Ibutilide Added to Propafenone for the Conversion of Atrial Fibrillation and Atrial Flutter
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OBJECTIVES
We evaluated the safety and efficacy of ibutilide when added to propafenone in treating both paroxysmal and chronic atrial fibrillation (AF) and atrial flutter (AFL).

BACKGROUND
The effects of ibutilide in patients with paroxysmal or chronic AF/AFL who were pre-treated with propafenone have not been previously evaluated.

METHODS
Oral propafenone was initially given in 202 patients with AF/AFL without left ventricular dysfunction. Intravenous ibutilide was administered in 104 patients in whom propafenone failed to convert the arrhythmia. Two different propafenone dosage regimens were used according to the duration of the presenting arrhythmia: patients with paroxysmal arrhythmia (n = 48) received 600 mg loading dose, and patients with chronic arrhythmia (n = 56) were receiving 150 mg three times a day as stable-dose pre-treatment.

RESULTS
Ibutilide offered an overall conversion efficacy of 66.3% (69 of 104 patients), 70.8% for patients with paroxysmal AF/AFL and 62.5% for patients with chronic AF/AFL. Ibutilide significantly decreased the heart rate (HR) and further prolonged the QTc interval (p < 0.0001). The degree of HR reduction after ibutilide administration emerged as the sole predictor of successful arrhythmia termination (p < 0.001). After ibutilide, one patient (1%) developed two asymptomatic episodes of non-sustained torsade de pointes, and 10 patients (9.6%) manifested transient bradyarrhythmic events; however, all bradyarrhythmic effects were predictable, occurring mostly at the time of arrhythmia termination. None of 82 patients who decided to continue propafenone after successful cardioversion had immediate arrhythmia recurrence.

CONCLUSIONS
Our graded approach using propafenone and ibutilide appears to be a relatively safe and effective alternative for the treatment of paroxysmal and chronic AF/AFL to both rapidly restore sinus rhythm in nonresponders to monotherapy with propafenone and prevent immediate recurrences of the arrhythmia. (J Am Coll Cardiol 2004;44:859–63) © 2004 by the American College of Cardiology Foundation

Managing atrial fibrillation (AF) or atrial flutter (AFL) is a continuing therapeutic challenge. Antiarrhythmic drugs play a major role during attempts to promptly restore and maintain sinus rhythm (SR), by which disabling symptoms are diminished and atrial electrophysiological and structural remodeling is averted (1,2). Of the currently available agents, intravenous ibutilide fumarate is considered one of the most effective in rapidly terminating AF/AFL (3–6). However, ibutilide is not available as an oral preparation, and thus, it cannot be subsequently used as long-term therapy to prevent recurrences of arrhythmia. On the other hand, the use of oral propafenone has been proven effective in terminating AF of recent onset and in preventing arrhythmia recurrences after cardioversion, but it has shown little promise for the conversion of chronic AF (7–9). We hypothesized that the addition of ibutilide in nonresponders to monotherapy with propafenone might be a useful method to improve subsequent cardioversion rates and maintenance of SR thereafter. This study evaluated the safety and clinical efficacy of this stepped-care combination therapy in the management of both paroxysmal and chronic AF/AFL.

METHODS
Patient population. Our study population included 202 patients with AF/AFL who were treated initially with propafenone. Two groups of patients were prospectively studied; those with persistent paroxysms of arrhythmia and patients with chronic arrhythmia. Patients with paroxysmal AF/AFL (n = 146) had prolonged and non-self-terminating arrhythmia episodes of <36 h duration with a well-defined clinical history of abrupt onset of palpitations and electrocardiographic (ECG) evidence of the arrhythmia. Patients with chronic AF/AFL (n = 56) had persistent arrhythmia of <6-month duration and were under continuous oral anticoagulation therapy for at least four weeks before cardioversion (international normalized ratio, 2.5 to 3.0). Only patients with normal left ventricular (LV) function as judged by two-dimensional echocardiography were enrolled in this trial.

