Chemical Cardioversion of Atrial Fibrillation or Flutter With Ibutilide in Patients Receiving Amiodarone Therapy

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Background—Ibutilide is a class III drug that is used for the cardioversion of atrial arrhythmias, but it can cause torsade de pointes. Amiodarone also prolongs the QT interval but rarely causes torsade de pointes. There are no studies in which the concomitant use of the 2 agents was examined. The purpose of the present study was to assess the efficacy and safety of cardioversion with combination therapy in patients with atrial fibrillation or flutter.

Methods and Results—The study included 70 patients who were treated with long-term oral amiodarone and were referred for elective cardioversion of atrial fibrillation (57 of 70, 81%) or flutter (13 of 70, 19%). Patients were taking amiodarone (153±259 days, mean±SD) and were administered 2 mg intravenous ibutilide. Left ventricular ejection fraction was measured with echocardiography. The QT intervals were measured on 12-lead ECG. Fifty-five patients (79%) had structural heart disease. Patients were in arrhythmia for 196±508 days before cardioversion, with a left ventricular ejection fraction of 50±11%. In patients with atrial fibrillation, 22 (39%) of 57 and 7 (54%) of 13 patients with flutter converted within 30 minutes of infusion. Thirty-nine patients who did not convert after ibutilide were treated with electrical cardioversion, and 35 (90%) of 39 patients were successfully converted. The QT intervals were further prolonged after ibutilide for the group from 371±61 to 479±92 ms (P<0.001). There was 1 episode of nonsustained torsade de pointes (1 of 70, 1.4%) after ibutilide.

Conclusions—The use of ibutilide converted 54% of patients with atrial flutter and 39% of patients with atrial fibrillation who were treated with long-term amiodarone. Despite QT-interval prolongation after ibutilide, only 1 episode of torsade de pointes occurred. Our observations suggest that combination therapy may be a useful cardioversion method for chronic atrial fibrillation or flutter. (Circulation. 2001;103:253-257.)

Key Words: ibutilide ■ amiodarone ■ torsade de pointes ■ cardioversion ■ atrial flutter ■ fibrillation ■ arrhythmia

Ibutilide fumarate is a new type of class III antiarrhythmic drug that is used for the acute cardioversion of atrial fibrillation and flutter. It prolongs action potential duration (APD) and refractory periods of normal ventricular and atrial tissue by enhancing the slow inward sodium current and blocking the rapid component of the delayed rectifier potassium current.1–5 Both actions account for its marked prolongation of the QT interval and associated risk for torsade de pointes.6–11 No detailed data are currently available on the concomitant use of other antiarrhythmic agents with ibutilide, particularly agents that prolong the QT interval.

Amiodarone is a very effective antiarrhythmic drug with a complex electrophysiological profile that shares characteristics of all 4 antiarrhythmic classes.12,13 It markedly prolongs the ventricular action potential and increases the QT-interval duration during long-term drug administration.13,14 However, the incidence of torsade de pointes due to amiodarone is low.15,16 Long-term amiodarone therapy is commonly used for the maintenance of sinus rhythm for patients with paroxysmal atrial fibrillation. With the recurrence of atrial fibrillation, the clinician is faced with a choice of electrical versus chemical cardioversion. There is only 1 limited study to date that has examined the use of ibutilide in patients already taking amiodarone.17 Such studies are of importance because the long half-life of amiodarone makes it impractical to discontinue the drug before the use of ibutilide.

Thus, the purpose of the present study was to assess the efficacy and safety of ibutilide administered to patients with atrial fibrillation or flutter who received long-term amiodarone therapy.

