Efficacy and Safety of Ibutilide Fumarate for the Conversion of Atrial Arrhythmias After Cardiac Surgery

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Background—Atrial arrhythmias occur commonly after cardiac surgery and are a cause of significant morbidity and increased hospital costs, yet there is no well-studied treatment strategy to deal with them expeditiously. The purpose of this study was to determine the efficacy and safety of ibutilide fumarate, an approved drug for the rapid conversion of atrial fibrillation and flutter, in patients after cardiac surgery.

Methods and Results—Patients with atrial fibrillation or flutter occurring 1 to 7 days after surgery and lasting 1 hour to 3 days were randomized to receive two 10-minute blinded infusions of placebo or 0.25, 0.5, or 1.0 mg of ibutilide fumarate. Treatment was considered successful if sinus rhythm was restored for any period of time by hour 1.5. A total of 302 patients were randomized, 201 with fibrillation and 101 with flutter. Treatment with ibutilide resulted in significantly higher conversion rates than placebo, and efficacy was dose related (placebo 15%; ibutilide 0.25 mg 40%, 0.5 mg 47%, and 1.0 mg 57%). Conversion rates at all doses were higher for atrial flutter than for atrial fibrillation. Mean time to conversion decreased as the dose was increased. Polymorphic ventricular tachycardia was the most serious adverse effect and occurred in 1.8% of the ibutilide-treated patients compared with 1.2% of patients who received placebo.

Conclusions—Ibutilide is a useful and safe treatment alternative for the atrial arrhythmias that occur after cardiac surgery. (Circulation. 1999;100:369-375.)

Key Words: fibrillation ■ atrial flutter ■ surgery ■ ibutilide ■ antiarrhythmia agents

Atrial arrhythmias after cardiac surgery occur in 15% to 40% of patients.1–3 Although the prophylactic use of β-adrenergic blocking agents decreases the incidence by as much as half, nearly 100 000 cases of atrial arrhythmia after cardiac surgery still occur each year in the United States.4–8 These arrhythmias, although not lethal, predispose to cerebrovascular accidents, can cause disabling symptoms (especially in patients with significant cardiac dysfunction), and are responsible for a prolonged length of stay and an increased hospital cost.3,9–13 Thus, measures to terminate these arrhythmias acutely would be clinically useful.

Ibutilide fumarate is a class III antiarrhythmic drug recently approved for the acute termination of atrial fibrillation (AF) and flutter (AFl).14,15 The patients in the studies that supported this claim had atrial arrhythmias not associated with cardiac surgery. We designed a placebo-controlled dose-ranging study to examine the efficacy and safety of ibutilide specifically in this clinical situation. Because this represents a unique patient population with a shorter duration of arrhythmia, we included a dose-range component that incorporated lower doses than currently recommended. This article is a report of that controlled study.

Methods

This was a double-blind, placebo-controlled, randomized, parallel-group, dose-response trial. Patients were enrolled at 29 sites in the United States. The protocol and a consent form were approved by a research panel at each institution.

Patients could be included in the study if they were 18 years or older, weighed <300 pounds, and, if female, were postmenopausal or surgically sterile. All patients had AF or AFl >1 hour and <3 days in duration that had occurred 1 to 7 days after coronary or valvular surgery or both. All patients were in normal sinus rhythm at
the time of surgery, had a corrected QT interval (QTc; Bazett’s correction) on 12-lead ECG of 440 ms, had never had torsade de points, and had never been exposed to ibutilide. All patients were hemodynamically stable, defined as having a systolic blood pressure >90 mm Hg and a diastolic pressure <105 mm Hg, and were free of heart failure or anginal symptoms at the time of enrollment. Other exclusion criteria included a heart rate <60 bpm, myocardial infarction within 30 days, severe hepatic impairment, hyperthyroidism, an electrolyte abnormality, treatment with any class I or III antiarrhythmic drug within 5 drug half-lives of enrollment, and treatment with pressor drugs other than low-dose dopamine or dobutamine.

Eligible patients were randomized to receive 10-minute intravenous infusions of placebo or 0.25, 0.5, or 1.0 mg of ibutilide fumarate. Patients weighing <60 kg were randomized to placebo or ibutilide fumarate 0.0025, 0.005, or 0.01 mg/kg. If the arrhythmia did not terminate within 10 minutes after the end of the first infusion, an identical second dose was given. The infusion was discontinued when the arrhythmia stopped or when there was a safety concern, such as a fall in systolic blood pressure to <90 mm Hg, an increase in the QTc to >600 ms, or the development of ventricular arrhythmia. No other antiarrhythmic drugs were permitted before hour 4 in treatment failures. To determine the effect of ibutilide alone in maintaining sinus rhythm over 24 hours, other antiarrhythmic agents were to be withheld over that time period in successfully treated patients. Electrical conversion was permitted any time after 90 minutes in treatment failures or in patients who relapsed after successful therapy.

