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Intravenous Dofetilide, a Class III Antiarrhythmic Agent, for the Termination of Sustained Atrial Fibrillation or Flutter

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Objectives. **This study sought to determine the safety and efficacy of a single bolus of intravenous dofetilide, a pure class III antiarrhythmic agent, for the termination of sustained atrial fibrillation or flutter.**

Background. **Dofetilide is a highly selective blocker of the rapid component of the delayed rectifier current causing action potential prolongation. These effects, and preliminary clinical data, suggest that it may be effective in the treatment of atrial fibrillation and flutter.**

Methods. **Ninety-one patients with sustained atrial fibrillation (75 patients) or flutter (16 patients) were entered into a double-blind, randomized multicenter study of one of two doses of dofetilide (4 or 8 μg/kg body weight) or placebo.**

Results. **Dofetilide effectively terminated the arrhythmia in 31% of patients receiving 8 μg/kg, a statistically significant difference from those receiving 4 μg/kg (conversion rate 12.5%, $p < 0.05$) or placebo (no conversion, $p < 0.01$). Patients with atrial flutter had a greater response to dofetilide (54% conversion rate) than those with atrial fibrillation (14.5% conversion rate, $p < 0.001$).**

Conclusions. **Intravenous dofetilide can convert sustained atrial fibrillation or flutter to sinus rhythm. However, its efficacy is greater in flutter—a response that contrasts with the poorer response seen with class I agents. This finding potentially represents an important advance in the pharmacologic termination of atrial flutter.**

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Antiarrhythmic therapy for atrial fibrillation or atrial flutter has two goals: 1) pharmacologic termination of the arrhythmia, and 2) maintenance of sinus rhythm after pharmacologic or electrical reversion. Although a number of antiarrhythmic agents are relatively effective in achieving one or both of these goals, the overall efficacy rate and prevalence of side effects are such that the continued development of newer agents is warranted. Quinidine, a class I antiarrhythmic agent, is still widely used in the United States. However, it has frequent noncardiac side effects, and concern about the potential for an adverse effect of quinidine on mortality (1) in patients treated for atrial fibrillation has led to a reconsideration of its role in treating this arrhythmia (1,2). Coupled with specific concerns about quinidine is a general interest in the development of alternative agents to the class I antiarrhythmic drugs, and attention is now focusing on agents that primarily prolong refractoriness rather than slowing conduction (3–5).

Dofetilide is a highly selective blocker of the inward potassium current and appears to specifically block the rapid component of the delayed rectifier current (I_{Kr}) (6–8). As such, it results in prolongation of the action potential duration, with a resultant increase in myocardial refractoriness, and is classified as a class III agent (9). Preliminary investigations with dofetilide show it to be effective in the prevention of ventricular arrhythmias (9–11), and an unblinded, uncontrolled study of intravenous dofetilide (12) suggested that it may be effective in the termination of both atrial fibrillation and flutter. The electrophysiologic properties of dofetilide, namely, a prolongation of refractoriness without conduction slowing, suggest that it might be particularly useful in atrial flutter. This arrhythmia is relatively refractory to termination by class I agents, and an alternative to electrical cardioversion would be an attractive option. The purpose of the present study was to investigate the efficacy and safety of two different intravenous doses of dofetilide compared with placebo for the termination of sustained atrial fibrillation or flutter and to investigate whether a differential effect of dofetilide was apparent on these arrhythmias.

Methods

Patients. This was a double-blinded study of intravenous dofetilide or placebo in 91 patients with atrial fibrillation or flutter recruited from 13 sites (see Appendix). Patients had sustained arrhythmia for a minimum of 2 weeks and a maximum of 6 months at the time of study entry. Rest ventricular response was at least 70 beats/min, and all patients with atrial fibrillation received a minimum of 2 weeks of therapeutic