Ibutilide in addition to propafenone was given to 104 patients who did not convert to SR with propafenone, in 48
patients with paroxysmal arrhythmia, and in the 56 patients with chronic arrhythmia.

The following exclusion criteria were applied: symptoms or clinical signs of congestive heart failure and unstable angina; prior myocardial infarction; obstructive pulmonary disease; depressed LV ejection fraction; severe valvular dysfunction; significant hepatic, renal, or metabolic disturbances; known dysthyroidism; alcohol intake; known sick sinus syndrome; major atrioventricular and intraventricular conduction disturbances; ventricular preexcitation and history of torsade de pointes; concomitant use of other antiarrhythmic drugs or beta-adrenergic blocking agents; pacemaker dependence; and pregnancy. All patients had serum electrolyte values within normal limits before treatment. Ibutilide was not administered if propafenone prolonged the QRS or the corrected QT (QTc) interval by >25%.

**Pharmacologic therapy and ECG analysis.** Ventricular rate control in patients with paroxysmal arrhythmia was attempted, whenever necessary, with intravenous diltiazem, administered initially as a bolus of 25 mg over 15 min, followed by continuous infusion of 10 mg/h to achieve a target resting heart rate (HR) <100 beats/min. In addition, heparin was administered upon admission with a bolus of 5,000 IU followed by infusion of 1,000 IU/h, further adjusted as required to keep the activated partial thromboplastin time at twice the upper normal limit. In patients with chronic AF/AFL, the use of oral diltiazem 90 mg three times a day was allowed.

Propafenone therapy was initiated in patients with paroxysmal AF/AFL as an oral loading dose of 600 mg, and if SR was not restored after 6 h, a second single dose of 150 mg was repeated. In case of restoration of SR in the emergency department, patients were not admitted to the hospital, and possible pharmacologic therapy was left to the discretion of the treating physician. Patients with nonconverted paroxysmal AF/AFL at the end of an 8-h initial observation period proceeded to the treatment phase with ibutilide. Most patients with chronic AF/AFL were asymptomatic (41 of 56, 73%) under continuous propafenone therapy with or without diltiazem, and 7 (8%) of them had prior failed conversion attempts with quinidine, but they all sought further treatment to restore SR. Thus, all patients with chronic AF/AFL were referred for elective cardioversion after they had initially been administered oral propafenone as outpatients, receiving 150 mg three times a day for a minimum of four days before admission to the hospital. This dose of propafenone remained the same throughout hospitalization, when indicated, to assist in maintaining SR once the arrhythmia had been converted with ibutilide.

Ibutilide was administered to all patients with paroxysmal and chronic arrhythmia in the coronary care unit under continuous monitoring at the same dose of 1 mg over 10 min intravenously, and if the arrhythmia was still present after 10 min, an additional dose of 1 mg over 10 min was infused. Drug infusion was terminated in case of any change in symptoms or rhythm or any adverse event that in the opinion of the investigator was threatening patient’s safety. Patients were monitored for at least 12 h after the administration of ibutilide. Successful cardioversion was defined as termination of AF/AFL within 90 min of the start of the first ibutilide infusion. Electrical transvenous direct-current cardioversion was attempted after a 4-h observation period if AF/AFL was not converted to SR.

Serial 12-lead ECGs were obtained to evaluate QRS, QT, and QTc intervals. A 24-h Holter recording was started in all patients before the onset of ibutilide administration to determine exact conversion time, arrhythmia, and HR analysis. The three-channel Galix MA-3C Holter system (Galix Biomedical Instrumentation Inc., Miami Beach, Florida) was used, utilizing 3.0 Software. The following time periods were taken to assess the effects of the drugs on the ECG variables: for propafenone, the last 5-min period before the initiation of the first ibutilide infusion; for ibutilide, the last 5-min period before arrhythmia termination if it was converted to SR or the first 5-min interval at the end of the second ibutilide infusion if the arrhythmia was not terminated.

