JACC Vol. 28, No. 1
July 1996:130–6

Efficacy of Intravenous Ibutilide for Rapid Termination of Atrial Fibrillation and Atrial Flutter: A Dose-Response Study

KENNETH A. ELLENBOGEN, MD, FACC, BRUCE S. STAMBLER, MD, FACC, MARK A. WOOD, MD, FACC, PHILIP T. SAGER, MD, FACC,* ROBERT C. WESLEY, JR., MD, FACC,† MARC D. MEISSNER, MD, FACC,‡ ROBERT G. ZOBLE, MD, PHD,§ LINDA K. WAKEFIELD, BS,‖ KIMBERLY T. PERRY, PHD,‖ JAMES T. VANDERLUGT, MD,‖ FOR THE IBUTILIDE INVESTIGATORS

Richmond, Virginia; Los Angeles and Long Beach, California; Allen Park and Kalamazoo, Michigan; and Tampa, Florida

Objectives. **Currently available antiarrhythmic drugs have limited efficacy for short-term, rapid termination of atrial fibrillation and atrial flutter.**

Background. **Ibutilide fumarate is an investigational class III antiarrhythmic agent that prolongs repolarization by increasing the slow inward sodium current and by blocking the delayed rectifier current. It can be administered intravenously and has a rapid onset of electrophysiologic effects.**

Methods. **The efficacy and safety of ibutilide were studied in 200 patients with atrial flutter >3 h in duration or atrial fibrillation 3 h to 90 days in duration. Patients were randomized to receive a single intravenous dose of placebo or an infusion of ibutilide fumarate at 0.005, 0.010, 0.015 or 0.025 mg/kg body weight over 10 min. Conversion was defined as termination of the atrial arrhythmia during or within 60 min after infusion. Forty-one patients received placebo and 159 received ibutilide (0.005 mg/kg [n = 41], 0.010 mg/kg [n = 40], 0.015 mg/kg [n = 38] or 0.025 mg/kg [n = 40]).**

Results. **The arrhythmia terminated in 34% of drug-treated patients. The rates of successful arrhythmia termination were 3% for placebo and 12%, 33%, 45% and 46%, respectively, for 0.005-, 0.010-, 0.015- and 0.025-mg/kg ibutilide. The placebo and 0.005-mg/kg ibutilide groups had lower success rates than all other dose groups ($p < 0.05$). The mean time to termination of the arrhythmia was 19 min (range 3 to 70) from the start of infusion. Successful arrhythmia termination was not affected by enlarged left atrial diameter, decreased ejection fraction, presence of valvular heart disease or the use of concomitant medications (beta-adrenergic blocking agents, calcium channel blocking agents or digoxin). Arrhythmia termination was not predicted by the magnitude of corrected QT interval prolongation but was associated with a shorter duration of atrial arrhythmia. The most frequent adverse events in ibutilide-treated patients were sustained and nonsustained polymorphic ventricular tachycardia (3.6%). All patients with sustained polymorphic ventricular tachycardia were successfully treated with direct current cardioversion and had no recurrence. The occurrence of proarrhythmia did not correlate with ibutilide plasma concentration.**

Conclusions. **These data demonstrate that ibutilide is able to rapidly terminate atrial fibrillation and atrial flutter.**

(J Am Coll Cardiol 1996;28:130–6)

Atrial fibrillation and atrial flutter represent the most common sustained arrhythmias seen in clinical practice. Rapid termination of atrial arrhythmias is severely limited by the absence of easily administered agents that have a high efficacy for arrhythmia termination and are rapid in onset of effect. Intravenous agents (procainamide, for example) used for the acute termination of atrial fibrillation and atrial flutter are associated with a low incidence of successful conversion and are limited by hypotension, necessitating slow administration. It would be clinically useful to have available an agent that is safe, easily administered over a short period of time and rapidly effective for the acute termination of atrial arrhythmias.

Ibutilide fumarate is a novel class III antiarrhythmic drug currently undergoing clinical trials. On the basis of extensive testing in different animal models, it appears to be effective for pharmacologic conversion of atrial flutter and atrial fibrillation by prolonging the effective refractory period and monophasic action potential duration in the atrium (1–3). Its cellular electrophysiologic mechanisms involve increasing a slow inward plateau sodium current and inhibiting the outward repolarizing potassium current (3–7). In contrast to class I agents, it does not appear to significantly slow conduction

From the Department of Medicine, Medical College of Virginia and McGuire Veterans Affairs Medical Center, Richmond, Virginia; *University of California at Los Angeles and Wadsworth Veterans Affairs Medical Center, Los Angeles, California; †Long Beach Veterans Affairs Medical Center, Long Beach California; ‡Wayne State University Medical Center and the Allen Park Veterans Affairs Medical Center, Allen Park, Michigan; §University of Florida Medical Center and the James A. Haley Veterans Affairs Medical Center, Tampa, Florida; and ‖Upjohn Company, Kalamazoo, Michigan. A complete list of the ibutilide study sites and principal investigators appears in the Appendix. This work was supported in part by a grant from the Upjohn Company, Kalamazoo, Michigan. Drs. Ellenbogen and Stambler are consultants to the Upjohn Company.

