Update on Antiarrhythmic Therapy: Dofetilide

QIONG WANG
Division of Cardiology, Department of Medicine and The Institute of Cardiovascular Science and Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

HUNG-FAT TSE

CHU-PAK LAU

Follow this and additional works at: https://www.jhkcc.com.hk/journal

Recommended Citation

This Review Article is brought to you for free and open access by Journal of the Hong Kong College of Cardiology. It has been accepted for inclusion in Journal of the Hong Kong College of Cardiology by an authorized editor of Journal of the Hong Kong College of Cardiology.
Update on Antiarrhythmic Therapy: Dofetilide

QIONG WANG, HUNG-FAT TSE, CHU-PAK LAU

From Division of Cardiology, Department of Medicine and The Institute of Cardiovascular Science and Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction

Dofetilide is one of the several novel methanesulfonamide compounds that selectively inhibits the rapid component of the delayed rectifier potassium current, IKr, thus prolonging the effective refractory period (ERP) and the action potential duration (APD) in both the atria and the ventricles. It has no effects on sodium and calcium channels, and therefore, has minimal effects on myocardial conduction velocity.1,2 Dofetilide can be administered either orally or intravenously, and has a rapid onset of action. It was recently approved in the United States for the maintenance and conversion of normal sinus rhythm in patients with atrial fibrillation (AF).3

Pharmacology

Dofetilide was selected for development from a series of bis(arylalkyl)amines which prolonged ERP in isolated cardiac tissue. A particularly advantageous structural feature was a methanesulfonamido moiety on both of the aryl rings. Dofetilide is a white crystalline solid with a melting point of 161 degC and a molecular weight of 441.6. The compound contains a tertiary amine function with a pKa of 7.0 and is moderately lipophilic.4

Dofetilide binds with high affinity to a population of noninteracting sites, inhibiting the rapidly activating component of the delayed rectifier potassium current (IKr) channel. The target IKr channel protein is encoded by the human ether-a-go-go-related gene (HERG).5 Dofetilide binds to the internal pore of the channel at a site that involves the serine residue at position 620 (Ser620) and blocks IKr channels at 10 to 30 nM.6 At these concentrations, it does not block IKs or the inward rectifier IKi, nor does it affect sodium or calcium currents. This yields a selective prolongation of action potential and increases the refractory period. The electrophysiological effect leads to QT interval prolongation, which can be both antiarrhythmic and proarrhythmic.7 On the other hand, dofetilide displays little affinity for alpha 2 and beta adrenoceptors, adenosine (A1), dopamine (D2), 5-HT2, muscarinic, or opioid receptor or dihydropyridine binding sites, which consequently has no other electrophysiological effects.

In contrast to other class III antiarrhythmic agents, such as amiodarone or sotalol, dofetilide selectively inhibits single channel, IKr, and widens APD.8,9 It prolongs the ERP in both atrial and ventricular tissues in normal subjects,10,11 as well as in acute ischemic animals.12 Intravenous administration of dofetilide in patients with ischemic heart disease also results in a dose-dependent increase in monophasic APD and ERP in the atria and ventricles.13,14 The associated QT interval prolongation was closely related to the plasma concentration of dofetilide after both iv and po administration.15,16 Its maximal effect on QT duration occurs 5 min after completion of iv infusion, or 2 ± 0.9 h post dosing po. There was an approximately 9 min lag between peak concentrations and peak effect on the QT interval after infusion of dofetilide.17 Dofetilide is typically rate dependent. The magnitude of increases in APD or ERP decrease as the rate of stimulation is increased.8,18 In vitro studies demonstrated that using dofetilide at a slower heart rate and increased intracellular Ca2+ would increase the risk of torsades de pointes.19
Dofetilide only prolongs repolarization by blocking the open state of IKr, thus it have no effects on the PR or RR, AH or HV intervals or QRS width or sinus node recovery time. Dofetilide had a positive inotropic effect not only in isolated heart muscles but also in the atria in patients immediately following cardioversion. It did not significantly affect the blood pressure, heart rate or any other hemodynamic variables in animal models, normal volunteers or patients with acute ischemic heart failure. Dofetilide had a positive inotropic effect not only in isolated heart muscles but also in the atria in patients immediately following cardioversion. It did not significantly affect the blood pressure, heart rate or any other hemodynamic variables in animal models, normal volunteers or patients with acute ischemic heart failure. Dofetilide also had a positive inotropic effect not only in isolated heart muscles but also in the atria in patients immediately following cardioversion. It did not significantly affect the blood pressure, heart rate or any other hemodynamic variables in animal models, normal volunteers or patients with acute ischemic heart failure.