**Statistics.** Continuous variables are reported as mean ± SD. A value of p ≤ 0.05 was considered statistically significant. The two-sided unpaired Student t test was used to compare normally distributed continuous data between conversion and non-conversion groups. Normality was tested by the Kolmogorov-Smirnov statistic at the p = 0.1 level. Changes in continuous ECG variables within groups before and after ibutilide treatment were evaluated using the paired t test. Categorical data were compared with Fisher exact test. Multiple logistic regression models with a forward stepwise approach were used to identify significant predictors of conversion. Statistical analyses were conducted with SPSS-PC, Version 10.0 (SPSS Inc., Chicago, Illinois).

**RESULTS**

**Conversion to SR.** Oral loading propafenone restored SR in 98 of 146 patients (67%) with paroxysmal arrhythmia. Ibutilide was evaluated in 104 hospitalized patients with AF/AFL: in the remaining 48 non-converters with paroxysmal arrhythmia and in the 56 patients with chronic arrhythmia receiving pre-treatment with propafenone (Table 1). Overall, the co-administration of the two agents showed a conversion efficacy of 66.3% (69 of 104 patients),
65.6% for AF (63 of 96 patients), and 75% (6 of 8 patients) for AFL. The success rates were 70.8% (34 of 48 patients) for patients with paroxysmal arrhythmia and 62.5% (35 of 56 patients) for those with chronic arrhythmia (Table 2).

**Addition of ibutilide.** Among the entire study population, compared with the effects of propafenone (paired t test), ibutilide significantly decreased the mean HR (from 81.1 ± 14.3 to 74.6 ± 14.5; p < 0.0001), increased the QT (from 382.3 ± 43.9 to 459.6 ± 53.7; p < 0.0001) and the QTc interval (from 443.1 ± 49.2 to 515.6 ± 43.6; p < 0.0001), and did not significantly change the QRS width (from 100.1 ± 11.4 to 103.3 ± 10.1; p = 0.3). The mean time to termination of AF/AFL from the beginning of ibutilide infusion was 38.9 ± 22.5 min (36.4 ± 23.8 min for paroxysmal and 36.4 ± 24.7 min for chronic arrhythmia; p = 0.5). Between converted and non-converted patients (unpaired t test), there were no statistically significant differences in demographics and clinical data (Table 2). However, ibutilide converters had significantly higher HRs (77.9 ± 15.6 vs. 68.8 ± 10.2; p = 0.001) and lesser prolongation of the QT interval (451.8 ± 60.5 vs. 472.6 ± 37.6; p = 0.04) than non-converters. On multiple logistic regression analysis, which evaluated age, gender, type of arrhythmia, onset of arrhythmia (paroxysmal or chronic), left atrium size, HR, QT and QTc intervals, and QRS width, only the difference in mean HR after ibutilide was found to independently predict conversion to SR (p < 0.001). There was an inverse relation between the degree of HR reduction after ibutilide with the conversion success (i.e., patients who exhibited higher HR reduction had lower probability of conversion) (Table 2).

Thirty-three patients who did not convert with ibutilide consented to electrical cardioversion, which was successful in 32 (97%) of 33 patients. None of the overall 82 patients who decided to continue propafenone therapy after successful cardioversion had immediate arrhythmia recurrence throughout their hospital stay (mean, 23.5 ± 5.9 h).

**Electrocardiographic effects of ibutilide.** We chose to separately analyze the effects of ibutilide in 49 patients with chronic AF who received long-term stable dosages of ibutilide and propafenone for AF.