The prespecified primary efficacy end point for this trial was conversion of the atrial arrhythmia for any period of time within 90 minutes of the start of the first infusion. Secondary end points included an analysis of adverse events, the effect of ibutilide and placebo on hemodynamics and laboratory assays, and the impact of changes in QT interval and concomitant medications on arrhythmia conversion rates. Adverse events were recorded by the investigator and tracked for 72 hours after the initial infusion.

All statistical tests were 2-sided and considered significant if they generated a \( P \) value \( \leq 0.05 \). For the primary efficacy variable, a logistic regression was performed on the relationship between response and ibutilide dose. For categorical variables, such as the

<table>
<thead>
<tr>
<th>TABLE 1. AFI/AF Conversion</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>AF only</td>
</tr>
<tr>
<td>AFI only</td>
</tr>
<tr>
<td>CABG only</td>
</tr>
<tr>
<td>Valve only</td>
</tr>
<tr>
<td>CABG plus valve</td>
</tr>
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</table>

Values are n/n (%).

\( *P \) Value from logistic regression analysis.

Figure 1. Cumulative success rate in restoring sinus rhythm after 1 or 2 infusions of placebo or 1 of 3 doses of ibutilide for patients with AF or AFI and for all patients combined.
relative incidence of AF or AFL across dose groups, \( \chi^2 \) calculations were performed. The significances of mean change from baseline to each follow-up reading of ECG intervals (QRS, QT, and QTc), blood pressures, and heart rates were analyzed within dose groups by use of paired \( t \) tests, and comparisons among dose groups were assessed by a 1-way ANOVA. With the use of logistic regression, separate analyses were performed on the relationships among response and ibutilide dose and either arrhythmia duration, ejection fraction, or use of concomitant medications (digoxin, \( \beta \)-adrenergic blockers, or calcium channel blockers). The test for interaction was significant if it generated a value of \( P \leq 0.10 \). If the test for interaction was not significant, the interaction term was removed from the model.

Results
A total of 302 patients (76% male) were randomized, 201 with fibrillation and 101 with flutter. The majority of the patients (208; 69%) had coronary artery surgery alone, 20% had valve surgery as the sole procedure, and 11% had both valve surgery and CABG. Preoperative ejection fraction was recorded from 80% of patients. Forty-nine percent of the patients had a normal ejection fraction, and 31% were reported to have had a decreased ejection fraction (\( \leq 40\% \)).

Conversion success is shown in Table 1. By 1.5 hours, sinus rhythm was restored in 15% of the placebo patients (13 of 84) and in 48% of the ibutilide-treated patients (104 of 218). The proportion of patients converting to sinus rhythm in each dose group is presented in Figure 1, which also illustrates success rates after the first or second infusion. Because of the repeated-dose design and because the ibutilide infusion was discontinued at the time of conversion, all patients did not receive the entire dose to which they were randomized. In relation to total dose actually received, 10 of 218 patients converted to sinus rhythm after receiving \( \leq 0.25 \) mg, 36 of 208 patients converted after receiving 0.26 to 0.5 mg, 44 of 127 patients converted after receiving 0.51 to 1 mg, and 14 of 44 patients converted after receiving \( >1 \) mg. The conversion rate for AFL was 78% in patients who received the 1-mg doses of ibutilide compared with 44% in AF patients. Table 1 also lists conversion rates for patients by type of procedure. Although there was a significant difference in patients with coronary or combined surgery, there were too few patients with valve surgery alone for any definitive conclusion to be reached.

The time to arrhythmia conversion is presented in Figure 2. Mean time to conversion was 36 minutes for the 0.25-mg group, 33 minutes for the 0.5-mg group, and 23 minutes for the 1-mg group. The range for all ibutilide-treated patients was 3 to 90 minutes. Of the 104 patients successfully converted with ibutilide, 65 (63%) remained in sinus rhythm for 24 hours. Figure 3 presents relapse rate over time for each arrhythmia stratum. A total of 8 (62%) of the 13 placebo-treated patients who had rhythm reversion remained in sinus rhythm for 24 hours.

