EDITORIAL COMMENT

Dofetilide: Is the Treatment Worse Than the Disease?*

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On October 1, 1999, the U.S. Food and Drug Administration (FDA) approved dofetilide (Tikosyn) for the treatment of persistent (nonparoxysmal) atrial fibrillation and flutter. However, the FDA cautioned: “Because Tikosyn can cause life-threatening ventricular arrhythmias, it should be reserved for patients in whom atrial fibrillation/flutter is highly symptomatic (1).” Dofetilide is the first new oral antiarrhythmic drug preparation approved for use in the U.S. in seven years, the last being d,l-sotalol in 1992. Unlike its antiarrhythmic cousin, ibutilide—which is approved only for parenteral administration and is used primarily for conversion of atrial tachyarrhythmias in a monitored hospital or emergency department setting—dofetilide is intended for the long-term, outpatient treatment of atrial fibrillation and atrial flutter.

Basic electrophysiology and pharmacology of dofetilide. Dofetilide exerts its antiarrhythmic effects during cardiac repolarization. During the normal cardiac action potential, outward K⁺ currents overwhelm the decaying inward Na⁺ and Ca²⁺ currents, thereby mediating cardiac repolarization. It has been demonstrated that the delayed rectifier current, I_K, consists of two components: a rapidly inactivating component, termed I_Kr, and a more slowly inactivating component, termed I_Ks (2). I_Kr and I_Ks are each carried by separate ion channel molecules (3). Dofetilide is a highly selective blocker of I_Kr and, therefore, is classified as a pure class III antiarrhythmic agent. The K⁺ channel blocking effects of class III antiarrhythmic drugs, such as dofetilide, result in a dose-dependent prolongation of the action potential duration (4–7), and hence, the QT interval. Prolongation of action potential duration is associated with an increase in the effective refractory period of cardiac tissues (8,9). While this increase in refractoriness is the mechanism responsible for the antiarrhythmic effect of dofetilide, excessive QT prolongation may trigger a disas-


*Editorials published in Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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formed with the use of an intention-to-treat approach. In DIAMOND-CHF, 311 of 762 (41%) dofetilide group patients died compared with 317 of 756 (42%) placebo group patients (p = NS). In DIAMOND-MI, 230 of 749 (31%) dofetilide group patients and 243 of 761 (32%) placebo group patients died (p = NS). These results suggested that dofetilide did not affect mortality in a group of high risk patients with congestive heart failure and left ventricular dysfunction (11,12).

The outcomes of 506 patients with persistent atrial fibrillation who entered the DIAMOND studies were analyzed as part of a DIAMOND substudy. All patients were randomly assigned to receive dofetilide (250 μg twice daily) or placebo. Patients with persistent atrial fibrillation at entry were followed on their assigned therapy for one month. If they remained in atrial fibrillation, they were eligible for cardioversion. During the first 30 days of treatment, 56 of 249 patients taking dofetilide versus 7 of 257 patients receiving placebo converted to sinus rhythm. An additional 50 patients receiving dofetilide and 28 patients receiving placebo were electrically cardioverted. Among those patients in whom sinus rhythm was restored, 35% of dofetilide patients versus 84% of placebo patients had relapses into atrial fibrillation. Finally, for all DIAMOND patients who were originally in sinus rhythm, the dofetilide group also had a significantly lower incidence of new-onset atrial fibrillation (2% vs. 10%).

In the SAFIRE-D trial, 325 patients with persistent atrial fibrillation or flutter were hospitalized and randomized to therapy with either placebo or dofetilide at one of three doses: 125 μg, 250 μg or 500 μg twice daily. Dofetilide dose was adjusted for QTc and creatinine clearance prior to hospital discharge. Using intention-to-treat analysis, the results showed that dofetilide at doses of 250 μg or 500 μg was more effective than placebo at converting patients with atrial flutter or fibrillation to sinus rhythm, but only the 500-μg dose was more effective than placebo at maintaining sinus rhythm for one year.

The EMERALD study was a randomized, double-blind, placebo-controlled trial of 546 patients with persistent atrial fibrillation. Patients were randomized to receive placebo, or dofetilide at one of three doses: 125 μg, 250 μg or 500 μg twice daily, or sotalol 80 mg twice daily. Between 76% and 90% of patients in the five groups achieved sinus rhythm after either pharmacologic or electrical cardioversion and entered the maintenance portion of the study. At 1 year, the specified primary end point of the study, 30%, 45% and 51% of the 125 μg, 250 μg and 500 μg dofetilide groups, respectively, 38% of the sotalol group, and 16% of the placebo group remained in sinus rhythm, free of recurrent atrial fibrillation. All of the active drug groups were statistically different from placebo.