### Table 2. Determinants of Conversion in 104 Patients With AF/AFL Treated With Ibutilide and Propafenone

<table>
<thead>
<tr>
<th></th>
<th>Paroxysmal AF/AFL (n = 48)</th>
<th>Chronic AF/AFL (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conversion</strong></td>
<td>Conversion (n = 34) No Conversion (n = 14) p</td>
<td>Conversion (n = 35) No Conversion (n = 21) p</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>60.7 ± 10.2 59.9 ± 13.8</td>
<td>63.4 ± 8.6 64.2 ± 7.7</td>
</tr>
<tr>
<td><strong>Men, n (%)</strong></td>
<td>25 (74) 13 (93)</td>
<td>22 (63) 10 (48)</td>
</tr>
<tr>
<td><strong>Duration of arrhythmia</strong></td>
<td>77.7 ± 47.6 h 72.9 ± 43.2 h</td>
<td>16.3 ± 7.3 days 15.4 ± 8.0 days</td>
</tr>
<tr>
<td><strong>Cardiovascular history, n (%)</strong></td>
<td>10 (21) 7 (16)</td>
<td>15 (27) 11 (20)</td>
</tr>
<tr>
<td><strong>Left atrial diameter, mm</strong></td>
<td>43.4 ± 7 41.2 ± 3.5</td>
<td>43.4 ± 5.2 45.1 ± 5.9</td>
</tr>
<tr>
<td><strong>Propafenone</strong></td>
<td>83.3 ± 15.2 88.2 ± 9.1</td>
<td>79.0 ± 15.7 73.0 ± 10.3</td>
</tr>
<tr>
<td>Mean ventricular rate (beats/min)</td>
<td>380.3 ± 59.1 381.6 ± 51.5</td>
<td>383.5 ± 35.7 378.2 ± 33.1</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>446.5 ± 54.1 473.2 ± 65.1</td>
<td>441.2 ± 32.3 424.3 ± 48.2</td>
</tr>
<tr>
<td><strong>Ibutilide added to propafenone</strong></td>
<td>79.8 ± 16.5 76.5 ± 9.8</td>
<td>76.5 ± 14.3 64.8 ± 9.8</td>
</tr>
<tr>
<td>Mean ventricular rate (beats/min)</td>
<td>458.1 ± 78.3 472.1 ± 39.7</td>
<td>450.7 ± 46.6 470 ± 40.4</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>531.0 ± 58.1 539.1 ± 22.7</td>
<td>509.3 ± 38.6 499.7 ± 35.8</td>
</tr>
</tbody>
</table>

AF/AFL = atrial fibrillation/atrial flutter; ECG = electrocardiographic.
propafenone with or without diltiazem assuming that the findings before and after ibutilide treatment would be entirely due to the additional effects of ibutilide. In these patients ibutilide significantly decreased the HR from 74.6 ± 9.7 to 70.3 ± 11.1 (p < 0.0001) and increased the QT interval from 381.7 ± 33.4 to 461.5 ± 44.6 (p < 0.0001) and the QTc interval from 428.1 ± 32.9 to 502.8 ± 37.8 (p < 0.0001) (paired t test).

**Adverse effects.** Propafenone treatment was discontinued in 3 (4.3%) of 69 patients after restoration of SR following ibutilide: in two patients due to dizziness and nausea and in one patient due to persistence of second-degree atrioventricular block type I. None of the patients necessitated interruption of ibutilide treatment due to acute untoward effects. After ibutilide administration and immediately before reversion of AF to SR, four patients were documented to have asymptomatic pauses (3.7 to 5.2 s), four patients had transient junctional rhythm for a mean of 7.5 ± 6 s, and two patients with chronic AF developed second degree atrioventricular block type I. None of these patients required insertion of a temporary pacemaker. There were two asymptomatic self-terminating episodes of torsade de pointes (15 and 8 QRS complexes, respectively) following ibutilide in one patient with chronic AF 5 min after conversion to SR. During ibutilide infusion, transient asymptomatic ventricular arrhythmias not requiring intervention were noted in three patients with chronic AF: one patient developed non-sustained runs of ventricular tachycardia of three consecutive beats, and two others had frequent premature ventricular complexes.

**DISCUSSION**

To our knowledge, this is the first study evaluating the effects of ibutilide in patients with both paroxysmal and chronic AF/AFL who were pre-treated with propafenone, which demonstrates the combined strength in improving pharmacologic conversion rates with a low risk of proarrhythmia and low probability of immediate arrhythmia recurrences.