Manuscript received June 23, 1995; revised manuscript received February 28, 1996, accepted March 11, 1996.

Address for correspondence: Dr. Kenneth A. Ellenbogen, Medical College of Virginia, P.O. Box 980053, Richmond, Virginia 23298-0053.

0735-1097/96/$15.00
PII 0735-1097(96)00121-0

(3,4). Ibutilide is associated with a low incidence of proarrhythmia in these animal models (1,2).

The purpose of this prospective trial was to determine the clinical safety and efficacy of intravenous ibutilide fumarate for the termination of atrial fibrillation and atrial flutter in patients. Other goals of this investigation were to assess the dose-response relation of ibutilide and to assess the tolerance and safety of this new agent in patients with these arrhythmias.

Methods

All patients were enrolled in this study after giving written informed consent to a protocol approved by the institutional review boards of each principal investigator's hospital. Two hundred patients with sustained atrial flutter (duration ≥3 h) or atrial fibrillation (duration 3 h to 90 days) were enrolled in this 24-h study to determine efficacy and to measure a dose-response relation for the conversion of atrial arrhythmias with ibutilide.

This study was a double-blind, randomized, placebo-controlled dose-response trial. To adequately assess the safety of increasing doses, the original protocol was conducted in two tiers. The first tier consisted of 50 patients randomized to receive a 10-min infusion of placebo or 0.005- or 0.010-mg/kg body weight of ibutilide fumarate. When safety was ascertained, the trial progressed to the second tier, in which patients were randomized to a 10-min infusion of placebo or 0.015 or 0.025 mg/kg of ibutilide. After completion of this tier, an additional 100 patients across all dose groups were randomized to receive placebo or a dose of 0.005, 0.010, 0.015, or 0.025 mg/kg of ibutilide, also over 10 min.

Patients were enrolled in this trial if they met the following eligibility criteria: a sustained rhythm of atrial flutter of ≥3 h duration or atrial fibrillation (duration 3 h to 90 days), hemodynamic stability during the atrial arrhythmia, with a systolic blood pressure >90 mm Hg, and no symptoms of unstable angina or uncontrolled heart failure. Patients were excluded from the study if they were of childbearing potential or had a myocardial infarction within the preceding 3 months. All class I or III antiarrhythmic drugs were discontinued for at least 5 half-lives. Patients with atrial fibrillation for >3 days received anticoagulant treatment for ≥2 weeks before administration of ibutilide. Control of the ventricular rate was permitted with digoxin, beta-adrenergic blocking agents, and calcium channel blocking agents.

Patients were stratified to equalize the number of patients with atrial flutter and atrial fibrillation in each tier and at each dose level. A medical history, physical examination, 12-lead electrocardiogram (ECG) and laboratory assays were reviewed by each investigator before entry of a patient into the study protocol. Each patient underwent two-dimensional echocardiography. A digoxin level was obtained if the patient was taking digoxin. Temporary right ventricular pacing was instituted with standby external transthoracic cardiac pacing or by placement of a temporary right ventricular pacing wire when clinically indicated. Patients were entered into the study after a 6- to 8-h fast before the infusion.

Continuous monitoring and recording of three ECG leads was begun 10 min before the infusion and continued until 30 min after the end of the infusion. Blood pressure measurements and single ECG lead monitoring were then performed from 10 min before to 24 h after infusion. Ibutilide levels were obtained at serial intervals (before infusion, at 10, 15 and 30 min, at 1, 1.5, 2 and 3 h, at arrhythmia termination and for significant adverse rhythm changes). Ibutilide infusion was stopped if the arrhythmia terminated or if the systolic blood pressure decreased to <90 mm Hg, new bundle branch block developed, QRS duration increased by ≥50%, the corrected QT (QTc) interval increased to >600 ms or any change in rhythm or atrioventricular (AV) conduction occurred that was thought to be a risk to patient safety (e.g., heart block, torsade de pointes). A 12-lead ECG was obtained 1 h after the infusion period, at the time of termination of the arrhythmia and for any significant rhythm changes within 1 h of termination of the infusion.

All statistics were expressed as mean value ± SD. A p value ≤ 0.05 was considered statistically significant. For the 12-lead ECGs, assessment of the significance of mean change from baseline to 1 h after the infusion period was made within treatment groups by using a two-sided paired *t* test. Comparisons among treatment groups of the mean change from baseline to 1 h after the infusion period were made by using a one-way analysis of variance (ANOVA) F test. The relation between the response and the ibutilide dose was analyzed by using a single chi-square test for two-way contingency tables. If the overall test yielded a significant result, an additional chi-square test for homogeneity of proportions was performed on each pairwise comparison to determine which doses differed with respect to response rate. The relation between arrhythmia conversion, ibutilide dose and each explanatory variable was analyzed by using a logistic regression model in which the response variable was conversion and the interaction term was dose by selected explanatory variable. If the test for interaction was not significant ($p > 0.10$), the interaction term was eliminated from the model.

