

Comparison of intravenously administered dofetilide versus amiodarone in the acute termination of atrial fibrillation and flutter

A multicentre, randomized, double-blind, placebo-controlled study

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Aims This study compared the efficacy and safety of intravenous dofetilide with amiodarone and placebo in converting atrial fibrillation or flutter to sinus rhythm.

Methods and Results One hundred and fifty patients with atrial fibrillation or flutter (duration range 2 h–6 months) were given 15-min intravenous infusions of 8 μg . kg−1 of dofetilide (n=48), 5 mg . kg−1 of amiodarone (n=50), or placebo (n=52) and monitored continuously for 3 h. Sinus rhythm was restored in 35%, 4%, and 4% of patients, respectively (P<0·001, dofetilide vs placebo; P=ns, amiodarone versus placebo). Dofetilide was more effective in atrial flutter than in atrial fibrillation (cardioversion rates 75% and 22%, respectively; P=0·004). The mean time to conversion with dofetilide was 55±15 min. Dofetilide prolonged the QTc interval (+16% at 20 min). Amiodarone substantially decreased the ventricular rate in non-converters (−18 beats . min−1, at 30 min). Two patients given dofetilide (4%) had non-sustained ventricular tachycardias, and four (8%) had torsade de pointes, in one case requiring electrical cardioversion.

Conclusion Intravenous dofetilide is significantly more effective than amiodarone or placebo in restoring sinus rhythm in patients with atrial fibrillation or flutter. However, when infused intravenously at this dose and rate, dofetilide causes a significant incidence of torsade de pointes.

Key Words: dofetilide, amiodarone, antiarrhythmic drugs, atrial fibrillation, atrial flutter, cardioversion.

Introduction

No optimal treatment to convert atrial fibrillation or atrial flutter to sinus rhythm is currently available. Electrical cardioversion is highly effective, but it is inconvenient, because it requires anaesthesia, and it does not protect against early recurrence of the arrhythmia[1,2]. The class IC drugs flecainide and propafenone, administered intravenously, have a high success rate in recent-onset atrial fibrillation without seriously proarrhythmic effects, but their efficacy is unsatisfactory in patients with long-standing arrhythmias[3–8]. The intravenously administered class IA drugs procainamide and disopyramide seem to be less effective[6,9–11] and may provoke hypotension and facilitate atrioventricular conduction, sometimes leading to high ventricular rates and haemodynamic compromise[9–12]. Moreover, all of these drugs have depressant effects on cardiac contractility and conduction, and their use is precluded in patients with congestive heart failure and conduction disturbances. Intravenous amiodarone is better tolerated, even in patients with depressed left ventricular function, but usually requires protracted infusion, and recently its efficacy has been questioned[9,13–15]. Finally, with class I and some class III drugs, conversion rates are lower in atrial flutter than in atrial fibrillation[4,7,11,12].

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Table 1  Exclusion criteria

- Female patients of childbearing potential
- Clinically unstable heart failure or distress (e.g. angina, dyspnoea) as a result of atrial fibrillation or flutter
- Resting ventricular rate of <60 beats . min\(^{-1}\) or RR interval of >4 s
- QRS interval of >180 ms or QT interval of >440 ms
- History or clinical signs of thyrotoxicosis
- History of cardiac surgery, myocardial infarction, unstable angina, or aborted sudden cardiac death within the last 3 weeks
- Known sick sinus syndrome or atrioventricular block of greater than first degree
- Cardiac pacemaker
- History of polymorphic ventricular tachycardia secondary to drugs
- Diastolic blood pressure of >110 mmHg or systolic blood pressure of <80 mmHg
- Major haematological, hepatic, or renal disease
- Plasma potassium level of <3 or >5.5 mmol . l\(^{-1}\), or known plasma magnesium level of <0.6 or >1.5 mmol . l\(^{-1}\)
- History of cardiac surgery, myocardial infarction, unstable angina, or aborted sudden cardiac death within the last 3 weeks
- Major haematological, hepatic, or renal disease
- Plasma potassium level of <3 or >5.5 mmol . l\(^{-1}\), or known plasma magnesium level of <0.6 or >1.5 mmol . l\(^{-1}\)
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- History of cardiac surgery, myocardial infarction, unstable angina, or aborted sudden cardiac death within the last 3 weeks
- Known sick sinus syndrome or atrioventricular block of greater than first degree

Methods

Patients

Patients of either sex, who were between 18 and 85 years old and who had had atrial fibrillation or atrial flutter lasting from 2 h to 6 months, were eligible for the study. Patients were not permitted to take any class I, III, or IV antiarrhythmic agents, tricyclic or tetracyclic antidepressants, anticonvulsants, or phenothiazines for at least five half-lives of such drugs before entering the study. Exclusion criteria are listed in Table 1.