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Abbreviations and Acronyms

ANOVA = analysis of variance
CI = confidence interval
ECG = electrocardiogram, electrocardiographic
I_{Kr} = delayed inward rectifier current
QTc = corrected QT interval

warfarin therapy before study entry. All antiarrhythmic drugs, as well as diltiazem, verapamil and beta-adrenergic blocking agents were withdrawn for at least 5 half-lives before study drug administration, and subjects receiving drugs that may prolong the QT interval, such as antidepressants or phenothiazines, were excluded. Serum potassium concentrations were required to be within the range 4.0 to 5.5 mEq/liter and serum magnesium 1.5 to 2.5 mEq/liter. Subjects >75 years old, women of childbearing potential, patients with pre-excitation syndromes and those with uncontrolled hypertension were excluded, as were patients with previous electrocardiographic (ECG) documentation of high degree atrioventricular block (unless protected by a permanent pacemaker), those with a QRS duration ≥180 ms or a QT interval >500 ms. The study was approved by the Institutional Review Board of each participating investigator's institution, and written informed consent was obtained from each patient.

Protocol. After a 30-min period of continuous ECG monitoring, patients received an infusion of randomly assigned therapy consisting of either 4.0 or 8.0 μg/kg body weight of dofetilide or placebo. The medication was administered as a 15-min infusion, and neither the investigator nor the patient were aware of the identity of the therapy. At the end of the infusion, subjects were continuously monitored for an additional 6 h, during which period no additional antiarrhythmic agents were administered.

During the baseline 30-min period, the period of infusion and the subsequent 45 min, heart rate and blood pressure were measured every 15 min. The ventricular response to atrial fibrillation was determined from a 1-min rhythm strip recorded every 15 min. A positive response to therapy was defined as conversion to normal sinus rhythm. Blood samples for serum dofetilide levels were obtained immediately before infusion, at the end of the infusion and at 15-min intervals for the next 45 min. In those patients converting to sinus rhythm, blood was drawn for analysis of dofetilide levels at the time of conversion. Plasma samples were frozen and stored at −20°C. Samples were later analyzed by a double-antibody radioimmunoassay (Harris Lab).

In the early stage of the study, subjects who did not revert to sinus rhythm after 1 h could receive an open label infusion of 8.0 μg/kg of dofetilide, provided that the initial infusion did not cause side effects and did not prolong the uncorrected QT interval by >80 ms. The identity of the initial infusion was not known at the time of the second infusion. This option to administer open label 8.0 μg/kg was terminated early in the study because of safety concerns originating from other ongoing studies of dofetilide that suggested that torsade de pointes might be more prevalent at higher dose levels. Only eight patients received this second infusion.

Statistical analysis. Comparison of conversion rates between groups was made by chi-square analysis and the Fisher exact test. A p value <0.05 was considered statistically significant. Ninety-five percent confidence intervals were calculated according to the standard method of Ghosh (13). Comparison of ECG variables in the treatment and placebo groups was made by the Kruskal-Wallis nonparametric analysis of variance test and Dunn's multiple comparisons test using commercially available statistical software (Instat).

Results

Ninety-one patients, recruited from 13 centers, were enrolled in the study. The baseline characteristics of patients in each of the three study arms were determined by history and clinical examination by the individual investigators and are reported in Table 1. These characteristics did not differ among groups. Seventy-five patients had atrial fibrillation, and 16 had atrial flutter. There was a nonsignificant trend toward a longer duration of arrhythmia in patients with atrial fibrillation than in those with atrial flutter (61 days, 95% confidence interval (CI) 48 to 74 vs. 37 days, CI 18 to 57, p = 0.08). The incidence of heart failure did not differ between patients with atrial flutter and those with atrial fibrillation. Patients were randomized to receive placebo (n = 30) or 4 μg/kg (n = 32) or 8 μg/kg (n = 29) of dofetilide. Of the eight patients receiving an open label infusion of dofetilide after the double-blind phase, five had received an initial infusion of placebo, one had received 4 μg/kg of dofetilide, and two had received 8 μg/kg of dofetilide.