**Effects of propafenone.** Our results of 67% efficacy of a single oral loading dose of 600 mg propafenone in converting paroxysmal AF are consistent with the 56% to 87% success rates within 8 h reported in other studies, confirming a higher conversion ability compared with both placebo and drugs that control the ventricular rate (10–12). The widely variable interindividual pharmacokinetics of the drug and the lack of significant correlation between plasma concentrations and its antiarrhythmic efficacy may account for the usefulness of this convenient oral loading approach in clinical practice (13,14).

**Addition of ibutilide.** Ibutilide’s antiarrhythmic actions result from its ability to prolong action potential duration and atrial effective refractory period predominantly by activating the sodium component of the plateau inward current and by blocking the rapid component of the delayed rectifier potassium current. In contrast with propafenone, ibutilide is devoid of beta-blocking effects, causes mild slowing of sinus rate and atrioventricular conduction, while having no significant effect on contractility (15,16). As a general consideration, the possible enhanced antiarrhythmic efficacy by adding ibutilide to propafenone may be primarily related to overlapping effects on the action potential duration and particularly on the prolongation of the atrial effective refractory period.

In previous studies, ibutilide monotherapy was found superior to placebo in terminating 35.0% to 70.6% of patients with AF and 58% to 75% of patients with AFL, whereby a short duration of the arrhythmia emerged as the main predictor of arrhythmia termination (3–6). In the present study, we demonstrated that the initial conversion efficacy of oral loading propafenone in patients with paroxysmal arrhythmia was 67% (98 of 146 patients). In the remaining 48 non-converters, ibutilide was successful in 34 patients (71%). Thus, the addition of ibutilide offered an additive conversion effect of approximately 23%, increasing the overall efficacy of the combination therapy up to 90%. For the patients with chronic arrhythmia of <6 months duration, the success rate of 64% should be given particular consideration if we keep in mind that all patients were nonresponders to propafenone and that all previous studies emphasize ibutilide’s efficacy in patients with AF of shorter duration lasting approximately <3 months (3–6). Moreover, it should be emphasized that our stepped-care approach of management prevented immediate recurrences; all successfully converted patients maintained SR during their short hospital stay (median, 24 h). This was not surprising because previous studies have shown that propafenone is effective in preventing immediate re-initiation of arrhythmia after the cardioversion procedure (17).

**Safety.** In contrast with the overall incidence of 4.3% of polymorphic ventricular tachycardia in ibutilide-treated patients reported in clinical trials, including 1.7% of patients in whom the arrhythmia was sustained and required cardioversion (15), only 1% of our study patients developed self-terminating episodes of torsade de pointes. The strict exclusion of patients with depressed LV function may be the main reason for this low incidence of proarrhythmia. Other potentially worrisome cardiac side effects manifested as sinus pauses and atrioventricular conduction disturbances in 9.6% of our study patients after instituting ibutilide therapy. However, all minor bradyarrhythmic effects were predictable, occurring within the first hours after the addition of ibutilide, mostly at the time of arrhythmia termination.

**Study limitations.** The low risk of proarrhythmia of our study population should not be extrapolated to patients with depressed LV ejection function. It is important to note that previous studies that have included patients with LV dysfunction and valvular heart disease have expressed concerns over a higher incidence of torsade de pointes after ibutilide (3,4). Besides, due to the lack of a patient group who received ibutilide monotherapy, we cannot compare the
proarrhythmia risk and the net ECG effects of our combination therapy with ibutilide alone. Another limitation of this study is the different propafenone dosing regimens used, based on the methodologic scheme in which the patients were enrolled.

**Conclusions.** Our proposed stepped-care pharmacologic approach by first using propafenone and then ibutilide to those who do not respond to propafenone appears to be a rational alternative for both rapidly terminating and preventing immediate recurrences of paroxysmal and chronic AF/AFL. This drug combination may limit ibutilide’s proarrhythmic response in patients with preserved LV ejection fraction. Ibutilide added to propafenone shows an additive efficacy up to 23% in arrhythmia conversion in patients with paroxysmal AF/AFL and up to 62.5% in patients with chronic arrhythmia who did not respond to propafenone.

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**REFERENCES**