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Published in:

Journal of the American College of Cardiology

DOI:

[10.1016/S0735-1097\(99\)00226-0](https://doi.org/10.1016/S0735-1097(99)00226-0)

Publication date:

1999

Document Version

Final published version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Choy, A. M. J., Darbar, D., Dell'Orto, S., & Roden, D. M. (1999). Exaggerated QT prolongation after cardioversion of atrial fibrillation. *Journal of the American College of Cardiology*, 34(2), 396-401. DOI: 10.1016/S0735-1097(99)00226-0

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Exaggerated QT Prolongation After Cardioversion of Atrial Fibrillation

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- OBJECTIVES** The purpose of this study was to test the hypothesis that the extent of drug-induced QT prolongation by dofetilide is greater in sinus rhythm (SR) after cardioversion compared with during atrial fibrillation (AF).
- BACKGROUND** Anecdotes suggest that when action potential-prolonging antiarrhythmic drugs are used for AF, excessive QT prolongation and torsades de pointes (TdP) often occur shortly after sinus rhythm is restored.
- METHODS** QT was measured in nine patients with AF who received two identical infusions of dofetilide: 1) before elective direct current cardioversion and 2) within 24 h of restoration of SR.
- RESULTS** During AF, dofetilide did not prolong QT (baseline: 368 ± 48 ms vs. drug: 391 ± 60 , $p = \text{NS}$) whereas during SR, QT was prolonged from 405 ± 55 to 470 ± 67 ms ($p < 0.01$). In four patients (group I), the SR dofetilide infusion was terminated early because QT prolonged to >500 ms, and one patient developed asymptomatic nonsustained TdP. The remaining five patients (group II) received the entire dose during SR. Although ΔQT was greater in group I during SR (91 ± 22 vs. 45 ± 25 ms, $p < 0.05$), plasma dofetilide concentrations during SR were similar in the two groups (2.72 ± 0.96 vs. 2.77 ± 0.25 ng/ml), and in AF (2.76 ± 1.22 ng/ml). ΔQT in SR correlated inversely with baseline SR heart rate ($r = -0.69$, $p < 0.05$), and QT dispersion developing during the infusion ($r = 0.79$, $p < 0.01$).
- CONCLUSIONS** Shortly after restoration of SR, there was increased sensitivity to QT prolongation by this I_{Kr} -specific blocker. Slower heart rates after cardioversion and QT dispersion during treatment appear to be important predictors of this response. (J Am Coll Cardiol 1999;34:396-401) © 1999 by the American College of Cardiology
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Although drugs that prolong the QT interval can suppress arrhythmias, their potential to cause excessive QT prolongation, leading to the development of the polymorphic ventricular tachycardia torsades de pointes (TdP), is well recognized. When such agents are used to treat atrial fibrillation (AF) or flutter, clinical anecdotes suggest that

TdP occurs more frequently after conversion to sinus rhythm (SR) rather than during the atrial arrhythmia (1-4).

The purpose of this study was to prospectively test the hypothesis that an action potential-prolonging antiarrhythmic drug would exert a greater effect on cardiac repolarization (as measured by the QT interval) shortly after restoration to SR compared with during AF or atrial flutter. Most QT-prolonging drugs (quinidine, sotalol, disopyramide, amiodarone) exert ancillary pharmacologic effects (e.g., autonomic blockade) that might confound testing of this hypothesis. Therefore, in this study, we used dofetilide, which exerts repolarization-prolonging effects due to block of the rapidly activating, outward potassium current, I_{Kr} (5,6). Dofetilide, which is devoid of significant other pharmacologic effects, prolongs refractoriness in most tissues, and its sole electrocardiographic (ECG) effect is QT prolongation (7,8). The efficacy of dofetilide in the acute cardioversion of AF or atrial flutter has been previously reported (9). The goal of the present study was to use the drug to determine whether the extent of QT interval change depended on whether the rhythm was AF or sinus and, if