Conversion to sinus rhythm. In the double-blind phase, 4 of 32 patients (12.5%, CI 5% to 28%) receiving the lower dose of dofetilide converted to sinus rhythm (including 2 with a history of heart failure) compared with 9 of 29 (31%, CI 17.3% to 49.2%) receiving 8 μg/kg (including 4 with a history of heart failure). No patient converted after receiving placebo. The response to 8 μg/kg was significantly greater than that to either placebo ($p < 0.001$) or 4 μg/kg of dofetilide ($p < 0.05$) but the conversion rate for patients receiving 4 μg/kg did not differ significantly from that for placebo. Three of the eight patients receiving the open label dose of dofetilide converted to sinus rhythm. The initial double-blind therapy in these three patients consisted of placebo in one subject, 4 μg/kg of dofetilide in one and 8 μg/kg in the third. Conversion to sinus rhythm after open label dofetilide was not included in the efficacy analysis of dofetilide.

Of 16 patients with atrial flutter on the prestudy electrocardiogram, 5 were randomized to receive placebo, 3 to 4 μg/kg and 8 to 8 μg/kg of dofetilide. No patient with atrial flutter received the open label dose of dofetilide. No patient with flutter receiving placebo reverted to sinus rhythm compared with one of three receiving the lower dofetilide dose and five of eight receiving the higher dose. Conversion to sinus rhythm

Table 1. Baseline Clinical Characteristics

	Dofetilide		
	4 μg/kg (n = 32)	8 μg/kg (n = 29)	Placebo (n = 30)
Mean age (yr)	63.6	65.7	66.5
Men	22	23	22
Women	10	6	8
Sustained AF	29	21	25
Sustained AFL	3	8	5
Duration of AF/AFL (mo)			
Median	1.4	1.4	1.7
Mean	2.2	1.8	2.6
Range	0.5–6.8	0.5–5.5	0.5–7.9
Mean left atrial size (cm)	4.4*	4.6†	4.5‡
Range	3–7	3–6	4–6
NYHA functional class			
I	11	11	16
II	18	13	9
III	3	4	5
IV	0	1	0
Cardiovascular disease§			
Arterial hypertension	14	16	14
Congestive heart failure	18	12	7
Idopathic dilated cardiomyopathy	8	5	4
Hypertrophic cardiomyopathy	0	1	2
Exertional angina	6	4	7
Myocardial infarction	4	5	6
Valvular heart disease	1	2	3
None	5	6	8

*n = 30. †n = 28. ‡n = 29. §More than one condition can coexist in a patient. Data presented are number of patients, unless otherwise indicated. AF = atrial fibrillation; AFL = atrial flutter; NYHA = New York Heart Association.

from flutter was sudden, without change in the ventricular response or evidence of slowing of the atrial rate. The overall response rate of 54% (6 of 11 patients) for subjects with atrial flutter receiving either dose of dofetilide was higher than the overall rate of 14.3% (7 of 49) of subjects with atrial fibrillation who received either dose of dofetilide ($p < 0.01$).

Effects on heart rate, blood pressure and ECG. As shown in Table 2, heart rate remained unchanged at the end of the infusion (15-min values). Dofetilide had no effect on blood pressure or QRS duration. The QTc intervals in the placebo group remained unchanged from baseline to after infusion, whereas a statistically significant increase in this interval occurred in dofetilide-treated patients. The maximal QTc interval did not differ between patients receiving 4 or 8 μg/kg.

The mean dofetilide plasma levels for patients receiving both doses of dofetilide are reported in Table 3. Peak levels were consistently higher in the higher dose group. Plasma levels were available at the time of conversion in six patients and ranged from 1.40 to 18.4 ng/ml. This wide range reflected the range of time at which conversion occurred after commencement of the infusion. Plasma levels in patients with conversion to sinus rhythm corrected for time of conversion, did not differ from those without conversion.