**Metabolism**

Dofetilide is completely absorbed after oral administration, and bioavailability ranges from 75 to 100% in subjects with normal renal function. Mean maximal plasma concentration is reached approximately 2.5 h (range of 1 to 4 h) after oral administration and the plasma half-life is 8 to 10 h (mean 9.5 h). Approximately 50% of the drug is excreted in the urine unchanged and the remaining 50% is metabolized in the liver to inactive metabolites. The elimination half-life from plasma is 7 to 13 h (8.1 ± 2.3 h) and the clearance is estimated to be 0.38 ± 0.05 l/h/kg during oral administration. Corresponding values were similar during iv administration (7.1 ± 1.3 h and 0.35±0.05 l/h/kg, respectively). Dofetilide is metabolized predominantly by the CYP3A4 of the cytochrome-450 family. As a result, it may interact with drugs such as erythromycin or ketoconazole, resulting in higher and potentially toxic levels of dofetilide. Despite its hepatic metabolism, dofetilide does not interact with digoxin, propranolol, or warfarin. In both volunteers and patients, drug clearance appeared to be independent of dose and showed very little variability among patients. The time to maximal plasma concentration was slightly delayed in the presence of food, although the overall absorption was not affected.

**Clinical Use**

An open dose-ranging study showed that 53% of 24 patients with AF were converted successfully to sinus rhythm. The success rate was 80% in patients with atrial flutter (AFL), but the number of patients in this study was small. In another study with 325 patients, dofetilide (500 mg po bid for 3 days) converted chronic AF/AFL to normal sinus rhythm safely and effectively with a comparatively low conversion rate of 32%. Kobayashi et al evaluated the efficacy of iv dofetilide in patients with paroxysmal AF of recent onset (< 7 days) and paroxysmal supraventricular tachycardia (PSVT). Intravenous dofetilide successfully converted AF to sinus rhythm in 7/13 (54%) at the dose of 2.5 to 5.0 µg/kg and prevented the induction of PSVT in 7/13 patients with a loading dose of 3 µg/kg followed by a maintenance dose of 2 µg/kg. In a double-blind, randomized multicenter study with dofetilide (4 or 8 µg/kg) or placebo, Falk et al demonstrated that dofetilide terminated AF in 31% of patients receiving 8 µg/kg and in 12.5% of those receiving 4 µg/kg, compared with zero conversion after placebo (p < 0.01). Meanwhile, dofetilide seemed to be more effective in converting patients with AFL than that with AF (14 versus 54%), though the number of patients with AFL was small. Similarly, a multicenter, randomized, double-blind, placebo-controlled trial of demonstrated that dofetilide (8 µg/kg iv) was effective in acute termination of AF of medium duration in 96 patients, with an efficacy rate as much as 2-fold higher in AFL.

The efficacy of dofetilide in patients with life-threatening sustained ventricular tachycardia (VT) or fibrillation (VF) was evaluated in a placebo-controlled study using a dose-ranging protocol. 24 Patients were studied at six incremental loading and maintenance infusion regimens. Sustained VT or VF was no longer inducible in 1/6 patients receiving placebo (p < 0.01). Meanwhile, dofetilide seemed to be more effective in converting patients with AFL than that with AF (14 versus 54%), though the number of patients with AFL was small. Similarly, a multicenter, randomized, double-blind, placebo-controlled trial of demonstrated that dofetilide (8 µg/kg iv) was effective in acute termination of AF of medium duration in 96 patients, with an efficacy rate as much as 2-fold higher in AFL.