Methods

Patient Population

The study population included 70 patients who were treated with long-term amiodarone and referred for elective cardioversion of...
atrial fibrillation (57 of 70, 81%) or atrial flutter (13 of 70, 19%) at our institution. In our pilot, retrospective study of 10 patients, combination therapy was found to be safe and associated with a similar conversion rate. The subsequent 60 patients were studied prospectively. Because there was no difference in efficacy between the groups, they were combined into 1 group for analysis. Four patients declined enrollment because of the experimental nature of the protocol. Patients were consecutively enrolled if they were >18 years of age, received a loading dose of amiodarone, and were maintained on an oral dose. None were taking additional antiarrhythmic medications, and all were hemodynamically stable during the atrial arrhythmia. If atrial fibrillation persisted for >48 hours, antiarrhythmia therapy was initiated before attempted cardioversion. Patients were not specifically excluded from the study if they if they had prolonged QT intervals on the 12-lead ECG before ibutilide therapy. None were excluded because of congestive heart failure, prior myocardial infarction or depressed left ventricular ejection fraction (LVEF), or a previous history of ventricular arrhythmias. All patients had normal serum electrolyte values before the study, including potassium (≥4 mEq/L) and magnesium (≥1.6 mEq/L) levels. Concurrent control of the ventricular rate with calcium channel blockers, β-adrenergic–blocking agents, or digoxin was permitted. The study was approved by the Committee on Human Research at the University of California, San Francisco.

Pharmacological Therapy
One milligram of ibutilide (Pharmacia & Upjohn, Inc) was infused intravenously through a peripheral vein over 10 minutes, followed by a 10-minute observation period and the infusion of an additional 1 mg over 10 minutes if the rhythm did not revert to sinus. No infusion was stopped because of arrhythmic events, hemodynamic compromise, or QT-interval prolongation. Patients underwent continuous ECG monitoring in a cardiac electrophysiology laboratory or intensive care unit. Monitoring was continued during and for 4 hours after the infusion. No patient received prophylactic intravenous magnesium before ibutilide treatment. All patients received either oral or intravenous loading of amiodarone (Cordarone; Wyeth-Ayerst, Inc), followed by ≥4 days of oral amiodarone. For the group as a whole, the duration of amiodarone therapy was 153±259 days (mean±SD; median 64 days). Three patients received 4 g amiodarone IV before oral dosing. If we exclude the 3 patients who received the intravenous load, the mean dosage of amiodarone was 316 mg/d.

Echocardiographic Evaluation
The enrolled patients underwent transthoracic echocardiography within 4 months of the study. Both the longitudinal left atrial (LA) size and the LVEF were quantified with the use of conventional techniques.

ECG Measurements
ECGs were recorded at a paper speed of 25 (20 patients) or 50 (50 patients) mm/s. Ten consecutive intervals were manually measured before and within 4 hours after ibutilide infusion, with premature ventricular complexes excluded. Only leads in which a clear T wave was present without a U wave were analyzed. The lead with the largest QT interval was measured, and the same lead was used for each patient. The RR intervals were measured as the interval between peak R-wave deflections. The QT intervals were measured as the interval between the initial QRS deflection and the end of the T wave. The corrected QT intervals (QTc) were calculated with the use of Bazett’s formula as QT interval/(RR interval)1/2. The intraobserver reliability was measured on separate days by 2 independent blinded observers and was 94% for RR intervals and 91% for QTc. The interobserver reliability was 95% for RR and 91% for QTc.

Statistical Analysis
The clinical characteristics of the patient groups (“converters” and “nonconverters”) were analyzed by the unpaired Student’s t test for interval data, and χ2 analysis was used for categorical data. Continuous variables were expressed as mean±SD. Logarithmic transformations were used for the interval data, and Fisher’s exact test was used for the categorical data when necessary. Logistic regression analysis was used to determine what baseline variables might predict conversion to sinus rhythm. Differences were considered statistically significant at P<0.05. The reliability coefficients were calculated with Cronbach’s theory of generalizability.

Results
Clinical Characteristics of Study Patients
Seventy patients (43 men, mean±SD age for all subjects 68±11 years, median age 70 years) were entered into the study. Five patients were treated with ibutilide during invasive electrophysiology study for radiofrequency ablation (4 for atrial flutter, 1 for typical atrioventricular node reentrant tachycardia). These patients developed intractable atrial fibrillation during the electrophysiology study and were administered ibutilide for conversion to sinus rhythm. The remaining 65 episodes were treated with ibutilide during elective cardioversion of atrial fibrillation or flutter. Nineteen patients also received calcium channel blockers, 24 patients received digoxin, and 15 received β-blocker agents.