Results

Study patients. The efficacy of ibutilide therapy was evaluated in 197 of the 200 patients who received the drug. Two patients were excluded from the efficacy analysis because they did not receive a dose of ibutilide consistent with the dose-response design: One patient had extravasation of the infusion, and one had a 15-min infusion, thereby receiving a dose 50% higher than the highest intended dose. Another patient, who did not have atrial fibrillation or atrial flutter before drug administration, was also excluded. Information on the study patients and their clinical characteristics is summarized in Table 1. There were no significant differences between the clinical characteristics of the patients receiving ibutilide or those receiving placebo. The mean age was 64 ± 9.5 years;

Table 1. Characteristics of the Study Patients

	Placebo			Ibutilide		
	Combined (n = 40)	AF (n = 20)	AFl (n = 20)	Combined (n = 157)	AF (n = 79)	AFl (n = 78)
Age	63 ± 9	65 ± 8	61 ± 10	64 ± 10	64 ± 9	64 ± 11
Male/female	92%/7%	100%/0%	85%/15%	89%/11%	90%/10%	88%/12%
LA enlargement	76%	63%	90%	74%	67%	80%
LA size (cm)	40 ± 12	34 ± 12	43 ± 11	34 ± 13	32 ± 12	36 ± 14
Decreased LV function	58%	44%	70%	48%	45%	50%
Duration of arrhythmia ≤30 days	67%	85%	50%	69%	72%	65%
Mean duration (days)	55 ± 221	83 ± 314	27 ± 25	60 ± 267	93 ± 374	27 ± 29
QT interval (ms)	363 ± 60	366 ± 71	360 ± 48	364 ± 48	365 ± 57	362 ± 38
QTc interval (ms)	436 ± 46	441 ± 49	432 ± 43	431 ± 40	436 ± 44	426 ± 36
Presence of valvular heart disease	57%	65%	50%	58%	61%	55%
Current digoxin use	62%	65%	60%	73%	67%	79%
*Beta-blocker use	15%	10%	20%	19%	18%	20%
*Calcium-channel blocker use (%)	37%	45%	30%	41%	42%	41%

*Medication taken within 24 h before ibutilide infusion. Data presented are mean value ± SD or number (%) of patients. AF = atrial fibrillation; AFl = atrial flutter; LA = left atrial; LV = left ventricular; QTc = corrected QT interval.

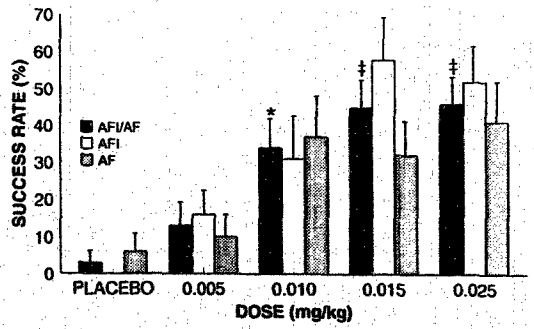
90% were men. Seventy-three percent of the patients with atrial flutter and 71% of those with atrial fibrillation had a history of heart disease other than atrial fibrillation or atrial flutter. Fifty-seven percent of the patients with atrial flutter and 78% of those with atrial fibrillation had a previous history of atrial arrhythmias. Seventy-one percent of the evaluable patients were receiving digoxin. The mean duration of the atrial flutter and atrial fibrillation before administration of ibutilide was 93 ± 374 days and 27 ± 29 days, respectively. Fifty-eight percent of the patients had significant valvular heart disease, and 50% had decreased left ventricular function as judged by two-dimensional echocardiography. Overall, 72% of patients had structural heart disease and 74% had significant left atrial enlargement.

Drug efficacy. The efficacy of the ibutilide infusion at each dose is shown in Figure 1. Treatment was considered successful if the arrhythmia terminated within 60 min of the end of the infusion. The rates of successful arrhythmia termination were 3% (n = 40) for placebo and 12% (n = 41) for 0.005 mg/kg, 33% (n = 39) for 0.010 mg/kg, 45% (n = 38) for 0.015 mg/kg and 46% (n = 39) for 0.025 mg/kg of ibutilide. Pairwise comparisons indicated no difference between the success rates in the placebo and the 0.005-mg/kg ibutilide dose group or among the success rates in the three higher dose groups (0.010, 0.015 and 0.025 mg/kg). The placebo and 0.005-mg/kg dose groups had significantly lower ($p \leq 0.05$) success rates than those of all other dose groups. Difference in the distribution of successes and failures across dose groups was statistically signficant for atrial flutter ($p = 0.0004$) and for atrial fibrillation ($p = 0.05$). The overall success rate of ibutilide-treated patients was 38% for those with atrial flutter and 2?% for those with atrial fibrillation ($p > 0.26$).