Markers of efficacy. In view of the minimal efficacy of 4 μg/kg of dofetilide to produce restoration of sinus rhythm, markers of efficacy were sought only in the higher dosage group. Other than the presence of atrial flutter, no clear-cut markers were identified that might predict which patients may

Table 2. Effect of Intravenous Dofetilide on Heart Rate and Corrected QT Interval*

	HR (beats/min)		QTc (ms)	
	Baseline	End of Infusion	Baseline	End of Infusion
Placebo infusion (n = 29)	87.9 ± 21	87.5 ± 20	434.5 ± 39	427.2 ± 38
Dofetilide				
4 μg/kg (n = 31)	89.0 ± 19	90.8 ± 17	437.9 ± 53	492.2 ± 60†
8 μg/kg (n = 28)	90.6 ± 18	90.1 ± 21	421.8 ± 43	491.1 ± 76†

*All patients were in atrial fibrillation or flutter at time of measurement. †$p < 0.01$ versus placebo at end of infusion; no significant difference between corrected QT intervals (QTc) at the two dofetilide doses was seen. Data presented are mean value ± SD. HR = heart rate.

Table 3. Mean Plasma Dofetilide Concentrations

Time From Start of Infusion (min)	Mean ± SD Dofetilide Concentration (ng/ml)	
	4 μg/kg	8 μg/kg
15*	4.35 ± 2.2	10.7 ± 5.2
30	2.4 ± 1.6	3.7 ± 1.6
45	1.8 ± 1.0	3.4 ± 1.6
60	1.7 ± 0.8	3.1 ± 1.3

*Levels at 15 min represent end of infusion.

respond to dofetilide. Specifically, there was no significant difference in the median arrhythmia duration in patients with (29.5 days, CI 9.9 to 73) than those without conversion (40 days, CI 32 to 71). Median QTc intervals in patients with conversion measured 30 min after drug infusion also did not differ from those without conversion (495 ms, 95% CI 442 to 582 vs. 478 ms, 454 to 516 ms), and no clinical indicator could be identified that appeared to favor conversion.

Adverse effects. Adverse effects of the dofetilide infusion were limited to the cardiovascular system. Torsade de pointes occurred in 2 (3.2%) of 62 patients who received at least one dose of dofetilide (during the double-blind infusion of 4 μg/kg in one; during open label infusion of 8 μg/kg after an initial placebo infusion in the other). Detailed rhythm strips were unavailable for review in the former patient, but the latter had a permanent pacemaker in the VVI mode that was pacing at 80 beats/min. The baseline QTc interval was 515 ms, primarily due to the widened, paced QRS complex. During the infusion of dofetilide, the QTc interval prolonged to >600 ms (precise measurement could not be made because of R on T ectopic beats), followed by multiple episodes of torsade de pointes. Two other patients, both of whom had received an initial infusion of placebo, developed marked QT prolongation associated with increasing premature ventricular contractions during open label infusion (8 μg/kg) of dofetilide. The infusion was terminated in one patient because the QTc interval increased from 400 ms at baseline to 620 ms during dofetilide infusion. Neither of these patients developed sustained or symptomatic arrhythmia. Three additional patients developed short runs of wide QRS complex tachycardia during the infusion of 8 μg/kg without hemodynamic consequences. In one of these patients, monomorphic wide QRS complex beats occurring during the 8-μg/kg infusion were, on review of the tracings, due to aberrantly conducted supraventricular beats. Inadequate documentation in the other two subjects precluded detailed analysis of the arrhythmia.

Discussion

This study indicates that intravenous dofetilide, a class III antiarrhythmic agent, may restore sinus rhythm in patients with atrial flutter or fibrillation of at least 2 weeks in duration. Conversion was more likely to occur in patients receiving 8 than 4 μg/kg, and atrial flutter was a more responsive arrhythmia than atrial fibrillation.

Previous studies. The relatively low conversion rate of 12.5% after 4 μg/kg and the higher rate of 31% after 8 μg/kg of dofetilide are in contrast to data of Suttorp et al. (12). These investigators studied 24 patients with atrial fibrillation or flutter treated with 2.5, 4 or 8 μg/kg of dofetilide, administered intravenously over 15 min and repeated 15 min after the end of infusion if conversion had not occurred. The overall efficacy rate was 53% for 19 patients with atrial fibrillation and 80% for 5 with atrial flutter.