Fifty-seven (81%) of 70 patients had atrial fibrillation, and the remaining 13 patients (19%) had atrial flutter. Fifty-five patients (79%) had structural heart disease, including hypertension (n=44), documented coronary artery disease (n=18), valvular disease (n=9), and previous ventricular tachycardia or fibrillation (n=4). One patient had end-stage renal disease and was dialysis dependent, and 4 patients had had a large myocardial infarction within the 2 weeks before ibutilide therapy. Five (7%) of 70 episodes of atrial fibrillation or flutter lasted <72 hours, whereas the remaining 65 episodes (93%) lasted ≥72 hours (mean±SD 196±508 days, median 66 days). At the time of cardioversion, 19 patients (27%) were in New York Heart Association class I, 35 patients (50%) were class II, 13 patients (19%) were in class III, and 3 patients (4%) were in class IV.

The LVEF on echocardiography for the entire study group was 50±11% (mean±SD; median 55%). The LA size for the group was 4.8±0.4 cm (mean±SD; median 4.8 cm).

Conversion Rates
Twenty-two (39%) of 57 patients with atrial fibrillation converted to sinus rhythm within 30 minutes of the ibutilide infusion, as did 7 (54%) of 13 patients with atrial flutter episodes. For 41 (59%) of 70 patients, ibutilide cardioversion failed. Of these 41 patients with initial ibutilide–treatment failures, subsequent electrical cardioversion failed for 4 patients, 35 patients converted with shock, and electrical cardioversion was not performed in the remaining 2 patients. The success rate for subsequent electrical conversion was 90% (35 of 39 patients) with a mean of 1.2 shocks (225 J). In the 2 patients for whom both ibutilide therapy and subsequent electrical cardioversion failed, external shock at 360 J for 2 or 3 attempts was unsuccessful. For 2 patients with atrial fibrillation, electrical cardioversion at 360 J first failed, but then the patients converted to sinus rhythm after receiving ibutilide therapy and 1 repeat shock of 360 J.
The only clinical variable on univariate analysis that predicted successful cardioversion with ibutilide was duration of the arrhythmia ($P<0.05$). Patients with shorter-duration arrhythmias were more likely to convert with ibutilide $(219\pm616$ versus $163\pm299$ days for nonconverters versus converters). For example, 12 patients (11 of 12 patients had atrial fibrillation) had an arrhythmia duration of $\leq7$ days before ibutilide infusion. Of these, 9 (75%) of 12 patients converted to sinus rhythm with ibutilide. Logistic regression analysis showed that the only clinical variable that predicted successful ibutilide conversion was also arrhythmia duration ($P<0.05$). There was a trend toward patients in NYHA class I or II (compared with those with class III or IV symptoms) being more likely to have successful conversion, but this finding was not statistically significant ($P=0.055$).

Neither LA size $(4.8\pm0.4$ versus $4.7\pm0.4$ cm for nonconverters versus converters; NS) nor LVEF $(49\pm11\%$ versus $52\pm11\%$ for nonconverters versus converters; NS) predicted successful cardioversion with ibutilide by univariate analysis. The following clinical variables also failed to predict conversion with ibutilide: age $(66\pm12$ versus $72\pm9$ years), sex $(61\%$ versus $62\%$ males), or duration of amiodarone therapy $(154\pm240$ versus $151\pm288$ days, all mean$\pm$SD and for nonconverters versus converters; NS).

**ECG Effects of Ibutilide**

The baseline QT interval was prolonged in most patients because they were treated with amiodarone. The QT intervals were markedly prolonged after ibutilide treatment for converters versus nonconverters. The QT interval increased from $371\pm61$ to $479\pm92$ ms after ibutilide for the entire group ($P<0.001$). The QT intervals in the nonconverter group $n=41$ increased from $376\pm59$ to $465\pm91$ ms after ibutilide ($P<0.01$). The mean heart rate decreased from $95\pm34$ to $69\pm23$ bpm for those who converted with ibutilide ($P<0.01$). There was a decrease in the mean heart rate in nonconverters after ibutilide (from $89\pm28$ to $81\pm26$ bpm; $P>0.05$), but this was not statistically significant.