Study design

This multicentre study, double blind for dofetilide-placebo and single blind for amiodarone, was conducted at 10 sites in Italy (see Appendix). At an initial screening visit, each subject had a relevant medical history taken and underwent a physical examination and a 12-lead electrocardiogram. In the 2 h before randomization, a blood sample was taken for routine laboratory tests of safety. A transthoracic echocardiogram was obtained before or within 24 h after administration of the study drug.

A baseline evaluation period lasted approximately 1 h. During this time, a Holter recorder was activated and was continued for at least 12 h. Subjects were randomized, in permuted blocks of six, to receive 15-min intravenous infusions of one of the following three treatments: (1) 8 \(\mu\)g . kg\(^{-1}\) of dofetilide, (2) 5 mg . kg\(^{-1}\) of amiodarone, or (3) placebo.

Randomized patients underwent continuous electrocardiographic monitoring from just before randomization until 3 h after the infusion. Blood pressure was recorded and a 12-lead electrocardiogram was obtained at the start and end of the baseline period, 3 h after the commencement of the infusion, at discharge, and, in patients who converted to sinus rhythm, at the time of conversion. Blood pressure and single-lead electrocardiograms were obtained at the beginning of the infusion; at 5, 10, 15, 20, 30, 60, 120, and 180 min; at 4 and 6 h; and at discharge. From the electrocardiograms, the QT interval was measured manually, and the ventricular rate was derived by integration over five cardiac cycles or 10 s.

Study treatment was discontinued if sinus rhythm was restored or if any of the following events occurred: (1) prolongation of the QT interval to >500 ms; (2) prominent U waves or any significant changes in T-wave morphology; (3) any electrophysiological event that the investigator considered to indicate proarrhythmia (e.g. torsade de pointes, ventricular tachycardia, ventricular fibrillation, supraventricular tachycardia). Patients whose arrhythmia did not convert to sinus rhythm within 3 h of the commencement of the infusion were considered therapeutic failures (non-responders) and
could be given standard treatment (e.g. electrical cardioversion).

Subjects were discharged no sooner than 12 h after the infusion began. At this time and at the follow-up visit 3 to 7 days later, a 12-lead electrocardiogram, an electrocardiographic rhythm strip, blood pressure measurement, a physical examination, and laboratory safety tests were repeated.

The primary end-points were (1) incidence of conversion to sinus rhythm within 3 h of the start of infusion and (2) incidence of side effects. Secondary end-points were (1) mean time to conversion and (2) ventricular rate in non-converted patients after drug treatment with respect to baseline.

The protocol was reviewed and approved by the European Ethical Committee and by local ethics committees, where present; was monitored according to Good Clinical Practices; and was conducted in accordance with the revised declaration of Helsinki (Hong Kong, 1989). All subjects provided written informed consent.

Statistical analyses

Conversion rates were compared with the Cochran–Mantel–Haenszel statistic, calculated according to the SAS procedure[18]. The predictive value of variables at baseline on the probability of conversion to sinus rhythm was assessed by multiple logistic regression analysis. The mean changes from baseline over time for mean blood pressure, heart rate, and QRS and QTc intervals were assessed in non-responders by analysis of covariance. The survival function for time to conversion was estimated by Kaplan–Meier analysis. Data are presented as means ± SE. A P value of <0.05 was considered statistically significant.

Results

Patients

One hundred and seventy-three subjects were screened; 158 of them were randomized: 50 (32%) to dofetilide, 54 (34%) to amiodarone, and 54 (34%) to placebo. Eight subjects (5%) from one centre (two given dofetilide, four given amiodarone, and two given placebo) were excluded from the efficacy analysis because timing of the electrocardiographic recordings could not be verified. Therefore, the efficacy analysis was performed on data from the remaining 150 patients: 48 (32%) given dofetilide, 50 (33%) given amiodarone, and 52 (35%) given placebo. Data from all 158 subjects were included in the safety analysis.