The study by Suttorp et al. (12) was not performed in blinded manner and although no difference in response rate was seen among dosage groups, the numbers are too small for statistical analysis. The mean duration of atrial arrhythmia in the Suttorp et al. study was 32 ± 43 days (range 1 to 150), and seven patients had an arrhythmia duration of <1 day. This finding is in contrast to those of the present study (mean duration of arrhythmia 62 days, range 14 to 240, median 42). The success of pharmacologic conversion of atrial fibrillation is related to the duration of the arrhythmia. In patients with atrial fibrillation of ≤1 week in duration, ~40% of those treated with placebo will convert to sinus rhythm within 24 h (14,15), and in subjects with recent-onset atrial fibrillation (≤48 h), the efficacy of short term drug therapy may be even higher (15). In contrast, arrhythmia duration ≥1 week rarely converts spontaneously, and drug efficacy decreases to the range seen in the present study (16). Thus, it is possible that in the Suttorp et al. study (12), either the inclusion of patients with a short arrhythmia duration or with less severe heart disease may have increased the likelihood of conversion. Our conversion rates are closer to those of a recently published small study (17) in which two of six patients with atrial fibrillation receiving 8 μg/kg of dofetilide and two of nine patients given 12 μg/kg of dofetilide had conversion to sinus rhythm, an overall response rate of only 27% (17).

Atrial flutter. A striking finding in the current study is the relatively high conversion rate in the group of patients with atrial flutter. Previous studies of type I antiarrhythmic agents (16,18,19) have suggested that pharmacologic conversion of atrial flutter is unusual and occurs less frequently than in patients with atrial fibrillation. In an early survey of the reported efficacy of procainamide, Kayden et al. (20) reported a conversion rate of only 13% in patients with atrial flutter compared with 88% of those with atrial fibrillation of ≤2 weeks in duration. Olshansky et al. (21) failed to produce pharmacologic conversion to sinus rhythm in any of seven patients treated with intravenous procainamide despite a prolongation of atrial cycle length in all seven. Class IC agents are also documented to have a poor efficacy in terminating atrial flutter (19). In contrast, our observations are consistent with those of the study by Suttorp et al. (12), in which 4 of 5 patients with atrial flutter reverted to sinus rhythm after dofetilide infusion, and with a recently published study (19) comparing dofetilide with flecainide, in which only 1 of 11 patients with atrial flutter reverted to sinus rhythm after 2 mg/kg of intravenous flecainide compared with 7 of 10 subjects receiving 4 to 8 μg/kg of dofetilide.

The conversion of atrial flutter with dofetilide is compatible with its class III properties. Atrial flutter is most commonly due to a macroreentrant arrhythmia around the right atrium (22). Drugs that primarily slow atrial conduction, such as flecainide, might not be expected to terminate atrial flutter, although the cycle length may be prolonged (3,19,23). Type IA agents, which both prolong refractoriness and slow conduction, may affect the atrium such that, although cycle length is slowed, an excitable gap persists allowing persistent arrhythmia (19). In contrast, selective prolongation of refractoriness would favor termination of the arrhythmia by decreasing the excitable gap. This effect of class III agents has been proved in experimental models (23), and the observation that atrial flutter cycle length lengthens minimally before conversion after dofetilide supports this as a mechanism in humans (19).

Adverse effects. A concern of therapy with class III agents is the potential for provocation of torsade de pointes. Action potential prolongation is associated with the development of early afterdepolarizations in animal models (24,25), and early afterdepolarizations are believed to be responsible for many cases of human torsade de pointes. As previously described (22,26), and as confirmed in the present study, dofetilide produces a significant prolongation of the QT interval. Torsade de pointes occurred in two patients in our study, neither of whom required specific treatment for the arrhythmia other than termination of the dofetilide infusion. Other cases of torsade have occurred with both oral and intravenous dofetilide (17), but preliminary data show that a dose based on creatinine clearance as well as weight may reduce the potential for excessive drug levels, at least in patients receiving oral therapy (Pfizer, data on file). Whether dofetilide has a greater or lesser propensity for the provocation of torsade de pointes than other class III agents, such as sotalol (27,28), remains to be determined.