**Adverse Effects**

There was 1 episode of nonsustained torsade de pointes in a 51-year-old woman during the first 10 minutes of the ibutilide infusion. The patient had pulmonary hypertension and severe mitral regurgitation with NYHA class III symptoms and was undergoing evaluation for mitral valve replacement. Her serum electrolyte values were all normal, including potassium and magnesium levels. The patient had atrial fibrillation for 6 weeks and had been treated with amiodarone for 3 weeks before ibutilide infusion. The QT interval increased from $398\pm42$ to $485\pm34$ ms ($P<0.01$) and the heart rate increased from $83\pm14$ to $86\pm24$ bpm with ibutilide. Electrical cardioversion was attempted the next day but was unsuccessful. The patient subsequently underwent uneventful mitral valve replacement.

There were no instances of sustained torsade de pointes, defined as polymorphic ventricular tachycardia that lasted $>30$ seconds or required shock to terminate the arrhythmia.$^{6–11}$ New or worsening symptoms of congestive heart failure were not observed after ibutilide therapy. There were no episodes of stroke, pulmonary or systemic emboli, or death reported in the 48 hours after treatment as an adverse event.

**Discussion**

The present study represents the first detailed report of the concomitant use of ibutilide in patients receiving long-term amiodarone therapy for the treatment of atrial fibrillation and flutter. There was only 1 episode of nonsustained torsade de pointes.

**Conversion Efficacy**

Conversion rates for atrial arrhythmias with combination therapy were consistent with those reported for ibutilide alone in previous large-scale, randomized clinical trials.$^{6–11}$ We found that 54% of patients with atrial flutter and 39% of patients with atrial fibrillation reverted to sinus rhythm within 30 minutes of the ibutilide infusion, similar to the rates reported for ibutilide alone.$^{6–11}$ We did find that patients with shorter-duration arrhythmias (ie, 75% of the patients with arrhythmias of $\leq7$ days in our study) were more likely to convert with ibutilide, which is in keeping with previous reports. In addition, we found that the subsequent administration of electrical DC cardioversion was safe and effective in 35 (90%) of 39 patients who initially failed to convert with ibutilide.

**Proarrhythmic Potential**

Torsade de pointes is the most serious proarrhythmic side effect of class III agents. Early afterdepolarizations (EADs) during phase 3 of the action potential that result in triggered activity appear to in part explain the genesis and maintenance of torsade de pointes.$^{24,25}$ Class IA and class III antiarrhythmic agents prolong APD and the QT interval and are associated with an increased risk of torsade de pointes. Amiodarone markedly prolongs the ventricular APD and increases the QT interval by 20%, yet the incidence of torsade de pointes with long-term use is estimated to be $<1\%.$$^{15,16}$

The low incidence of torsade de pointes with long-term amiodarone therapy may be multifactorial. Recent evidence suggests that the dispersion of repolarization is a critical factor in the maintenance of torsade de pointes.$^{12,14–16}$ The ventricular myocardium normally displays some heterogeneity of refractoriness, with the M (or middle) cells displaying the longest APD of the ventricular subtypes.$^{26,27}$ EADs originate from M cells and canine Purkinje fibers.$^{28}$ Amiodarone prolongs the APD of all ventricular canine cell subtypes but does so the least in M cells, thereby reducing the transmural dispersion of repolarization.$^{26,27}$ This finding contrasts with most class III drugs, which preferentially prolong the M-cell APD and exaggerate transmural heterogeneity. This action may in part explain why amiodarone is associated with a relatively low torsade de pointes risk. In addition, amiodarone blocks the slow inward calcium current and suppresses calcium-dependent EADs in canine Purkinje fibers induced by barium, which may contribute to the development of torsade de pointes.$^{28}$ Finally, its ability to exert $\beta$-adrenergic receptor antagonism may also help suppress triggered activity.$^{13–16}$
Ibutilide is a class III antiarrhythmic drug that is used for the cardioversion of atrial arrhythmias. The incidence of ibutilide-induced torsade de pointes is reported in up to 8.3% of patients treated for the conversion of atrial arrhythmias. Torsade de pointes in these cases is likely due to its effects on EADs and marked prolongation of ventricular repolarization.\textsuperscript{4–11} The QT interval normalizes within 2 to 4 hours after infusion, increases in a dose-dependent fashion, and may correlate with its conversion efficacy.\textsuperscript{4–11}