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During the conduct of this work, Dr. Choy was a recipient of an American Heart Association Fellowship-in-Training Award from the American Heart Association (Dallas, Texas) and the Derrick Dunlop Fellowship from the British Heart Foundation (London, U.K.). Dr. Roden is the holder of the William Stokes Chair in Experimental Therapeutics, a gift from the Daiichi Corporation. This study was supported in part by grants (GM07569 and RR00095) from the United States Public Health Service (Bethesda, Maryland), and from Pfizer Central Research (Groton, Connecticut). This study was conceived, and approval obtained from funding agencies and the Institutional Review Board, by Dr. Roden. Drs. Choy, Darbar and Dell'Orto were responsible for identification and recruitment of study participants, and actual conduct of the studies described, under the supervision of Dr. Roden. The manuscript was prepared by Drs. Roden and Choy.

Manuscript received July 28, 1998; revised manuscript received March 19, 1999, accepted April 23, 1999.

Abbreviations and Acronyms

AF	=	atrial fibrillation
ANP	=	atrial natriuretic peptide
ECG	=	electrocardiographic/electrocardiogram
QTd	=	QT dispersion
SR	=	sinus rhythm
TdP	=	torsades de pointes

there was a difference, what the underlying mechanism(s) might be.

METHODS

Participants. Twelve patients (nine male, three female) with AF (n = 9) or atrial flutter (n = 3) scheduled for elective direct current cardioversion were recruited consecutively from the Arrhythmia Service at Vanderbilt University Medical Center. All participants had a history of hypertension. Coronary artery disease was present in four, and diabetes in four. All participants provided written informed consent, and the study was approved by the Vanderbilt University Institutional Review Board.

Patients were enrolled into the study if they met the following eligibility criteria: AF or atrial flutter of more than 24 h but less than 12 months duration in whom elective direct current cardioversion was planned; therapeutic anticoagulation for at least two weeks before study entry, unless the arrhythmia was atrial flutter; normal biochemical and hematologic parameters and no symptoms of unstable angina or decompensated congestive heart failure. Women of childbearing potential and patients with previous adverse reactions to QT-prolonging drugs were excluded. All patients had a full medical history, physical examination, urinalysis, 12-lead ECG, biochemistry and hematologic examination before entry into the study. Patients were admitted to the Clinical Research Center at Vanderbilt University for continuous monitoring of cardiac rhythm while all antiarrhythmic therapy was stopped 48 h before the study. Because dietary sodium can influence atrial natriuretic peptide (ANP) release (10) and QT interval (11), a sodium-controlled diet was given to all subjects during this period and for the duration of the study. Oral digoxin was used for rate control if required, and other atrioventricular nodal blocking agents were withheld for >24 h before entry to the study.

Protocol. Each patient was scheduled to receive two infusions of dofetilide, each after a 6- to 8-h overnight fast: the first infusion during AF and the second during SR, within 24 h of cardioversion. If the AF infusion did not restore SR, scheduled cardioversion was performed the same day. On the morning of each study day, an intravenous line was inserted in each arm of the supine patient, one for drug administration and the other for blood sampling of plasma

drug concentrations; serum potassium and magnesium and plasma ANP and norepinephrine.

Intravenous dofetilide (Pfizer, Groton, Connecticut) was administered in a three-stage infusion over 100 min. The first six patients received 5.25 $\mu\text{g}/\text{kg}$ over 100 min: 0.198 $\mu\text{g}/\text{kg}/\text{min}$ for 5 min, 0.065 $\mu\text{g}/\text{kg}/\text{min}$ for 35 minutes, then 0.033 $\mu\text{g}/\text{kg}/\text{min}$ for 60 min. In the next six patients, the dose was 8 $\mu\text{g}/\text{kg}$ over 100 min, and the rates of the three infusions were 0.3, 0.1 and 0.05 $\mu\text{g}/\text{kg}/\text{min}$, with the same infusion durations. Each patient received the same infusions on both study days. Infusion rates were based on pharmacokinetic data describing the disposition kinetics of dofetilide boluses in human participants and were designed as previously described (8,12) to rapidly achieve and then maintain stable plasma concentrations in the 1.5- to 2.5-ng/ml range. Electrocardiograms were recorded at baseline and every 10 min during the infusion.