Short runs of wide QRS complex tachycardia were seen in three patients during dofetilide infusion while the patients were still in atrial fibrillation. Dofetilide manifests electrophysiologic features that may predispose to aberrant ventricular conduction, and aberrant conduction during atrial fibrillation may be difficult to distinguish from short runs of ventricular tachycardia. Crijns et al. (29) performed an electrophysiologic study in a patient receiving dofetilide who manifested periods of wide QRS complex tachycardia. Dofetilide caused an increased propensity to aberrant conduction. However, the same investigators (30) also reported isolated bundle branch reentry in a patient with coexistent dofetilide-induced aberrantly conducted supraventricular beats during atrial fibrillation, thus raising the possibility that the drug may predispose to sustained bundle branch reentry in susceptible patients. At least one of three patients with nonsustained wide QRS complex arrhythmias in our study had aberrantly conducted atrial fibrillation confirmed by the presence of identical complexes after atrial premature beats once sinus rhythm had been restored. As noted, inadequate data in the other two patients precluded a diagnosis of the origin of their wide QRS complex beats.

In contrast to the proarrhythmia provoked by dofetilide, no patient developed evidence of hemodynamic deterioration despite a history of heart failure in 30 of the 61 patients receiving active drug. Although only a single dose of the drug was given, the lack of a negative hemodynamic effect is compatible with findings in previous animal studies (31) and probably relates to the pure class III actions of dofetilide.

Conclusions. Intravenous dofetilide was effective in terminating some cases of atrial fibrillation of moderate duration but was significantly more effective in terminating atrial flutter. The effect of dofetilide on atrial flutter, which is generally considered a relatively pharmacologically resistant arrhythmia, is consistent with the pure class III effect of dofetilide and confirms observations in small unblind, nonrandomized studies of intravenous dofetilide (12,19,22). Although the higher dose of dofetilide (8 μg/kg) was more effective in arrhythmia termination, the propensity to cause torsade de pointes in some patients limits further investigation into the antifibrillatory effects of higher doses.

Intravenous dofetilide has potential as a short-term antiarrhythmic agent in patients with atrial flutter, but in this study it was considerably less effective in patients with atrial fibrillation. The efficacy of a drug for terminating an arrhythmia is not necessarily equivalent to its efficacy for preventing recurrence, and ongoing studies are evaluating the safety and efficacy or oral dofetilide for prevention of recurrent atrial fibrillation and flutter.

Appendix

The Intravenous Dofetilide Investigators

Rodney H. Falk, MD, *Boston City Hospital, Boston, Massachusetts* (20 patients randomized); Steven Singh, MD, *Veterans Affairs Medical Center, Washington, D.C.* (17 patients randomized, 4 patients screen failure); Bramah N. Singh, MD, PhD, *Veterans Affairs Wadsworth Hospital Medical Center, Los Angeles, California* (10 patients randomized, 1 patient screen failure); Bruce Shively, MD, *Veterans Affairs Hospital, Albequerque, New Mexico* (9 patients randomized); James Maloney, MD, *Cleveland Clinic, Cleveland, Ohio* (6 patients randomized); Koonlawee Nademanee, MD, *Denver General Hospital, Denver, Colorado* (6 patients randomized, 2 patients screen failure); Raymond Yee, MD, *University Hospital, London, Ontario, Canada* (6 patients randomized); Gregory K. Feld, *University of California San Diego Medical Center, San Diego, California* (6 patients randomized); *Dan Roden, MD, Vanderbilt University, Nashville, Tennessee* (5 patients randomized, 1 patient screen failure); John Onufer, MD, *Cardiovascular Associates, Ltd., Hague Medical Center, Norfolk, Virginia* (4 patients randomized); John C. Somberg, MD, *University of Health Sciences, The Chicago Medical School, North Chicago, Illinois* (3 patients randomized); Elliot M. Antman, MD, *Brigham and Women's Hospital, Boston, Massachusetts* (2 patients randomized); Lameh Fananapazir, MD, *National Institutes of Health, Bethesda, Maryland* (2 patients randomized).

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