**Does dofetilide expose patients to a significant long-term risk of ventricular proarrhythmia?** Dofetilide prolongs the action potential duration and QT interval in a concentration-dependent fashion (6,8). Reports of the early incidence of torsade de pointes by QT-prolonging antiarrhythmic agents range from 0.5% to 8% (15–19). During dofetilide clinical studies, treatment was initiated during in-hospital monitoring until presumed steady state had been achieved. QT intervals were measured before each dose and a downward dose adjustment was permitted. Before 1994, however, patients participating in the dofetilide trials were assigned doses without regard to their baseline creatinine clearance, and doses up to 750 μg twice daily were allowed. After the occurrence of a number of cases of torsade de pointes, dosage was adjusted based on creatinine clearance and the 750 μg twice-daily dose level was eliminated. Following these changes, a substantial reduction in the incidence of torsade de pointes was noted. In DIAMOND-CHF, the incidence of torsade de pointes decreased from 7 of 146 (4.8%) to 18 of 616 (2.9%) using the amended protocol. Overall, torsade de pointes (≥10 beats) was observed in 25 of 762 (3.3%) DIAMOND-CHF patients, 7 of 749 (0.9%) DIAMOND-MI patients, 12 of 1,377 (0.9%) patients in supraventricular arrhythmia trials and 11 of 443 (2.5%) patients in ventricular tachycardia trials (10).

Most, but not all, documented episodes of torsade de pointes occurred during the in-hospital therapy initiation period; therefore, excess fatalities were rare. Risk factors for torsade de pointes included a higher dose, female gender, baseline QT >450 ms, greater QTc increase during loading and a history of a sustained ventricular tachycardia. It is important to note that patients with QTc >460 ms, resting heart rates <50 beats/min or a history of polymorphic ventricular tachycardia were excluded from these trials.

While the short-term risk of dofetilide-induced torsade de pointes appears well established from available clinical data, the long-term proarrhythmic risk of this agent is not known. Indeed, assessment of the long-term proarrhythmic potential of any antiarrhythmic agent is extremely difficult, especially in a population of patients with significant left ventricular dysfunction and a well established history of ventricular tachyarrhythmias, similar to the patients evaluated by Mazur et al. (20) and reported in the current issue of the *Journal*. This evaluation of risk is even more problematic when the proarrhythmic potential is (at least partly) related to the QT interval duration at the time of the suspicious arrhythmic event. Since the QT interval duration may be dynamic and can be measured only using surface electrocardiography, verification of QT interval prolongation at the time of the presumed proarrhythmic event may be difficult.

Nevertheless, to my knowledge, the report by Mazur et al. (20) is the first to evaluate the long-term antiarrhythmic and proarrhythmic effects of dofetilide in patients with significant left ventricular dysfunction who have received an implantable cardioverter-defibrillator (ICD) system for treatment of ventricular tachyarrhythmias. They analyzed data from a multicenter study of 174 ICD patients who were randomly assigned to receive placebo or dofetilide. The clinical profile of these patients appears similar to the typical
ICD patient: 88% male, 77% with ejection fraction <35%, with the majority having had ventricular tachycardia (79%) as opposed to ventricular fibrillation (21%). The starting dose of dofetilide, 500 µg twice daily, was adjusted downward based on estimates of creatinine clearance, or if the corrected QT interval increased by 15% over baseline after starting treatment with the drug. During periods of in-hospital treatment, patients were monitored with continuous ECG recording. During a planned one-year period of drug treatment, 131 of the 174 patients received therapy from their ICD (either antitachycardia pacing or shock). Episodes of ventricular tachyarrhythmias detected and treated by the ICD were analyzed using intracardiac electrograms stored in the ICD devices. The ICD devices do not record nonsustained episodes of tachycardia that fail to satisfy programmed detection criteria (rate or duration). Unfortunately, in the present study, there was no standardization of ICD programming for rate detection zones, tachycardia duration requirements or the rate of back-up anti-bradycardia pacing. Using prospectively developed criteria, the stored episodes were scored in a blinded fashion as monomorphic ventricular tachycardia, polymorphic ventricular tachycardia or ventricular fibrillation. In addition, the onset of each detected episode of tachycardia was declared as pause-dependent if a specifically defined “short-long-short” sequence was seen at the initiation of the tachycardia. Stored electrograms showing episodes of pause-dependent polymorphic ventricular tachycardia may be equivalent to pause-dependent torsade de pointes. However, accurate measurements of the QT interval duration cannot be made from intracardiac recordings, but instead would require a simultaneously obtained surface ECG.