The success rates for termination of atrial flutter or atrial fibrillation were not affected by the concomitant use of calcium channel blockers, digoxin or beta-blockers. The mean time to termination of the atrial arrhythmia from the beginning of infusion was 19 ± 15 min (range 3 to 70). Seventy percent of conversions to sinus rhythm occurred within 20 min of the start of infusion (Fig. 2). There was a trend suggesting that the highest dose was associated with the shortest time to conversion to sinus rhythm ($p = 0.059$). The mean time to arrhythmia termination was longest (24 ± 16 min) in the 0.015-mg/kg dose group but only 12 ± 7 min in the 0.025 mg/kg dose group. The overall success rate was not associated with ejection fraction or presence of an enlarged left atrium or valvular heart disease. The mean ibutilide concentration and range of ibutilide concentrations were not significantly different between patients whose arrhythmias were or were not terminated.

There was a statistically significant effect of duration of arrhythmia (truncated at 90 days) on termination of atrial flutter and atrial fibrillation. The mean duration of the prestudy atrial arrhythmia in the patients with a successful arrhythmia termination was 18 ± 24 days versus 27 ± 27 days in patients without arrhythmia termination ($p = 0.03$). Among ibutilide-treated patients, with an arrhythmia duration treat-

Figure 1. Termination of atrial flutter (AF)/fibrillation (AFl). Success rate (mean ± SEM) for ibutilide infusion versus placebo for all 197 evaluable patients. *$p \leq 0.001$, ‡$p \leq 0.0001$.



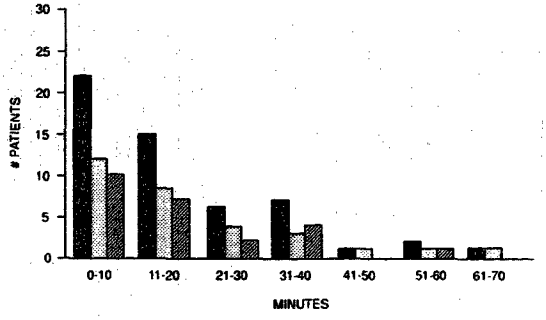


Figure 2. Time to arrhythmia termination for patients with atrial fibrillation (**hatched bars**) or atrial flutter (**dotted bars**), or both (**solid bars**), who had successful reversion to sinus rhythm.

ment was successful in 42% of those ≤30 days as opposed to 16% of those with an arrhythmia duration >30 days ($p = 0.002$).

ECG. The QT and QTc intervals were significantly prolonged at the end of the 0.010- and 0.025-mg/kg ibutilide doses. Both intervals were significantly prolonged from baseline at 1 h in all ibutilide dose groups (Fig. 3A). The QTc interval increased by 25 ms or 5.5% ($p < 0.05$ vs. placebo) at 1 h after the 0.005-mg/kg ibutilide dose, by 19 ms or 4.2% after the 0.010-mg/kg dose ($p < 0.05$ vs. placebo), by 44 ms or 9.3% after the 0.015-mg/kg dose ($p < 0.05$ vs. placebo and 0.010-mg/kg dose) and by 52 ms or 10.7% after the 0.025-mg/kg dose ($p < 0.05$ vs. placebo and 0.005- and 0.010-mg/kg doses). There was no difference between patients with and without successful arrhythmia termination in any ibutilide group with respect to the degree of QTc prolongation (Fig. 3B), ($p > 0.16$). There was no statistically significant difference in the QRS interval across all dose groups.

Systemic variables. There was no clinically significant effect of the ibutilide infusion on systolic and diastolic blood pressures. The mean blood pressure was 133 ± 21/81 ± 11 mm Hg at baseline, 132 ± 24/85 ± 12 mm Hg midway through the infusion and 130 ± 22/79 ± 12 immediately after infusion. Hypotension after the start of the infusion was seen in 3.8% of patients. Of the six patients who experienced hypotension, two were receiving other drugs that were thought to be responsible for the decrease in blood pressure.

Patient outcomes. Successful conversion to sinus rhythm occurred in 53 patients receiving ibutilide and in 1 patient receiving placebo. Among the remaining 143 patients, the arrhythmia was electrically cardioverted to sinus rhythm in 51, terminated by pacing in 19, terminated spontaneously after 70 min in 7, converted with other medications in 6 and not converted during the 24-h follow-up time period in 60.