In our study, the incidence of nonsustained torsade de pointes was 1.4% (1 of 70 patients; 95% CI 0.1% to 8.8%), and no patients had sustained torsade de pointes. This result compares favorably with that from other ibutilide reports. In a study of 180 patients who received ibutilide for cardioversion, 8.3% had torsade de pointes, including 3 patients with sustained arrhythmia who required external shock.\textsuperscript{10} Other studies have found the incidence of significant ventricular arrhythmias to be 4%, 3.4%, 3.6%, and 8.3% and that of sustained torsade de pointes to be 0.0%, 1.7%, 2.5%, and 0.9%, respectively, after ibutilide infusion.\textsuperscript{6–8,11} The event rate of torsade de pointes in our study for combination therapy is not significantly worse than that described with ibutilide therapy alone.

\textbf{Comparison With Other Studies}

It should be emphasized that the present study included patients who would have been excluded from prior ibutilide studies. We did not stop the ibutilide infusion because of QT\textsubscript{C} prolongation, development of bradycardia, or other potentially proarrhythmic events, which is in contrast to previous published reports.\textsuperscript{6–8,10} Despite these high-risk characteristics, we encountered only 1 episode of nonsustained torsade de pointes.

The study conversion rate to sinus rhythm with ibutilide compares favorably with those of other studies. Ibutilide was found to convert 35% to 64% of patients with atrial fibrillation and 58% to 76% of patients with atrial flutter, with a higher conversion rate for those with arrhythmias of a shorter duration.\textsuperscript{4–11} Few studies to date have looked at the conversion efficacy for ibutilide in patients with chronic arrhythmias of >4 months’ duration. Our study was biased toward the inclusion of patients with longer-duration arrhythmias (83% had their arrhythmias ≥1 week), which may underestimate the true efficacy of conversion with combination therapy in patients with shorter-duration arrhythmias.

\textbf{Study Limitations}

The study population consisted mainly of patients with a normal to only mildly depressed LVEF (50±11%), although on study enrollment, 50% of the patients were in NYHA class II and 16% were in class III or class IV. This reflects our clinical patient population treated with long-term amiodarone. Thus, our results may not be generalizable to patients with markedly depressed myocardial function. Previous reports have suggested that the presence of heart failure and cardiomyopathy are risk factors for torsade de pointes after ibutilide.\textsuperscript{4–11} Therefore, the incidence of torsade de pointes may be higher in a patient population with more severe cardiomyopathy. It is likely that our study somewhat under-estimates the true conversion rate with the 2 medications, because it was necessary to proceed (for logistical reasons) with cardioversion within 30 minutes after the ibutilide infusion.

The referring physicians determined the duration of amiodarone therapy before ibutilide infusion. Thus, a majority of patients were treated on a long-term basis (mean 153 days) with amiodarone before enrollment. Finally, this study focused only on patients treated concurrently with long-term amiodarone and ibutilide. Our results should not be extended to patients treated with other antiarrhythmic agents or treated with amiodarone for <4 days.

\textbf{Clinical Implications}

We describe the first detailed report with combination amiodarone and ibutilide therapy. The efficacy of combined therapy appears to be similar to that of previously published reports of cardioversion with ibutilide alone.\textsuperscript{7–11} There was 1 episode of nonsustained torsade de pointes. This was the only proarrhythmic event observed despite marked further prolongation of the QT interval after combination therapy. It should be emphasized that the preserved LVEF in our patient population may account for the low incidence of adverse effects in this study. Greater caution is required in the treatment of a group of patients who have depressed myocardial function with combination therapy.

The study data suggest that combination pharmacological therapy with amiodarone and ibutilide may be a useful adjunct to current cardioversion protocols for atrial fibrillation or flutter, particularly for atrial arrhythmias of shorter duration.

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