Mazur et al. (20) found that ICD patients receiving dofetilide had an increased incidence of total episodes of torsade de pointes (recorded by surface ECG) and pause-dependent polymorphic ventricular tachycardia (recorded by ICD device) when both the in-hospital loading and follow-up periods were included, compared with a clinically similar group receiving the placebo (p < 0.05). However, while 11% (10/87) of the dofetilide patients had episodes that occurred after the prescribed in-hospital loading period, the long-term incidence of pause-dependent polymorphic ventricular tachycardia was not statistically greater in the dofetilide group (11%) than the placebo group (5/87 patients, 6%). Whether all these late episodes of pause-dependent polymorphic ventricular tachycardia were really torsade de pointes cannot be determined since the ICD electrogram evidence of pause-dependent polymorphic ventricular tachycardia could not be correlated with simultaneous prolongation of QT interval duration. It is, in fact, unlikely that all these pause-dependent episodes were torsade de pointes because patients receiving the placebo (and who would not be expected to have QT prolongation and torsade de pointes) had a significant rate of pause-dependent polymorphic ventricular tachycardia (6%). It is possible that all patients with significant left ventricular dysfunction share a common risk for pause-dependent polymorphic ventricular tachycardia (regardless of whether it is “true” torsade de pointes due to QT prolongation), even in the absence of treatment with QT interval-prolonging agents. This suggestion is supported by the observation that in 13 patients (four receiving dofetilide, nine receiving placebo), the first QTc recorded after an episode of pause-dependent polymorphic ventricular tachycardia was not statistically different in the dofetilide-treated patients compared with the patients receiving the placebo.

Taken together, this and previously reported data (10) suggest that the risk of dofetilide-induced torsade de pointes is low when using strict dosing criteria guided by the patient’s renal function, QT interval and concomitant drug therapy. However, as always, while the risk is small, it should be balanced against the risk posed to the patient by the target arrhythmia and the alternative treatment options available. Finally, while not statistically significant, the trend of the long-term data presented by Mazur et al. (20) should alert cardiologists and cardiac electrophysiologists to the potential for long-term proarrhythmia associated with the use of I_{kr} blocking agents, particularly in patients with significant left ventricular dysfunction. Clearly further study with more patients and longer follow-up will be necessary.

What is the role of dofetilide in the management of cardiac arrhythmias? In the past 15 years, there has been a revolution in the treatment of cardiac arrhythmias. The two greatest achievements of modern therapeutic cardiac electrophysiology have been the development of the radiofrequency electrode catheter ablation technique and the ICD system. Most forms of supraventricular tachycardia, including atrioventricular nodal reentrant tachycardia, atrioventricular reciprocating tachycardia utilizing an accessory connection and many forms of atrial flutter and atrial tachycardia are now routinely cured by catheter ablation using radiofrequency energy. Even selected patients with paroxysmal atrial fibrillation may now be curable with radiofrequency ablation (21). Patients with persistent or chronic atrial fibrillation with rapid, medically uncontrollable ventricular rates that threaten the development of a tachycardia-induced cardiomyopathy may be best managed by complete ablation of the atrioventricular junction followed by implantation of a permanent pacemaker system. A large percentage of patients with structurally normal hearts and idiopathic right or left ventricular tachycardias can be cured using radiofrequency ablation. The ICD systems are routinely implanted for secondary prevention in patients with structural heart disease who have suffered an episode of sustained ventricular tachycardia or ventricular fibrillation. Also, ICD systems are increasingly implanted for primary prevention in high risk patients with inducible ventricular tachycardia. Studies are currently in progress to evaluate the empiric implantation of ICD systems in high risk patients without electrophysiologic guidance. Consequently, drug therapy for patients with cardiac arrhythmias has been largely marginalized to patients with atrial fibrillation, ICD
patients receiving frequent, clinically appropriate shock or pacing therapies, or patients with non-life-threatening arrhythmias that remain uncured after attempts at catheter ablation.

The traditional limitations of drug therapy for cardiac arrhythmias have been the low efficacy of the available agents and the potential for side effects, particularly ventricular proarrhythmia. In general, treatment of ventricular or supraventricular tachyarrhythmias using class IA or IC drugs in patients with significant structural heart disease is contraindicated (22). The class III agent d,l-sotalol is also problematic in patients with structural heart disease given evidence that treatment of these patients with the pure dextroisomer of sotalol was associated with excess mortality, possibly due to torsade de pointes (23). Even in ICD patients with significant left ventricular dysfunction, drug-induced bradycardia and congestive heart failure may limit treatment with racemic sotalol. From the standpoint of proarrhythmia potential, amiodarone is considered the safest antiarrhythmic agent for treatment of cardiac arrhythmias (24). While amiodarone may cause torsade de pointes, the reported incidence is rare. However, amiodarone has other, potentially significant limitations, including organ toxicity and significant bradyarrhythmias.