There was a statistically significant prolongation in the QT and QTc intervals between before the dose was administered and the time of arrhythmia conversion for all ibutilide dose groups, but there was no difference in any dose group in the magnitude of QTc prolongation at minute 30 between patients who were and were not successfully converted. Mean rate-corrected QT prolongation for patients who converted to sinus rhythm was 34 ms for placebo and 31, 70, and 76 ms for the 0.25-, 0.5-, and 1-mg ibutilide dose groups, respectively.
There were no other clinically significant differences in any ECG parameter. The success rate was not statistically different between patient groups who had normal or decreased left ventricular ejection fractions or between those who were and were not treated with β-adrenergic or calcium channel blocking agents. There was, however, a suggestion of a benefit of concomitant digoxin therapy: 65% of digoxin-treated patients who received 1.0 mg of ibutilide had successful conversion to sinus rhythm compared with 31% of patients who were not receiving a digitalis glycoside ($P=0.025$).

Table 2 lists the adverse effects in the trial. There were no significant differences in noncardiovascular adverse effects among the ibutilide and placebo dose groups. Likewise, the incidence of nonarrhythmic cardiovascular adverse effects was similar among groups. Ibutilide did not have a significant clinical effect on blood pressure. Heart rate decreased primarily as a result of rhythm reversion, with heart rate at 1.5 hours being reduced by 1.3 bpm for placebo and 15.4 bpm for the 1-mg ibutilide dose compared with baseline ($P<0.05$). There were more ventricular arrhythmias in patients treated with ibutilide, including ventricular premature depolarizations, nonsustained monomorphic ventricular tachycardia, and polymorphic ventricular tachycardia, both sustained (lasting >30 seconds or requiring an intervention for termination) and nonsustained. All 4 patients who developed torsade de pointes were in the 1.0-mg ibutilide group; 2 episodes occurred toward the end of the first 1-mg infusion, and the other 2 occurred at 2 and 5 minutes after the end of the second 1-mg infusion. One patient developed nonsustained torsade de pointes, which rapidly progressed to a sustained arrhythmia. This patient was reported as having both arrhythmias.

The 2 patients who developed sustained arrhythmia were successfully treated with intravenous magnesium therapy and with cardioversion or pacing. Three of these 4 patients had decreased ejection fraction. The single case of torsade de pointes that occurred in the placebo group occurred 27 hours after the initial infusion, during treatment with procainamide. There were no deaths, strokes, or myocardial infarctions. An

<table>
<thead>
<tr>
<th>Table 2. Adverse Events</th>
<th>Drug (n=218)</th>
<th>Placebo (n=84)</th>
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</thead>
<tbody>
<tr>
<td><strong>Noncardiovascular, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (7.3)</td>
<td>7 (8.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (2.8)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (1.8)</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Fever</td>
<td>5 (2.3)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>4 (1.8)</td>
<td>4 (4.8)</td>
</tr>
<tr>
<td><strong>Cardiovascular, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>6 (2.8)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1 (0.5)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Extrasystoles</td>
<td>10 (4.6)</td>
<td>0</td>
</tr>
<tr>
<td>Nonsustained monomorphic VT</td>
<td>7 (3.2)</td>
<td>0</td>
</tr>
<tr>
<td>Nonsustained polymorphic VT</td>
<td>3 (1.4)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Sustained polymorphic VT</td>
<td>2 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>18 (8.3)*</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

VT indicates ventricular tachycardia.

*Patients with multiple types of ventricular arrhythmia are only counted once in this category.
Finally, the effect of ibutilide on atrial defibrillation energy that was needed to convert patients who failed ibutilide or placebo treatment was examined. The mean number of joules was 225 and 128 for AF and AFl patients, respectively, who received ibutilide compared with 300 and 187 J in placebo-treated patients. These differences were not statistically significant.

Discussion

Atrial arrhythmia is a clinical problem in several settings, including after cardiac surgery. Although they are rarely life threatening, atrial arrhythmias are associated with a risk for thromboembolism and cause significant disability.\(^{13,16,17}\) Traditionally, patients with AF have been treated with rate-control measures and systemic anticoagulation for several weeks before any attempts have been made to restore sinus rhythm. This treatment strategy may lead to longer hospital stays and may serve to perpetuate the arrhythmia. There is burgeoning evidence that “AF begets AF” by causing electrophysiological changes that favor its persistence and recurrence.\(^{18}\) For these reasons, there is increasing interest in measures that may be used to restore sinus rhythm sooner, thus obviating the need for anticoagulation and long-term antiarrhythmic drug therapy with its inevitable toxicity.\(^{19}\) Although many drugs have been used for this indication orally and intravenously with positive results,\(^{20–24}\) ibutilide was the first agent specifically designed, developed, and approved for this indication in the United States.\(^{14,15}\) It has a well-described efficacy and safety profile in medical patients who develop AF and AFI.

