPD6, CYP2D, CYP2DL1, CYP11D6, P450C2D, P450DB1, CYP2D7AP, CYP2D7BP, CYP2D7P2, CYP2D8P2, and P450-DB1 are other names for this gene. The monooxygenases known as cytochrome P450 proteins catalyze a variety of reactions that are involved in drug metabolism and the synthesis of cholesterol, steroids, and other lipids. This endoplasmic reticulum-localized protein is known to metabolize up to 25% of commonly prescribed pharmaceutical.⁹ CYP1A2 gene is located in 15q24.1 exon 7. CYP1A2 is a monooxygenase that catalyzes numerous reactions implicated in drug metabolism and cholesterol, steroid, and lipid synthesis. The enzyme's endogenous substrate is unknown. This enzyme's xenobiotic substrates include aflatoxin B1, acetaminophen and caffeine.,¹⁰

An enzyme called a CYP2D6 is involved in the metabolism of many different types of medications.. This enzyme metabolize many drugs, among others: α -Adrenoceptor blockers

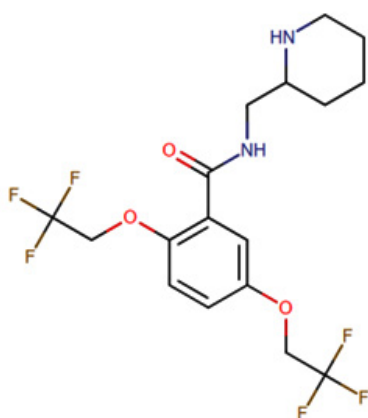


Fig. 1. Flecainide.⁴

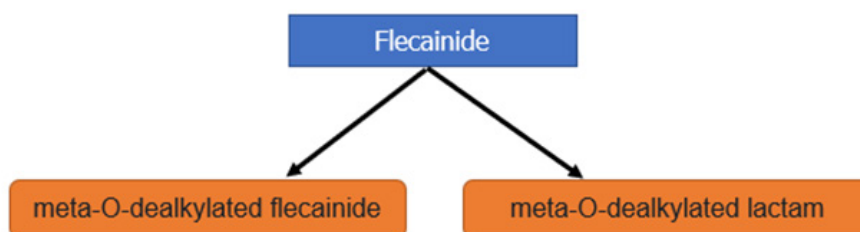


Fig. 2. Metabolite of flecainide⁴

(metoprolol, propranolol, timolol), Neuroleptics (haloperidol, risperidone etc), Antiarrhythmic drugs (propafenone etc).¹¹ This enzyme metabolizes amitriptyline and other antidepressants such as nortriptyline, paroxetine and others.^{11,12} The CYP2D6 polymorphism describes genetic changes within the CYP2D6 gene that affect an individual's level of enzyme activity. Based on their CYP2D6 enzyme activity, people can be categorized into several phenotypes as a result of these genetic variations. Genetic polymorphisms give rise to a variety of CYP2D6 phenotypes. These phenotypes fall into the general categories of poor metabolizers (PMs), intermediate metabolizers (IMs), normal metabolizers (NMs), and ultra rapid metabolizers (UMs). The degree of CYP2D6 enzyme activity varies depending on the phenotype, which can have a big impact on how people metabolize medications. The metabolism of flecainide is affected by variations in CYP2D6 activity. CYP2D6 uses flecainide as a substrate. The hepatic enzymes CYP2D6 and CYP1A2 convert flecainide to m-O-dealkylated flecainide (MODF), which is then oxidized to m-O-dealkylated lactam. Flecainide is eliminated in the urine in an unchanged form in about 30% of the whole dose.^{13,14,15} Flecainide clearance is decreased by 21% in intermediate metabolizers (IM) and by 42% in poor metabolizers (PM) due to impaired CYP2D6 activity.^{16,17} Patients with reduced CYP2D6 activity, for example on IMs and PMs show decreased metabolism.¹³ The alleles *10, *17, *36, and *41 caused a decrease in enzyme activity. There is no enzyme activity in alleles *3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *15, *16, *18, *19, *20, *21, *38, *40, *42, *44, *56, and *62. These alleles were responsible for the PM phenotype in both homozygotes and heterozygotes. CYP2D6*2, *3, *4, *5, *10, *17, and *41 are thought to cause changes in drug clearance and response.¹⁸

Riset by Miao Hu 2012 found that the pharmacokinetics of flecainide did not differ significantly between CYP2D6 *10 genotypes. Comparing individuals with CYP1A2*1A/1F and at least one CYP2D6 variant allele, those with CYP1A2*1F tended to have greater clearance of flecainide and lower systemic exposure.¹⁹

Clinical Implications

Because it can affect the effectiveness and safety of numerous drugs, the CYP2D6

polymorphism has important clinical implications. Individuals with PMs of CYP2D6 may have undesirable side effects or adverse effects. Frequently reported adverse effects of flecainide are dizziness (30%) and visual disturbances (28%), which often occur simultaneously. Side effects such as headaches, nausea, dyspnoea, and chest pain occur in 6-9% of patients.²⁰ Flecainide-induced constipation is more common (21, %) in PM patients than in EM patients without the conditions.⁶ Research by Nutulaghanti *et al*, 2022 (case report) showed that over effect of flecainide can cause LBBB (left bundle branch block). Flecainide toxicity occurs due to sodium channel toxicity. This causes a decrease in electrical conduction in the left ventricular myocardium leading to ventricular LBBB²¹. However, individuals with UMs may metabolize medications too quickly, resulting in inadequate therapeutic doses.

Challenges and Future Directions

Using flecainide and other drugs to implement personalized medicine techniques presents difficulties like the price of genetic testing, the requirement for established criteria, and the interpretation of complicated genetic data. The advantages of adjusting flecainide treatment to specific patients, however, become more apparent as genomic technologies develop and our knowledge of pharmacogenomics increases.

CONCLUSION

There is a suspicion that the metabolic process of flecainide is facilitated by the enzyme CYP2D6, whilst the impact of CYP1A2 is minor. The role of CYP2D6 in the metabolism of flecainide is clear, mean while the precise involvement of CYP1A2 in the metabolic process of flecainide remains uncertain. Limited study has been conducted thus far regarding the involvement of CYP1A2 in the metabolism of flecainide, as well as the impact of CYP1A2 polymorphisms on alterations in flecainide pharmacokinetics.

ACKNOWLEDGMENT

Cancellor of Universitas Muhammadiyah Surakarta, Indonesia.

Conflict of Interest

None to declare.

Funding Source

This research was funded by Universitas Muhammadiyah Surakarta, Indonesia with no: 301.49/A.3-III/FK/2023

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