Blood sampling and assays. Venous samples were collected at baseline (5 min before dofetilide infusion) for serum potassium and magnesium, plasma norepinephrine and plasma ANP. Serum potassium and magnesium and plasma norepinephrine were analyzed by Roche Biomedical Laboratories (Newark, New Jersey) and LabCorp (Burlington, North Carolina), respectively. Samples for measurement of plasma dofetilide were collected at baseline and at specified time points during infusion, and were analyzed by high pressure liquid chromatography (Pfizer Central Research, Groton, Connecticut). Plasma ANP was measured by radioimmunoassay as previously described (13) (AD Struthers, University of Dundee Medical School, U.K.).

QT analysis. All ECGs were recorded with the patient resting supine, using an analog system at 25-mm/s paper speed, 10-mm/mV gain and 40-Hz low pass filter setting. The ECGs were analyzed using a semiautomated digitizing program by a single observer. Intraobserver variability was examined by randomly selecting 50 ECGs to be reanalyzed by the same observer; the coefficient of variation was 4% to 6%. To examine for interobserver variability, independent duplicate determinations were made by a second blinded observer; the coefficient of variation between patients was 8% to 10%. The QT interval was measured in a precordial lead (V2 or V3) from the onset of the QRS to the end of the T wave, as extrapolated from the maximum negative slope of the T wave to the baseline. During both AF and SR, in the presence of a U wave greater than 25% of the amplitude of the T wave, the QTU interval was similarly measured. In each patient, the same precordial lead was measured in AF and SR. The mean of five consecutive QT intervals measured in AF and SR was used. The limb leads were not used in this analysis because when the underlying rhythm was AF, it was not possible to distinguish low amplitude U waves from coarse fibrillatory activity in the limb leads. Similarly, since U waves tend to occur in some leads and not others, ΔQT (the change in QT) was not measured in a single lead, but rather QT in all precordial leads was

measured, and the mean of the differences in each lead was used to calculate ΔQT .

Dispersion of the QT interval (QTd) during SR was calculated as the difference between maximal and minimal QT intervals occurring in any of the 12 leads, and adjusted using the formula $QTd = (\text{maximum QT} - \text{minimum QT})/\sqrt{\text{number of leads measured}}$ (14). For the reasons outlined above, QTd was not measurable when the underlying rhythm was AF. Mean heart rate was calculated in both AF and SR from five consecutive complexes.

Analysis of the difference in QT and heart rate before and after infusion during AF and during SR was performed by using analysis of variance with repeated measures. Differences in ΔQT in all patients and by subgroup were tested using the paired and unpaired Student *t* test where appropriate. All tests were two tailed, and a *p* value of <0.05 was considered to be significant. All data are presented as mean \pm 1 SD.

RESULTS

Twelve patients participated in the study, three women and nine men. One patient cardioverted from atrial flutter to SR after 60 min of infusion. The remaining 11 patients received the entire 100-min infusion of dofetilide during AF without cardioversion to SR. After dofetilide infusion, three patients did not electrically cardiovert and were withdrawn from the study.

All of the remaining nine patients received the second infusion during SR. In four patients, the infusion was terminated early (2 after 20 min, 1 after 30 min and 1 after 60 min) because of QT prolongation to more than 500 ms in at least two ECG leads. One of these participants developed asymptomatic, recurrent runs of TdP self-terminating after up to 17 beats and lasting over 10 min after stopping the infusion. The remaining patients (group II) completed the second infusion. The mean time from cardioversion to SR infusion was 19 ± 2 h. There was no relationship between the time between cardioversion and the outcome of the SR study.

Three patients in group I and two patients in group II received the higher dose of dofetilide. There were no significant differences in the clinical or demographic characteristics between group I and group II, and the durations of AF and previous treatments were similar. No other adverse effects and no significant changes occurred in systolic and diastolic blood pressure during the infusion in both AF and SR.