Adverse arrhythmic events. Polymorphic ventricular tachycardia developed in six patients receiving ibutilide (3.6%). It was nonsustained (i.e., did not require electrical termination) in two and sustained (i.e., required electrical termination) in four. The four episodes of sustained polymorphic ventricular

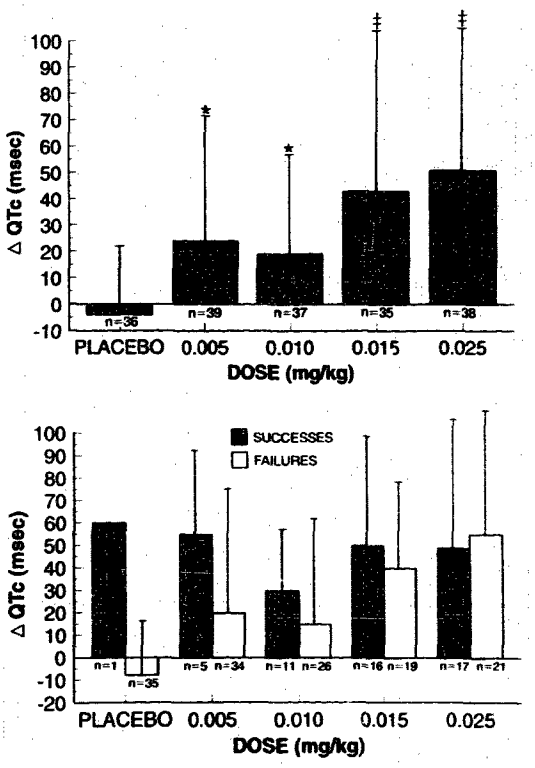


Figure 3. The mean ± SD change in corrected QT interval (ΔQTc) from the baseline interval at 1 h for patients receiving placebo and those receiving each dose of intravenous ibutilide infusion. **A,** Data for the groups as a whole. **B,** Data for patients with (SUCCESSES) and without (FAILURES) successful conversion to sinus rhythm. *$p \leq 0.01$, ‡$p \leq 0.001$.

tachycardia occurred 6, 7, 10 and 27 min, respectively, after the start of infusion and were successfully electrically cardioverted to sinus rhythm. No patient experienced a second episode of sustained polymorphic ventricular tachycardia. The two episodes of nonsustained polymorphic ventricular tachycardia occurred 3 and 11 min, respectively, after the start of infusion. Polymorphic ventricular arrhythmias were seen with ibutilide doses of 0.010, 0.015 and 0.025 mg/kg. The occurrence of proarrhythmia did not correlate with plasma ibutilide concentration.

All six patients with polymorphic ventricular tachycardia had decreased left ventricular function. Three of the six had a history of congestive heart failure and three had a baseline QTc interval >440 ms. The clinical characteristics and patient outcomes are described in Table 2.

Discussion

Antiarrhythmic drugs have been shown to have only limited efficacy for the rapid pharmacologic conversion of atrial fibril-

Table 2. Patients With Polymorphic Ventricular Tachyarrhythmias

Pt No.	Age (yr)/ Gender	Ibutilide Dose (mg)	Baseline QTc (s)	Onset of Polymorphic VT	NYHA CHF Class EF	Treatment QTc (s)	Intervention
				Nonsustained Polymorphic Ventricular Tachycardia			
1	74/M	0.63	0.469	1 min after infusion	III/45%	0.531	None; spontaneous termination
2	65/M	0.54	0.453	3 min into infusion	II/decreased	0.464	None; spontaneous termination
				Sustained Polymorphic Ventricular Tachycardia			
3	65/M	0.66	0.417	7 min into infusion	II/30%	0.680	3 g $MgSO_4$, DCC
4	45/M	1.2	0.448	17 min after infusion	II/25%	0.549	DCC
5	67/M	1.4	0.410	Immediately after infusion	II/35%	0.640	1 g $MgSO_4$, DCC
6	40/M	1.9	0.384	6 min into infusion	II/45%	0.561	DCC ×2

CHF = congestive heart failure; DCC = direct current cardioversion; EF = ejection fraction; M = male; $MgSO_4$ = magnesium sulfate; NYHA = New York Heart Association; Pt = patient; QTc = corrected QT interval; VT = ventricular tachyarrhythmia.

lation and atrial flutter. Antiarrhythmic drugs can be given orally, but it often takes 1 to 3 days for steady state levels to be reached and arrhythmia conversion to occur. Procainamide is the only commercially available intravenous agent for the pharmacologic conversion of atrial arrhythmias in the United States, and its use is limited by a high incidence of hypotension, low efficacy rate and an infusion duration of up to 1 h.

In the present study, we demonstrated that ibutilide is a relatively safe and effective antiarrhythmic agent that, when administered as a 10-min infusion for termination of atrial fibrillation or atrial flutter, results in arrhythmia conversion in a significant percentage of patients. Ibutilide infusion was well tolerated and resulted in few side effects. Continuous ECG monitoring should be maintained for at least 1 h after termination of the infusion because of the risk of polymorphic ventricular tachycardia (e.g., torsade de pointes). Efficacy for termination of atrial arrhythmias was associated with only one clinical variable: duration of the atrial arrhythmia before administration of ibutilide.