The clinical characteristics of the patients at baseline were comparable between the three groups (Table 2). Thirty-one patients (21%; 12 given dofetilide, 9 given amiodarone, and 10 given placebo) had a primary diagnosis of atrial flutter, and the remainder had atrial fibrillation. In the majority of patients, the arrhythmia had lasted longer than 7 days.

Conversion to sinus rhythm

On the basis of the intention-to-treat analysis, the arrhythmias in 17 of 48 (35%) patients given dofetilide, 2 of 50 (4%) given amiodarone, and 2 of 52 (4%) given placebo converted to sinus rhythm within the 3-h study period (P<0.001, dofetilide vs placebo; P=ns, amiodarone vs placebo) (Fig. 1). The mean time to conversion in dofetilide responders was 55±15 min after the infusion began. Most dofetilide responders (11 of 17; 65%) experienced conversion within 30 min. The curves of conversion time in the three groups of patients are reported in Fig. 1.

By multiple logistic regression, the conversion efficacy of dofetilide was significantly higher in atrial flutter than in atrial fibrillation (P=0.004). Conversion rates at 3 h were 75% vs 22% respectively (Fig. 2).

A greater proportion of patients responded to dofetilide if their arrhythmia had lasted <7 days (9 of 21; 43%) than did those whose arrhythmia had lasted >7 days (8 of 27; 30%), but by multiple logistic regression, this difference was not statistically significant (P=0.59).

Predictors of drug efficacy

Because of the low conversion rates in patients treated with amiodarone or placebo, predictors of drug efficacy were statistically analysed only for patients treated with dofetilide. Apart from the primary diagnosis, the mean heart rate, QT intervals, duration of the arrhythmia, and size of the left atrium did not significantly influence the odds of converting to sinus rhythm in dofetilide-treated patients (Table 3).

Effects on blood pressure and electrocardiographic parameters

The mean blood pressure showed a modest but statistically significant decrease from baseline in all three groups. The mean maximal reduction (adjusted for baseline values) was 4.3±1.4 mmHg in the dofetilide-treated group (P=0.003), 6.9±1.4 mmHg in the amiodarone-treated group (P<0.001), and 5.3±1.4 mmHg in the placebo-treated group (P<0.001). No overall difference was found in the adjusted means between the three groups (P=ns). One patient given amiodarone experienced mild asymptomatic hypotension.

The variations from baseline in mean heart rate for non-responders are shown in Fig. 3. Both dofetilide and amiodarone produced statistically significant reductions in mean heart rate adjusted for baseline values.
However, while in dofetilide patients the heart rate reduction was modest (maximum $-6 \pm 4$ beats $\cdot$ min$^{-1}$ at 30 min, $P=0.005$) and no longer detectable at 120 min, amiodarone produced a drop in heart rate that was significant 10 min after the start of the infusion ($P=0.005$), being maximal at 30 min ($-18 \pm 2$ beats $\cdot$ min$^{-1}$, $P<0.001$) and still persisting at 2 and 3 h ($P<0.001$).

At 5 min after the start of the infusion, the mean QTc interval (adjusted for baseline values) in dofetilide-
treated patients increased significantly (15.3 ± 4.3 ms; $P=0.001$). It reached its maximal value at 20 min (65.7 ± 8.1 ms; $P<0.001$) and slowly decreased thereafter, although it was still increased relative to baseline (33.5 ± 5.6 ms, $P<0.001$) at the end of the 3-h observation period. The mean QTc interval (adjusted for baseline values) did not change with either amiodarone or placebo (see Fig. 4).

No effect was noted on the duration of the QRS interval in patients receiving dofetilide, amiodarone, or placebo.