In a multicenter open trial, the Dofetilide Arrhythmia Study Group further evaluated the electrophysiological effects, antiarrhythmic efficacy and the safety of different doses of iv dofetilide in 50 patients with sustained inducible monomorphic VT who had previously been unsuccessfully treated with 0 to 7 (median 3) other drugs. Dofetilide was administered over 60 min at doses of 1.5, 3, 6, 9 and 15 µg/kg iv. Doses of 3 to 15 µg/kg prolonged the QTc interval by...
DOFETILIDE

13.4 to 14.2%, the ventricular ERP by 7.9 to 20.6% and the ventricular functional refractory period by 7.3 to 25%. The corresponding plasma dofetilide concentrations ranged from 1.45 ± 0.52 to 6.48 ± 1.31 ng/ml. At these doses, iv dofetilide suppressed or slowed inducible VT in 41% patients (17/41), compared with 0/9 patients receiving the inactive dose of 1.5 µg/kg. Furthermore, dofetilide prolonged the interval to first all-cause implantable cardioverter defibrillator (ICD) shocks, but not the interval to first ICD intervention (antitachycardia pacing and or shock) in 174 patients implanted with a ICD.35 Intravenous dofetilide also reduced the amount of energy required for converting VF to normal sinus rhythm by approximately 2 to 3 J in patients with ICD.36

A total of 3000 patients with either acute myocardial infarction or congestive heart failure (CHF) requiring hospitalization were enrolled in the DIAMOND (Danish Investigations of Arrhythmia and Mortality on Dofetilide) trial, beginning in 1994.37 Of these, 1518 patients with symptomatic CHF and severe left ventricular dysfunction were recruited into the randomized, double-blind DIAMOND-CHF trial. The mortality rate was not significantly different between the dofetilide and placebo group, but dofetilide was effective in converting AF, preventing its recurrence and reducing the risk of hospitalization for worsening heart failure. Furthermore, dofetilide could be used safely even in patients with severe forms of CHF and severe left ventricular dysfunction were recruited into the randomized, double-blind DIAMOND-CHF trial. The mortality rate was not significantly different between the dofetilide and placebo group, but dofetilide was effective in converting AF, preventing its recurrence and reducing the risk of hospitalization for worsening heart failure. Furthermore, dofetilide could be used safely even in patients with severe forms of CHF and severe left ventricular dysfunction.
Conclusion

Dofetilide selectively inhibits the rapid component Ik of the delayed rectifier potassium current to prolong the APD and ERP in the atrial and ventricular myocardium. It targets only one cardiac ion channel with no effects on the sinus node, cardiac conduction system and other extracardiac organs. Dofetilide is a promising compound for the treatment of life-threatening ventricular arrhythmias as well as for prevention of recurrent AF/AFL, and is currently approved in the United States for the treatment of AF. Intravenous dofetilide may represent a valuable alternative to direct current cardioversion for acute termination of AF/AFL. Furthermore, dofetilide does not increase mortality in patients with clinically significant structural heart disease and reduced left ventricular function. Therefore, like amiodarone, dofetilide can be used to prevent AF recurrence and thus reduce the risk of hospitalization due to worsening heart failure in patients with CHF. The clinical role of dofetilide in the treatment of ventricular arrhythmias requires further evaluation.

The major concern with the use of dofetilide is the development of serious arrhythmias, in particular torsades de pointes. The infusion of dofetilide should be carefully adjusted and patients with atrial fibrillation should be closely evaluated with in-hospital cardiac monitoring during and after the cardioversion period to avoid excessive QT prolongation.

References

3. FDA approves Pfizer antiarrhythmic medicine Tikosyn. Pfizer Inc PRESS RELEASE 1999 October 05.
21. Mortensen E, Yang T, Refsum H. Class III antiarrhythmic action...