Previous studies. Other studies have examined rapid short-term termination of atrial fibrillation or atrial flutter with intravenous procainamide and flecainide (Table 3). Fenster et al. (8) studied the efficacy of an intravenous infusion of procainamide for conversion of atrial fibrillation in 26 patients. Conversion occurred in 15 patients (58%). The patients with arrhythmia conversion had a significantly shorter mean duration of atrial fibrillation (6 days vs. 79 days in patients without conversion). Halpern et al. (9) studied the efficacy of intravenous procainamide for cardioversion of atrial fibrillation in 21 patients. Conversion to sinus rhythm occurred in nine patients (43%) and was predicted by both left atrial size and duration of atrial fibrillation. In contrast to the current study, all patients with arrhythmia had a duration of atrial fibrillation <24 h. In a prospective, controlled and randomized crossover study, Madrid et al. (10) compared the efficacy of procainamide and flecainide for treatment of acute atrial fibrillation in 80 patients with recent onset of the arrhythmia (<24 h). Patients with any signs of heart failure, conduction system disease or acute ischemia were excluded. Conversion to sinus rhythm was achieved in 65% of those treated with procainamide. Serum levels of drug and atrial size did not differ between patients with and without arrhythmia conversion. Fujiki et al. (11) studied the efficacy of intravenous procainamide and disopyramide in patients with atrial fibrillation of ≤72 h duration. Conversion to sinus rhythm was achieved with class Ia drugs in 64% of patients. Left atrial diameter was not a predictor of class Ia drug failure, but 86% of patients had no organic heart disease. There is little information about how long conversion to sinus rhythm took in these patients. These trials were primarily limited to patients with atrial fibrillation of short duration. Trials studying the efficacy of intravenous flecainide in patients with atrial fibrillation (12–14) have shown a marked reduction in rate of arrhythmia conversion in patients who have had atrial fibrillation for ≥10 days.

Results from a prospective nonrandomized trial comparing procainamide with ibutilide for rapid conversion of atrial fibrillation or atrial flutter in 67 patients (15) showed a superior conversion rate with ibutilide. After administration of ibutilide, conversion to sinus rhythm occurred in 47% of patients with atrial flutter and 42% of patients with atrial fibrillation; in contrast, the conversion rate with procainamide was 0% and 9% for atrial flutter and atrial fibrillation, respectively. Intravenous procainamide was associated with a significant risk of hypotension, whereas ibutilide did not produce hypotension or ventricular proarrhythmia during or after infusion. Procainamide was administered at a rate of 50 mg/min up

Table 3. Trials of Antiarrhythmic Drugs for Rapid Termination of Atrial Fibrillation

First Author (ref no.)	Patients (no.)	Design	Efficacy	Duration of AF (days)	Incidence of Ventricular Proarrhythmia
Fenster (8)	26	Open label IV procainamide	58%	38 ± 68*	13%
Halpern (9)	21	Open label IV procainamide	43%†	6 ± 20	Not stated
Fujiki (11)	36	Open label IV procainamide	64%	≤72 h	Not stated
Madrid (10)	80	IV procainamide vs. IV flecainide	65% (procainamide) 92% (flecainide)	<24 h	0%
Stambler (15)	67	IV procainamide vs. IV ibutilide vs. IV placebo	9% (procainamide) 45% (ibutilide) 0% (placebo)	37 ± 37	0%
Volgman (16)	86	IV ibutilide vs IV procainamide	51% (ibutilide)——→ 20% (procainamide)——→	23 ± 26 19 ± 26	1.6% (ibutilide)
Ellenbogen (present study)	197	IV ibutilide vs. IV placebo	34% (ibutilide) 3% (placebo)	27 ± 29	3.6%
Crijns (12)	20	IV and oral flecainide	77%——→ 0%——→	<24 h >24 h	Not stated
Goy (13)	69	IV flecainide	79% <10 days 38% >10 days	49 ± 45	0%
Borgeat (14)	30	IV flecainide——→ (vs. oral quinidine)	86% (flecainide)→<10 days 22% (flecainide)→>10 days	95 ± 4	0%
Bianconi (17)	150	IV dofetilide vs. IV amiodarone vs. IV placebo	35% (dofetilide) 4% (amiodarone) 4% (placebo)	Not stated	8.3% (dofetilide)

*Mean duration 6 ± 7 days, for patients with arrhythmia conversion, 79 ± 88 days for patients without arrhythmia conversion. †All patients with arrhythmia conversion had atrial fibrillation for <24 h. AF = atrial fibrillation; IV = intravenous; ref = reference.

to a total dose of 12 to 15 mg/kg. Patients receiving ibutilide or procainamide did not differ significantly with respect to any clinical variable. The mean duration of atrial fibrillation/atrial flutter in that study was 37 ± 37 days; patients had a mean left atrial size of 4.3 ± 0.7 cm and an ejection fraction of 45 ± 11%. A preliminary report from a prospective randomized trial comparing the efficacy of intravenous ibutilide and intravenous procainamide in 86 patients with atrial fibrillation (16) also showed a superior rapid conversion rate with ibutilide. Patients were randomized to receive either up to 2 mg of ibutilide as three infusions or up to 1,200 mg of procainamide as three infusions. The arrhythmia conversion rate was 51% for ibutilide versus 20% for procainamide. Differing conversion rates among various studies (Table 3) reflect not only differing drug efficacy, but also variability in patient population, particularly due to differences in the duration of atrial fibrillation and the presence of structural heart disease.