**Adverse events**

Four of the dofetilide-treated patients (8%) experienced episodes of torsade de pointes. Electrolyte levels were normal in all four patients, and no clear relationships were found with either sex (one man and three women) or underlying disease (one patient with congestive heart failure and valvular heart disease, one patient with valvular heart disease, one patient with borderline hypertension and diabetes, and one patient with no prior history of serious illness). In two of the patients, the torsade de pointes was asymptomatic and self-terminating, requiring no treatment other than discontinuation of the drug. In the third subject, the arrhythmia occurred 8 min after the start of the infusion. The drug was continued and the arrhythmia recurred, degenerating 8 min later into ventricular flutter, which led to syncope and required electrical cardioversion. In the fourth patient, the torsade de pointes began 2 min after the infusion was completed; it was treated successfully with the administration of magnesium sulfate and lidocaine.

Four other dofetilide-treated patients (8%) experienced self-terminating electrophysiological events that were attributed to the study drug. Two of these events were isolated non-sustained ventricular tachycardia, one at the end of the infusion and the other nearly 2 h later. In a third patient, premature ventricular beats with frequent couplets began 12 min after the start of infusion and continued until 3 h later. The fourth patient had a prolongation of the QTc interval from a baseline value of 439 ms to 577 ms at 10 min, when the infusion was stopped. This patient’s QTc interval peaked at 716 ms 10 min later (i.e. 20 min after the start of the infusion) and was still >500 ms at the 6-h point. By 12 h, the QTc interval had returned to the baseline value, and it remained normal at follow-up.

One amiodarone-treated patient (2%) experienced a single episode of mild hypotension that began 45 min after the start of the infusion and lasted for 13 min.

**Discussion**

This study demonstrated that intravenous dofetilide was more effective than intravenous amiodarone and
Table 3  Clinical and electrocardiographic characteristics in the dofetilide-treated patients at baseline, by response to the drug

<table>
<thead>
<tr>
<th></th>
<th>Patients whose arrhythmia converted</th>
<th>Patients whose arrhythmia did not convert</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation/atrial flutter</td>
<td>11/10†</td>
<td>108/21†</td>
<td>0.039</td>
<td>0.004-0.360</td>
<td>0.004</td>
</tr>
<tr>
<td>Duration of arrhythmia (&gt;7/≤7 days)</td>
<td>8/13†</td>
<td>71/58†</td>
<td>1.582</td>
<td>0.283-8.51</td>
<td>0.594</td>
</tr>
<tr>
<td>Size of left atrium</td>
<td>42.0 ± 1.4 mm‡</td>
<td>44.5 ± 2.0 mm‡</td>
<td>0.966</td>
<td>0.894-1.044</td>
<td>0.369</td>
</tr>
<tr>
<td>Mean heart rate</td>
<td>96.9 ± 4.5 bpm‡</td>
<td>94.8 ± 3.8 bpm‡</td>
<td>1.000</td>
<td>0.952-1.050</td>
<td>0.991</td>
</tr>
<tr>
<td>QTc interval</td>
<td>329.4 ± 9.2 ms‡</td>
<td>336.6 ± 7.7 ms‡</td>
<td>0.987</td>
<td>0.960-1.015</td>
<td>0.341</td>
</tr>
</tbody>
</table>

*By multiple logistic regression.
†Numbers of patients.
‡Mean ± SE.

Figure 3  Change from mean heart rate at baseline (dashed line at 0), in beats . min⁻¹, for the three groups of patients over the 3-h observation period after the start of the infusion. ● = dofetilide; ▲ = amiodarone; □ = placebo.

Figure 4  Change from mean QTc interval at baseline (dashed line at 0), in ms, for the three groups of patients over the 3-h observation period after the start of the infusion. ● = dofetilide; ▲ = amiodarone; □ = placebo.

placebo in converting atrial fibrillation and flutter to sinus rhythm and that it was more effective in atrial flutter than in fibrillation. These results concur with those of five previous clinical trials on the use of intravenous dofetilide in atrial fibrillation or flutter that have been published[19-23].

Table 4 summarizes the results of these previous studies. By pooling the results, the efficacy of dofetilide in converting atrial fibrillation and atrial flutter to sinus rhythm was 25% and 65%, respectively, figures that are similar to those observed in our study (22% and 75%).

Our results also indicate that a 15-min infusion of 15 mg . kg⁻¹ of amiodarone has no effect in interruption of atrial fibrillation or flutter. This can be explained by the fact that — given the complex pharmacokinetics of the drug — the study period of 3 h may be not enough
In atrial flutter, interrupted by drugs that prolong refractoriness than by those that depress conduction.