Atrial arrhythmias are frequent after cardiac surgery, and their emergence causes significant morbidity and delays in patient discharge.\(^{10}\) The conservative treatment strategy of rate control and anticoagulation alone has merit, because these arrhythmias are almost always self-limited, but it also obligates the use of anticoagulation with its attendant risks.\(^{25}\) Prophylaxis with β-adrenergic blocking agents has some benefit, but the magnitude of protection has proven to be inadequate to significantly affect the cost of hospitalization and length of stay.\(^{11,26}\) Small and in many cases poorly controlled studies of arrhythmia termination have been performed with a number of antiarrhythmic drugs after cardiac surgery, with some indication of effectiveness.\(^{20–24,27}\) Pacing to entrain and terminate AFI and direct-current cardioversion of AF or AFI are also frequently used in this clinical scenario with good results. With evidence of its safety and effectiveness in nonsurgical studies and with knowledge of its rapid onset and offset of effect, we hypothesized that ibutilide would be particularly useful in this patient group.\(^{28}\) The results of the present study were relatively straightforward. The efficacy of the drug was superior to placebo and was preserved across several strata, and there was a clear dose response. Efficacy was at least comparable to and perhaps slightly better than that observed in dose-response studies in nonsurgical groups. As in other studies, the drug worked better for AFI than for AF, perhaps owing to the presence of a more discrete reentrant circuit in the former arrhythmia.\(^{29,30}\)

There was also a suggestion that the optimal dose in patients treated for AF might be 0.5 mg, unlike AFI patients, who benefited from the higher 1.0-mg dose. Rhythm reversion was associated with QT prolongation, but the extent of the prolongation was not a predictor of the success of the drug. Importantly, efficacy was preserved in patients with cardiac dysfunction.

The safety of the drug was also consistent with that seen in other trials.\(^{14,15}\) Noncardiac and nonarrhythmic cardiac adverse effects were uncommon and were not different between placebo and drug-treated patients. However, significantly more ventricular arrhythmias were seen with ibutilide. Much of this difference was explained by a differential incidence of single premature beats and nonsustained monomorphic ventricular tachycardia. In light of an analysis of prior studies in which the latter finding has been reported, many of these cases may have actually represented aberrant conduction of a regular atrial arrhythmia rather than a ventricular arrhythmia, because this drug does affect distal conduction system function.\(^{31}\) The drug prolonged the QT interval, probably by a combination effect of activation of a slow sodium channel and blockade of the rapidly activating delayed rectifier potassium current (\(I_{\text{Kr}}\)), and caused torsade de pointes.\(^{32,33}\) All of the patients in the present study who had torsade de pointes after ibutilide had AF and received 1.0 mg; 3 of the 4 had diminished left ventricular function. However, the overall incidence of polymorphic ventricular tachycardia was lower in the present study than in others. Because the numbers are small, it is not possible to determine whether this was a true difference or was due to chance. It is conceivable that the patients in the present study were more stable, because many had recently undergone revascularization surgery. They also had higher resting heart rates, which might provide protection against this arrhythmia, which is known to occur more often in the setting of resting bradycardia.\(^{34}\) In any event, patients responded to therapy in each case; there were no deaths or prolonged resuscitations. As in other studies, all of the episodes of torsade de pointes after ibutilide occurred within the first several minutes of the infusion when the patient was still under close observation in a setting in which resuscitation was easily accomplished.

Although the present study did prove the value of ibutilide for the conversion of AF and AFI, it provided no experience in the use of ibutilide for arrhythmia conversion in patients who are currently receiving a class I or III antiarrhythmic drug. The dose-response effect in patients with AFI did not...
plateau, and it is conceivable that higher doses might result in increased efficacy in this group, although potentially this may also increase the risk of proarrhythmia. Because other class I or III antiarrhythmic agents were to be withheld for 24 hours in patients who were converted to sinus rhythm with ibutilide, there was no systematic attempt to determine the best oral maintenance drug to use after conversion in this study. In previous studies, oral maintenance therapy was withheld for 4 hours, which is the basis for the current usage recommendations. Likewise, we did not examine whether ibutilide treatment had a positive impact on length of stay or the cost of hospitalization, although prompt arrhythmia treatment should have facilitated hospital discharge in patients who had no other reason to stay.

We conclude that ibutilide constitutes a useful addition to the list of options available for the treatment of atrial arrhythmias after cardiac surgery. It is effective and safe when used in a carefully supervised clinical setting and does not interfere with other measures, such as the use of oral antiarrhythmic drugs or electrical cardioversion, that may be subsequently used.

Appendix

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