Information on the efficacy of other intravenous agents (e.g., amiodarone and dofetilide) for termination of atrial flutter or atrial fibrillation is being collected in several ongoing clinical trials (17). The efficacy of intravenous sotalol and ibutilide for acute termination of atrial fibrillation and flutter is being compared in large prospective double-blind placebo-controlled trials currently underway.

Ibutilide. Ibutilide is a unique antiarrhythmic agent that is now currently undergoing clinical trials. It has minimal hemodynamic effects, and its major electrophysiologic effects lead to its characterization as a class III agent. It lengthens the effective refractory period in both the atrium and ventricle while having little effect on conduction in normal cardiac tissue. It prolongs the action potential duration and effective refractory periods in both the atria and the ventricles. It maintains class III effects on refractory period prolongation even at rapid paced rates. These electrophysiologic effects may be mediated by multiple cellular actions. Testing of ibutilide in animal models of atrial flutter and atrial fibrillation has demonstrated a high incidence (>90%) of successful reversion to sinus rhythm.

Currently, additional human studies are being conducted with ibutilide on the basis of these findings. Results of a repeated dose double-blind randomized placebo-controlled trial of a fixed 1-mg dose followed by 0.5 mg or a fixed 1-mg dose alone given to 242 patients demonstrated an arrhythmia conversion rate of up to 63% (18). This dosing regimen was derived on the basis of results of this dose-ranging study in which maximal efficacy was determined to be between 0.015 to 0.025 mg/kg. There did not appear to be a relation between the development of polymorphic ventricular tachycardia and dose in our trial. Furthermore, in these trials (15,18) the majority of patients had atrial arrhythmias of several weeks' duration.

The risk of polymorphic ventricular arrhythmias in our study was 3.6%. A recent preliminary study of intravenous dofetilide for the acute termination of atrial fibrillation and atrial flutter (17) reported an incidence of torsade de pointes of ~8%. Three recently reported studies assessing the risk of polymorphic ventricular tachycardia during *oral* quinidine loading (19–21) reported an incidence of polymorphic ventricular tachycardia of 9%, 12% and <25%, respectively. These studies underscore the relatively high risk of polymorphic

ventricular tachycardia in patients receiving antiarrhythmic agents for short- or long-term conversion to sinus rhythm.

Potential clinical role. Ibutilide is rapidly effective, well tolerated and is an option for rapid pharmacologic conversion of atrial fibrillation or atrial flutter. There are several clinical situations in which such an agent might be useful. These include patients presenting with atrial fibrillation or atrial flutter of brief duration, patients who are not candidates for short-term anticoagulation and patients who may need urgent restoration of sinus rhythm, as in the surgical postoperative period. The incidence of polymorphic ventricular tachycardia may be higher in the postoperative setting, where electrolyte shifts may be greater. Patients with infrequent episodes of atrial fibrillation, and patients not receiving long-term maintenance antiarrhythmic drug therapy who have recurrent episodes of atrial fibrillation can be treated with ibutilide. In such patients, rapid determination of response to pharmacologic therapy allows the clinician to expedite patient management. If the infusion does not cause conversion of the rhythm, direct current cardioversion can still be safely performed later. The use of ibutilide, like the initial use of any antiarrhythmic agent, requires cardiac monitoring. Physicians using ibutilide must be aware of the potential for sustained polymorphic ventricular tachycardia requiring electrical cardioversion. However, because the pharmacologic activity of ibutilide is short acting, long-term monitoring may not be required. Further ongoing studies comparing ibutilide with procainamide and sotalol will help determine its role in our clinical armamentarium.

Appendix

Study Sites and Principal Investigators

Karen J. Beckman, *University of Oklahoma Medical Center, Oklahoma City, Oklahoma*; John P. DiMarco, MD, PhD, *University of Virginia Medical Center, Charlottesville, Virginia*; Kenneth A. Ellenbogen, MD, *Medical College of Virginia and McGuire VA Medical Center, Richmond, Virginia*; Nancy C. Flowers, MD, *Medical College of Georgia and VA Medical Center, Augusta, Georgia*; Peter R. Kowey, MD, *The Lankenau Hospital, Wynnewood, Pennsylvania*; Marc D. Meissner, MD, *Allen Park VA Medical Center, Allen Park, Michigan*; Philip T. Sager, MD, *University of California at Los Angeles and Wadsworth VA Medical Center*; Robert C. Wesley, Jr., MD, *Long Beach VA Medical Center, Long Beach, California*; Robert G. Zobie, MD, PhD, *James A. Haley VA Medical Center, Tampa, Florida.*