QT intervals. Data are presented in Figure 1 for the first 100 min of the infusion during both AF and SR. In group I, data for the first 20 min are shown, as this was the time point that all four patients reached in SR. Baseline QT in AF and SR was not significantly different (AF vs. SR: 386 ± 49 and 420 ± 39 ms, *p* = NS). There was minor QT prolongation with dofetilide during AF, but the change was not significant (baseline and 100 min infusion: 386 ± 49

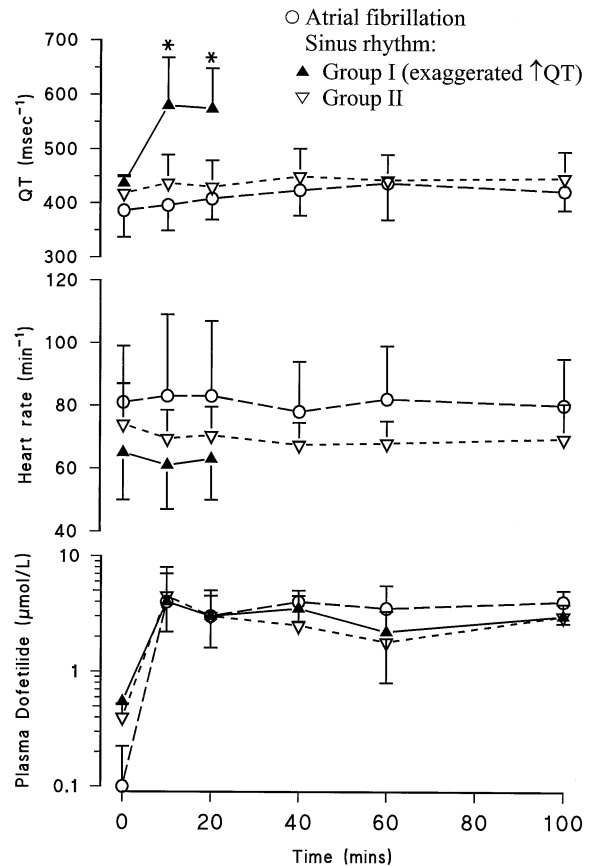


Figure 1. Precordial QT (top), heart rate (middle) and plasma dofetilide (bottom) during dofetilide infusion in atrial fibrillation or flutter and after cardioversion to normal sinus rhythm (SR). Group I patients are those in whom the SR infusion was stopped prematurely for excess QT prolongation. Group II patients received the whole dofetilide infusion in SR. **p* < 0.01 vs baseline.

and 420 ± 60 ms, *p* = NS). The increment in QT produced by dofetilide infusion during SR in group II was similar to that seen in AF (412 ± 52 ms at baseline vs. 459 ± 62 ms at end-infusion, *p* = NS). In contrast, in group I, dofetilide administered during SR increased QT from 432 ± 15 to 580 ± 63 ms after 20 min infusion (*p* < 0.01 baseline vs. 20 min).

Other differences—AF versus SR. Despite the significantly different QT responses during AF and SR, plasma dofetilide concentrations were comparable on the two study days (Fig. 1). Baseline heart rate in AF (81 ± 17 beats/min) was higher than in SR (68 ± 15 bpm), although this was not statistically significant. Dofetilide infusion did not significantly alter heart rate in either AF or SR (Fig. 1).

There was no significant difference in mean serum potassium before infusion during AF and SR (4.3 ± 0.1 mEq/liter and 4.1 ± 0.1 mEq/liter, respectively). Mean serum magnesium was normal in all patients before infusion in AF and SR. Atrial natriuretic peptide during AF was elevated, 167 ± 89 pg/ml (normal range 7.3 to 32.4 pg/ml)

and fell after cardioversion to 71 ± 46 pg/ml ($p = 0.04$). Plasma norepinephrine fell after cardioversion from 127 ± 47 pg/ml to 91 ± 59 pg/ml ($p = \text{NS}$).