With this backdrop, dofetilide has arrived on the scene. Atrial fibrillation and atrial flutter are not considered to be imminently life-threatening arrhythmias. While patients with these conditions are at increased risk of embolic stroke or tachycardia-induced cardiomyopathy, these atrial arrhythmias do not cause sudden arrhythmic death (in the absence of a manifest accessory pathway). Consequently, physicians and their patients with atrial tachyarrhythmias must carefully evaluate any potential treatment option that has a demonstrated life-threatening proarrhythmic potential. For patients with typical clockwise or counterclockwise atrial flutter, or other readily curable supraventricular tachyarrhythmias, radiofrequency catheter ablation appears to be preferable to long-term treatment with dofetilide. In experienced hands, the risk of this curative treatment option is extremely low with very high success rates for these arrhythmias. Alongside class IC and III agents, dofetilide may have a role in the treatment of atrial fibrillation in patients lacking significant structural heart disease. For selected patients with minimal or no structural heart disease and evidence of a focal origin for their atrial fibrillation, a curative ablation procedure should also be considered, particularly for those patients who have failed to respond to medical therapy. The years of clinical experience with amiodarone, in my opinion, still make it the first choice for medical treatment of highly symptomatic atrial fibrillation in patients with significant left ventricular dysfunction.

According to the dofetilide package insert (10), the incidence of torsade de pointes (≥10 beats) in the closely monitored and controlled clinical trials ranged as high as 3.3% in patients with structural heart disease. I believe the “real world” risk of torsade de pointes is as yet undefined in this population of patients, particularly in the routine environment of day-to-day clinical medicine in which regular patient follow-up is not assured, medical noncompliance is the norm and renal function in elderly diabetic patients with congestive heart failure may change with little advance notice. In addition, patients may self-treat with any number of over-the-counter medications and may unavoidably receive treatments from a wide variety of unsuspecting clinicians who may prescribe a variety of antibiotics, antihistamines, or antiulcer medications or change the doses of previously prescribed agents, including potassium, diuretics and digoxin. In a world filled with imperfect patients and imperfect doctors, more clinical experience and research is necessary before judging that dofetilide is as safe and as effective as amiodarone in this patient population. Clearly, a head-to-head comparison of amiodarone and dofetilide for the treatment of atrial fibrillation in this group of patients would be welcome.

Ironically, dofetilide may find its most useful niche in the treatment of problematic ventricular tachyarrhythmias in patients with ICD systems. As noted by Mazur et al. (20), dofetilide treatment was associated with a trend to a decreased frequency of multiple episodes of monomorphic ventricular tachycardia, suggesting that the agent may reduce the number of recurrences of this type of ventricular tachycardia. In addition, dofetilide treatment was associated with a significantly increased rate of successful antitachycardia pacing in ICD patients. These data are consistent with two small studies showing dofetilide was also effective in acutely suppressing inducible sustained ventricular tachycardia during serial electrophysiologic testing in approximately 45% of patients (25,26). Under the protective cover of an ICD device, electrophysiologists and cardiologists may be more accepting of potential rare episodes of ventricular proarrhythmia, as long as the antiarrhythmic effects of the dofetilide prove beneficial. Consequently, many electrophysiologists and cardiologists are likely to gain valuable clinical experience with dofetilide while using the drug to manage problematic atrial or ventricular tachyarrhythmias in their ICD patients.

Regardless of the revolutionary and evolutionary changes in interventional electrophysiology, there will always be a need for effective and safe antiarrhythmic drugs. Patients undergoing unsuccessful attempts at an ablative cure, as well as ICD patients experiencing frequent, painful, but clinically appropriate shocks, will require palliative antiarrhythmic drug therapy. This need may only increase as our population ages and ICD implantation is extended to a role in primary prevention of sudden arrhythmic death in high risk patient groups. Consequently, it is possible that the pharmaceutical industry may seek to employ even greater numbers of patients with implantable ICD systems in clinical trials of antiarrhythmic drugs, both to evaluate the effectiveness of these agents to suppress ventricular arrhythmias, and also to investigate the antiarrhythmic efficacy and proarrhythmic potential of these agents in the case of
non-life-threatening, but difficult-to-treat, atrial tachyarrhythmias.

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