Dofetilide: Electrophysiologic Effect, Efficacy, and Safety in Patients with Cardiac Arrhythmias

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KEYWORDS

• Atrial fibrillation • Atrial flutter • Cardiac arrhythmias • Dofetilide • Heart failure • Proarrhythmias • Torsades de pointes

KEY POINTS

- Dofetilide is a class III antiarrhythmic agent with a selective blockade of rapid component of delayed rectifier potassium current (IK_r).
- Dofetilide was found to be safe in patients after myocardial infarction and those with congestive heart failure and left ventricular systolic dysfunction (ejection fraction of less than 35%).
- An important adverse effect of dofetilide is its potential proarrhythmic risk of ventricular tachyarrhythmias, mostly torsades de pointes.
- Because dofetilide has about an 80% renal excretion, dose adjustment is required in patients with impaired renal function.
- Dofetilide should not be given or discontinued if the QTc is greater than 500 ms.

INTRODUCTION

Despite many challenges in the medical management of atrial fibrillation (AF) and disappointments in the use of antiarrhythmic drug (AAD) therapy in the maintenance of sinus rhythm, AAD therapy remains the mainstay in the management of AF.[1–3] Because of significant adverse effects of many old and newly developed AAD for rhythm control of AF, development of new AADs has been slow. The last AAD that received US Food Drug Administration (FDA) approval was dronedarone.[4,5] Despite early enthusiasm that dronedarone was effective in preventing hospitalization as a surrogate endpoint, the subsequent analysis of dronedarone showed increased mortality in patients with heart failure and permanent AF.[6,7] Dofetilide, on the other hand, appears reasonably safe and effective when used in appropriately selected patients, that is, the right drug for the right patient. Dofetilide was initially tested in patients with post-myocardial infarction (MI) and in those with congestive heart failure (CHF) and low ejection fraction that constitutes a high-risk patient group.[8–11] Among the different classes of AAD that were developed in the last 2 decades, dofetilide was the first specific K^+ channel blocker. Specific ion channel blockers and atrial selective agents are concepts that are appealing and are becoming more popular for the manufacturers to develop and medical community to test and use.[3,12–19] In this review, the AA properties and safety of dofetilide as a prototype of selective K^+ channel blocker are discussed.

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Approval of dofetilide by the FDA was based on the data from the DIAMOND study on the efficacy of dofetilide in the treatment of post-MI and CHF that also had AF and atrial flutter (AFL).[8–11]

ELECTROPHYSIOLOGIC EFFECTS OF DOFETILIDE

Dofetilide, like sotalol, is a methane sulfonanilide derivative[20] and belongs to the class III AAD with a prominent effect of blockade of the rapid component of delayed rectifier potassium channel (I_{Kr}). It also increases the late sodium current activity at lower concentration; therefore, it prolongs action potential duration (APD) in atrial, ventricular, and Purkinje cells. It also increases the atrial effective refractory period (ERP) more than the ventricular ERP.[21,22]

Thus, it is more effective in atrial arrhythmias that are due to re-entry than other mechanisms. In principle, K^+ currents are responsible for most parts of the repolarization and are divided into at least 2 major components: the rapidly activated components I_{Kr} and a slower activating component I_{Ks}.[23] Each component is mediated by separate genes (ie, I_{Kr} by hERG and I_{Ks} by Kv LQT_1), respectively.[24,25] There are also other K^+ channels in the atria, such as $I_{K,ATP}$, I_{Kur}, $I_{K,Ach}$, I_{SK}, $I_{SK,Ca}$, and I_{K2P}.[15,26,27] In this regard, dofetilide is a specific blocker of I_{Kr}, and because I_{Kr} is responsible for most of the repolarization blockade of I_{Kr}, produces action potential prolongation, which translates to QT prolongation.[21,22] This effect carries the risk of QT prolongation and can potentially be arrhythmogenic.[28,29]

Ion channel transport during depolarization and repolarization is well described in the articles by Voigt and Dobrev and Skibsybye and Ravens (see Voigt N, Dobrev D: Atrial-selective potassium channel blockers; and Skibsybye L, Ravens U: Mechanism of proarrhythmic effects of potassium channel blockers in this issue) and does not need to be repeated here.

Class III AADs demonstrate a dose-dependent property but have a reverse use dependent effect, that is, the effect is more pronounced at slower than faster rates.[21,30] This effect is counterproductive during clinical arrhythmias such as AF/AFL wherein the drug is less effective at faster heart rates.[31–35] Similarly, lower intracellular K^+ concentrations potentiate effects of K^+ channel blockers, whereas high intracellular K^+ concentrations blunt its effect.[21,35] This effect has clinical relevance in that hypokalemia increases the risk of QT prolongation and proarrhythmias (mainly torsades de pointes [TdP]) more than normal K^+ hemostasis. On the other hand, hyperkalemia reduces the efficacy of class III agents such as dofetilide. Experimental studies by Baskin and Lynch[35] and Sedgwick and colleagues[36] have shown the effect of K^+ channel blockers is higher in atrial than ventricular myocardial cells.[21,37] Some K^+ currents are also present in the sinus node; thus, K^+ channel blockers reduce the spontaneous activity of the sinus node cells causing a sinus bradycardia.[24]

Class III AAD effects on APD are reversible by β-adrenergic stimulation such as isoproterenol.[38]

K^+ channel blockers at higher doses exert antifibrillatory effects.[39]

Dofetilide does not exert negative inotropic effect nor induce hypotension. In other words, dofetilide does not produce significant hemodynamic effect.[40]

EFFECT OF DOFETILIDE ON EXPERIMENTAL MODELS OF ATRIAL ARRHYTHMIAS

In general, class III agents such as dofetilide prolong APD and ERP; therefore, they are more effective against arrhythmias that are due to re-entrant mechanisms than those with triggered activity.[21]

Studies by Li and colleagues[41] investigated the electrophysiologic effect and efficacy of dofetilide in 2 different models of AF, that is, rapid atrial pacing-induced atrial remodeling and tachypaced heart failure model. Interestingly, dofetilide was more effective in the tachypace-induced heart failure AF model where the mechanism of AF was due to macro-re-entry. Where prolongation of the ERP decreases the excitable gap, hence the re-entry does not maintain and thus terminate the tachycardia. In contrast, dofetilide was less effective in the atrial pacing-induced AF model, whereby in this model, the mechanisms of AF was due to multiple wavelet re-entry, whereby dofetilide decreased the number and slowed re-entry circuits but did not terminate AF. This difference was assumed by the investigators because of its different electrophysiologic mechanism of AF in each model.[41]

ANTIARRHYTHMIC EFFECTS OF DOFETILIDE

The Clinical Trials of Dofetilide

The initial studies evaluated dofetilide in a large Danish Trial (Danish Investigation of Arrhythmia and Mortality on Dofetilide [DIAMOND]) in patients with post- MI, CHF with reduced left ventricular (LV) systolic function, and AF (**Table 1**); these are discussed later.

DIAMOND Trials

Antiarrhythmic effects of dofetilide and its clinical efficacy in atrial and ventricular arrhythmias