Differences between groups I and II. Whereas there was no significant difference in QT at baseline (431 ± 14 vs. 411 ± 52) between the two groups, QT at 10 and 20 min of the SR infusion was significantly longer in group I than in group II (10 min: 585 ± 80 vs. 443 ± 71 ms; 20 min: 580 ± 63 vs. 432 ± 27 ms both, $p < 0.05$). Thus, ΔQT was significantly greater in group I compared with group II (91 ± 22 vs. 45 ± 25 ms, $p < 0.05$). Group I tended to have slower heart rates compared with group II (62 ± 17 vs. 74 ± 13 bpm), although this difference was not statistically significant. There was a significant correlation between baseline heart rate and ΔQT ($r = -0.69$, $p < 0.05$).

QT dispersion. QT dispersion during SR increased with dofetilide infusion from 30 ± 6 ms at baseline to 42 ± 15 ms at 20 min, but this change was not statistically significant. However, QTd measured at 20 min of infusion correlated significantly with ΔQT ($r = 0.79$, $p = 0.01$). The correlation was similar when QTd was calculated without correction for the number of leads measurable ($r = 0.76$, $p = 0.019$). Again, QTd tended to be greater in group I patients compared with group II patients (49 ± 15 vs. 38 ± 8 ms, $p = \text{NS}$).

DISCUSSION

The major finding of this study is that there is increased sensitivity to the QT-prolonging effects of dofetilide in some patients after restoration of SR compared with during AF. This exaggerated QT response was not seen during AF at comparable plasma drug concentrations in the same patients. Slower heart rates postcardioversion and increasing QT dispersion during dofetilide infusion were associated with exaggerated QT response, but no other clinical or demographic characteristic identifying patients at risk was identified. Serum potassium, which we have previously shown to be an important modulator of drug-induced QT prolongation (15), was not significantly different during AF and SR, or between the two groups during SR, and therefore does not appear to modulate this differential QT response to dofetilide.

Only one of the 12 patients in this study was cardioverted by intravenous dofetilide, whereas previous studies report conversion to sinus rhythm by intravenous dofetilide in 15% to 58% (9,16,17) of patients with AF and 54% to 83% (9,17) of those with atrial flutter. It is likely that the rate of infusion accounts for this difference, as animal data indicate that the rate of infusion is a crucial determinant of the extent to which pharmacologic effects are observed with an I_{Kr} blocker (18). The total dose of dofetilide used in this study was comparable to those in previous studies, but the rate of infusion was lower and was specifically chosen to study the effects of dofetilide on QT prolongation in the

two rhythms, rather than to achieve pharmacologic cardioversion.

The QT intervals in this study are presented uncorrected for heart rate. The relationship of QT to heart rate in AF appears to be different from that in SR (19) and correction by Bazett's formula (20) appears to undercorrect the QT. In addition, correction of the QT interval by Bazett's formula would have been inappropriate at the very slow or fast heart rates seen in some of our patients (21). However, it has been reported that under conditions of rest versus exercise, the relationship of the QT interval to heart rate is less strongly correlated, and QT interval is relatively unchanged with regard to heart rate (22).

Mechanism of increased QT sensitivity. The finding of a correlation between heart rate and the extent of change in QT may be a manifestation of the property of reverse use-dependence displayed by many action potential-prolonging antiarrhythmics (23). However, this characteristic is not likely to explain the near-total lack of QT change in AF (or in group II), in the face of a striking increase—at marginally slower heart rates—in group I. Moreover, some in vitro and clinical studies have suggested that over this range of heart rates, dofetilide does not exert prominent reverse use-dependence (24,25).