Sedgwick, 1995\textsuperscript{22} & 4/15 (27) & — & 4/15 (27) & 2/15 (13) \\
Frost, 1997\textsuperscript{24} & 26/65 (40)* & 6/11 (55) & 13/61 (21) & 2/61 (3.3) \\
Total & 21/84 (25) & 17/26 (65) & 64/175 (37) & 4/175 (2.3) \\

\*Three patients had atrial flutter.

Effects on blood pressure and electrocardiographic parameters

In this study, intravenous dofetilide produced a mild, clinically insignificant reduction in mean blood pressure as well as in the ventricular rate of patients remaining in atrial fibrillation. The drug did not affect the duration of the QRS interval. This previously recognised lack of a depressant action on vasomotor tone, cardiac pump function, and the conduction system is a unique characteristic that distinguishes pure class III agents from the other available antiarrhythmic drugs, allowing their use even in patients who have depressed cardiac function or excitation–conduction disturbances.

As previously described\textsuperscript{20,26}, the increase in the duration of ventricular repolarization by dofetilide was statistically significant. This effect appeared very early: prolongation of the QTc interval was evident after only 5 min of infusion of the drug, reaching a maximal mean increase over baseline of 15.8% at 20 min and then slowly decreased. The QTc interval was still prolonged (+8.7%) and statistically significantly at the end of the 3-h study period.

Amiodarone, in contrast, had no effect on repolarization, which could account for the complete lack of antiarrhythmic efficacy we observed with this mode of administration of the drug.
The effects of the two study drugs on the ventricular rate of patients who continued to experience atrial fibrillation were different. While the effect of dofetilide on this parameter was minimal (maximum of 6 beats min⁻¹ at 30 min), amiodarone induced a significant decrease in ventricular rate, that was maximal (~18 beats min⁻¹) at 30 min and persisted at 3 h. These findings agree with the observation that an intravenous bolus of amiodarone exerts no class III action, as attested by its lack of effect on ventricular repolarization, but possesses definite antiadrenergic activity[27-29].

**Adverse events**

The only notable adverse effect that was considered to be related to the intravenous administration of dofetilide was the induction of torsade de pointes, which is common to all class III drugs and is a consequence of its mode of action. The incidence of torsade de pointes in our patients was 8%, which is higher than that observed in most of the previous studies of intravenous dofetilide in atrial fibrillation and flutter (Table 4).

The incidence of torsade de pointes with ibutilide, which was approved recently in the United States for the acute treatment of atrial fibrillation and flutter, is higher than that seen to date with intravenous dofetilide. In a review of several controlled clinical trials involving 586 patients[30], and in two subsequent large clinical trials[25,31], the incidences of torsade de pointes were 4.3%, 8.3% and 6.4% respectively. In 1-7% of these cases, the arrhythmia was sustained and required electrical cardioversion.

In this study, the occurrence of torsade de pointes was not predicted by any characteristic at baseline. It occurred during or shortly after the infusion of the drug in four patients, only one of whom required electrical cardioversion. In the one patient whose arrhythmia was sustained, leading to syncope and requiring electrical cardioversion, subsequent analysis of the Holter recording revealed that an asymptomatic short run of the arrhythmia had occurred minutes before but had been unnoticed. Conceivably, if it had been recognized properly and the drug infusion had been stopped according to the protocol, the sustained arrhythmia could have been avoided. This finding underscores the need for careful monitoring during the use of this class of drugs and the need to restrict their use to only experienced physicians in a proper setting (in which a defibrillator is readily available). Under such conditions, the occurrence of this ventricular proarrhythmia can be managed safely.

**Conclusion**

Dofetilide, given as a short intravenous infusion, is more effective than amiodarone and placebo in rapidly converting atrial fibrillation and atrial flutter to sinus rhythm. Its efficacy is particularly valuable in atrial flutter, in which class I drugs have a low capability of conversion. Dofetilide has no effect on vasomotor tone, cardiac inotropism, or the excitation–conduction system. One must expect a defined incidence of torsade de pointes with the use of intravenous dofetilide, as with other class III antiarrhythmic agents, but its occurrence is limited to the peri-infusion period, and it can be managed safely by monitoring patients closely.

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**References**


Appendix: The Italian Intravenous Dofetilide Study Group

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