References

1. Buchanan LV, Turcotte UM, Kabell GG, Gibson JK. Antiarrhythmic and electrophysiologic effects of ibutilide in a chronic canine model of atrial flutter. J Cardiovasc Pharmacol 1993;33:10–4.
2. Buchanan LV, Kabell G, Brunden MN, Gibson JK. Comparative assessment of ibutilide, D-sotalol, clofilium, E-4031, and UK-68,798 in a rabbit model of proarrhythmia. J Cardiovasc Pharmacol 1993;22:540–9.
3. Nabih MA, Prcevski P, Fromm BS, et al. Effect of ibutilide, a new class III agent, on sustained atrial fibrillation in a canine model of acute ischemia and myocardial dysfunction induced by microembolization. PACE 1993;16:1975–83.
4. Cimini MG, Brunden MN, Gibson JK. Effects of ibutilide fumarate, a novel antiarrhythmic agent, and its enantiomers on isolated rabbit myocardium. Eur J Pharmacol 1992;222:93–8.
5. Lee KS. Ibutilide, a new compound with potent class III antiarrhythmic activity, activates a slow inward Na current in guinea pig ventricular cells. J Pharmacol Exp Ther 1992;262:99–108.
6. Yang T, Snyders DJ, Roden DM. Ibutilide, a methanesulfonamilide antiarrhythmic, is a potent blocker of the rapidly-activating delayed rectifier K+ current (Ikr) in AT-1 cells: concentration, time-, voltage- and use-dependent effects. Circulation 1995;91:1799–806.
7. Lee KS, Tsai TD, Lee EW. Membrane activity of class III antiarrhythmic compounds; a comparison between ibutilide, d-sotalol, E-4031, sematilide and dofetilide. Eur J Pharmacol 1994;234:43–53.
8. Fenster PE, Comess KA, Marsh R, Katzenber C, Hager WD. Conversion of atrial fibrillation to sinus rhythm by acute intravenous procainamide infusion. Am Heart J 1983;106:501–4.
9. Halpern SW, Ellrodt G, Singh BN, Mandel WJ. Efficacy of intravenous procainamide infusion on converting atrial fibrillation to sinus rhythm. Br Heart J 1980;44:589–95.
10. Madrid AH, Moro C, Marin-Huerta E, Mestre JL, Novo L, Costa A. Comparison of flecainide and procainamide in cardioversion of atrial fibrillation. Eur Heart J 1993;14:1127–31.
11. Fujiki A, Yoshida S, Tani M, Inoue H. Efficacy of Class Ia antiarrhythmic drugs in converting atrial fibrillation unassociated with organic heart disease and their relation to atrial electrophysiologic characteristics. Am J Cardiol 1994;74:282–3.
12. Crijns HJG, Van Wijk LM, Van Gilst WH, Kingma JH, Van Gelder K, Lie K. Acute conversion of atrial fibrillation in sinus rhythm: clinical efficacy of flecainide acetate. Comparison of two regimens. Eur Heart J 1988;9:634–8.
13. Goy JJ, Kaufmann U, Kappenberger L, Sigwart U. Restoration of sinus rhythm with flecainide in patients with atrial fibrillation. Am J Cardiol 1988;62:38D–40D.
14. Borgeat A, Goy J-J, Maendly R, Kaufmann U, Grbic M, Sigwart U. Flecainide versus quinidine for conversion of atrial fibrillation to sinus rhythm. Am J Cardiol 1986;58:496–8.
15. Stambler BS, Wood MA, Belz MK, Sperry RE, VanderLugt JT, Ellenbogen KA. Electrophysiologic determinants of pharmacologic conversion of human atrial fibrillation and flutter: enhanced efficacy of ibutilide, a new class III antiarrhythmic drug [abstract]. Circulation 1993;88(Pt 2):I-445.
16. Volgman AS, Stambler BS, Kappagoda C, et al. Comparison of intravenous ibutilide versus procainamide for the rapid termination of atrial fibrillation or flutter [abstract] PACE 1996;19(Pt II):608.
17. Bianconi L, Dinelli M, Pappalardo A, et al. Comparison of intravenously-administered dofetilide versus amiodarone in the acute termination of atrial fibrillation and flutter. A multicenter, randomized, double-blind, placebo-controlled study. Circulation 1995;92 Suppl I:I-774.
18. Stambler BS, Portnow AS, Wood MA, et al. Proven efficacy of repeated dose intravenous ibutilide, a class III antiarrhythmic drug, for rapid termination of chronic atrial flutter or fibrillation: results of a multicenter placebo-controlled study. J Am Coll Cardiol 1995;25:230A.
19. Daoud EG, Niebauer MJ, Man KC, Strickberger SA, Kou W, Morady F. Prospective assessment of quinidine-induced QT prolongation and proarrhythmia in hospitalized patients. J Am Coll Cardiol 1995;25:220A.
20. Halinen MO, Huttunen M, Paakkinen S, Tarssanen L. Comparison of sotalol with digoxin-quinidine for conversion of acute atrial fibrillation to sinus rhythm. (The sotalol-digoxin-quinidine trial). Am J Cardiol 1995;76:495–8.
21. Hohnloser SH, Van De Loo A, Baedeker F. Efficacy and proarrhythmic hazards of pharmacologic cardioversion of atrial fibrillation: prospective comparison of sotalol versus quinidine. J Am Coll Cardiol 1995;26:852–8.