Although baseline bradycardia identifies patients at risk for drug-induced QT prolongation in this and other (26) studies, we do not believe that the small differences in baseline heart rates are sufficient to completely explain the striking QT prolongation we observe in group I. We therefore suspect that other, as yet unidentified mechanisms conferred increased risk in this group. One possibility is an altered neurohormonal milieu, such as changing sympathetic nervous activity (27,28) or ANP levels (29); this could modulate a change in drug sensitivity by altering the magnitude of one or more of the multiple currents that control repolarization (30–32). Another possibility is that some of these patients had subclinical mutations in the genes encoding repolarizing channels, as has previously been reported (33); this could then reduce total “repolarization reserve” (34), with QT prolongation becoming exaggerated upon exposure to a blocking drug such as dofetilide.

Study limitations. All the patients in this study had AF associated with long-standing hypertension, and other cardiovascular disease was present in most. It remains undetermined if increased sensitivity to dofetilide or other drugs is similarly seen after restoration of SR from lone AF or AF associated with noncardiovascular disease. The small size of this study may also represent a limitation, particularly in interpreting ANP and norepinephrine data. We considered studying larger numbers, but the development of TdP in one patient and analysis of available QT data convinced us that our central hypothesis had been tested. Further studies will be required to more fully elucidate the suggestions from our data of a role for ANP, norepinephrine or genetic factors in mediating the exaggerated QT prolongation seen

in group I during SR. The Food and Drug Administration's Cardiorenal Advisory panel recently recommended approval for the marketing of oral dofetilide for maintenance of SR after conversion of AF. The major adverse effect in the summary data presented was TdP. The incidence in patients with supraventricular arrhythmias was low, 0.8% (11/1,346), after maneuvers were implemented to reduce the risk, including screening patients for excessive QT prolongation and hospitalizing patients during initiation of therapy. Whether other markers implicated here might help further reduce this risk, or allow out patient drug initiation in some subsets, will require further study.

The correct method to measure QT interval, especially in the presence of a U wave, is not established. When the underlying rhythm was AF, we could not distinguish U waves from fibrillatory activity, and so we used measurement of QT only. When an obvious QTU complex developed during SR, we included the U wave in determining QT and in the calculation of QT dispersion. Because a goal of this study was to evaluate susceptibility to TdP, and because large U waves are common with the development of TdP (35), we feel this approach is justified here.

Clinical implications. We did not study participants again days or weeks after SR was restored, so we have no data as to whether the susceptibility identified here is transient or remains as long as SR remains. The clinical anecdotes that in part prompted this study suggest the susceptibility is transient. In addition, it has been reported that normal volunteers receiving sotalol (like dofetilide, an I_{Kr} blocker [36]) display greater QT prolongation with initial doses that with chronic therapy, achieving the same plasma concentrations (37). The mechanism(s) underlying this effect are unknown, but a similar phenomenon could contribute to the susceptibility we observed here.

From a practical point of view, the present data further reinforce the concept that patients receiving QT-prolonging antiarrhythmics for maintenance of SR should be closely evaluated in the immediate postcardioversion period to detect excessive QT prolongation. Such monitoring, in our view, should include assessment, preferably in multiple leads, by individuals sensitized to issues of QT lability and of postpause QTU duration and morphology. Our data indicate that this sensitivity is present for at least 24 h, although future studies would be required to determine whether monitoring the QT for a shorter period of time after cardioversion might be sufficient to detect patients displaying this exaggerated response. Our data also indicate that QT dispersion in SR may be a marker of undesirable QT prolongation.

New class III antiarrhythmic drugs, many of which include an important component of I_{Kr} block (38), appear to have potential in the treatment of acute and chronic atrial arrhythmias. The main disadvantage with these otherwise well tolerated antiarrhythmic agents is their potential to cause excessive QT prolongation and development of TdP.

Our data suggest that the QT response to one of these drugs, dofetilide, during AF does not predict the response after restoration to SR, and that exaggerated QT responses may occur in predisposed individuals. Monitoring of the QT interval in all patients after restoration of SR and dose adjustment may be prudent, particularly in the presence of bradycardia and increasing QT dispersion during treatment.

Acknowledgments

Physicians on the Vanderbilt Arrhythmia Service supported the study by referring patients. Kris Norris, RN assisted with the infusions.

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