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Conversion Efficacy and Safety of Intravenous Ibutilide Compared With Intravenous Procainamide in Patients With Atrial Flutter or Fibrillation

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Objectives. **This multicenter study compared the efficacy and safety of ibutilide versus procainamide for conversion of recent-onset atrial flutter or fibrillation.**

Background. **Ibutilide fumarate is an intravenous (IV) class III antiarrhythmic agent that has been shown to be significantly more effective than placebo in the pharmacologic conversion of atrial flutter and fibrillation to sinus rhythm. Procainamide is commonly used for conversion of recent-onset atrial fibrillation to normal sinus rhythm.**

Methods. **One hundred twenty-seven patients (age range 22 to 92 years) with atrial flutter or fibrillation of 3 h to 90 days' (mean 21 days) duration were randomized to receive either two 10-min IV infusions of 1 mg of ibutilide fumarate, separated by a 10-min infusion of 5% dextrose in sterile water, or three successive 10-min IV infusions of 400 mg of procainamide hydrochloride.**

Results. **Of the 127 patients, 120 were evaluated for efficacy: 35 (58.3%) of 60 in the ibutilide group compared with 11 (18.3%) of 60 in the procainamide group had successful termination within 1.5 h of treatment ($p < 0.0001$). Seven patients were found to have violated the protocol and were not included in the final evaluation. In the patients with atrial flutter, ibutilide had a significantly higher success rate than procainamide (76% [13 of 17] vs. 14% [3 of 22], $p = 0.001$). Similarly, in the atrial fibrillation group, ibutilide had a significantly higher success rate than procainamide (51% [22 of 43] vs. 21% [8 of 38], $p = 0.005$). One patient who received ibutilide, which was found to be a protocol violation, had sustained polymorphic ventricular tachycardia requiring direct current cardioversion. Seven patients who received procainamide became hypotensive.**

Conclusions. **This study establishes the superior efficacy of ibutilide over procainamide when administered to patients to convert either atrial fibrillation or atrial flutter to sinus rhythm. Hypotension was the major adverse effect seen with procainamide. A low incidence of serious proarrhythmia was seen with the administration of ibutilide occurring at the end of infusion.**

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Ibutilide fumarate is a selective intravenous (IV) class III antiarrhythmic agent recently approved for the treatment of atrial fibrillation and flutter. Previous studies with ibutilide showed that it is significantly more effective than placebo in the pharmacologic conversion of atrial flutter and fibrillation to sinus rhythm (1,2). Ventricular proarrhythmia, a concern with any antiarrhythmic agent, may occur during the use of ibutilide (3,4).

Procainamide has not been approved in the United States for use in atrial fibrillation or flutter; however, its use has been found to be safe and effective in converting recent-onset atrial fibrillation to normal sinus rhythm after IV doses ranging from 300 to 1,200 mg (5–7). The purpose of this study was to compare the safety and efficacy of intravenous ibutilide fumarate with intravenous procainamide for the termination of recent-onset atrial flutter or fibrillation.

Methods

This multicenter study used a double-blind, randomized, parallel-group, active-control, repeated-dose design in which patients were stratified according to presenting arrhythmia (atrial flutter or fibrillation) and duration of arrhythmia (24 h or >24 h). Patients were randomized to receive either ibutilide or procainamide. Patients in the ibutilide group received up to two 10-min IV infusions of 1 mg of ibutilide, separated by a 10-min infusion of 5% dextrose in sterile water. Patients in the procainamide group received up to three 10-min IV infusions

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Abbreviations and Acronyms

AV = atrioventricular
IV = intravenous
ECG = electrocardiogram, electrocardiographic
QTc = corrected QT interval

of 400 mg of procainamide. The infusion was discontinued at the time of arrhythmia termination or an adverse event.

Patients. Patients enrolled were >18 years of age, had body weights >132 lb and <300 lb and had no previous exposure to ibutilide. Enrollment into the study was limited to six men for every four women enrolled at each site, with the exception of participating Veterans Affairs Medical Centers. Female patients were surgically sterile or postmenopausal. All patients had sustained atrial flutter or fibrillation persisting for at least 3 h and <90 days. If atrial fibrillation was present for >3 days, patients received the appropriate anticoagulation therapy before receiving study medication, unless transesophageal echocardiography confirmed that no atrial clot was present. Patients considered for entry had corrected QT intervals (QTc) ≤440 ms on a 12-lead electrocardiogram (ECG), were hemodynamically stable (ventricular heart rate ≥60 beats/min, systolic blood pressure ≥90 mm Hg, diastolic blood pressure ≥60 mm Hg) and were without symptoms of unstable angina or congestive heart failure. There were no specific inclusion or exclusion criteria for patients who may have recently had coronary artery bypass graft procedures. All patients were required to have had serum sodium and magnesium levels within the normal range, serum potassium levels ≥4.0 mEq/liter, liver function tests <2 times the upper limit of normal values and serum creatinine levels ≤2.0 mg/ml. Patients were excluded if they had histories of myocardial infarction within the previous 30 days, torsade de pointes, second- or third-degree heart block, congestive heart failure (New York Heart Association class III or higher) or any serious medical condition that could interfere with the conduct or interpretation of the study results. Human subjects' approval was obtained by each site, and written informed consent was obtained from each patient. On enrollment, a patient was randomized into one of the two treatment groups.

Concurrent participation in another drug study or receipt of an investigational drug within 30 days of the infusion was not permitted. Atrioventricular (AV) node blockers, including calcium-channel blockers, beta-blockers and digoxin, were permitted for rate control. Class I or III antiarrhythmic medications were discontinued at least five half-lives before infusion of the study medication. Patients taking amiodarone were excluded. Administration of additional antiarrhythmic medication was delayed until 6 h after the end of the infusions if the arrhythmia was not successfully terminated by the study medication or if a malignant ventricular arrhythmia developed. If the arrhythmia was terminated successfully by the study medication, additional antiarrhythmic medication was delayed until at least 24 h after the start of infusion. Other noninvestigational medications were limited to those essential to the patient's care.

The infusion was terminated on conversion of the arrhythmia. It was also terminated if there was any change in rhythm or AV conduction that was not hemodynamically tolerated or, in the opinion of the investigator, that was threatening (or potentially threatening) the patient's safety. Such changes included new bundle branch block, >50% increase in QRS duration, QTc interval >600 ms, a new or repetitive form of ventricular premature depolarization or hypotension (a decrease in systolic blood pressure >20 mm Hg or to a level <80 mm Hg). Intravenous fluids could be administered to increase the blood pressure.

Study procedures. The baseline period was defined as the 10 min before the beginning of the first infusion (−10 to 0 min). Data collected during the baseline period included laboratory evaluations, blood pressure and heart rate, a 12-lead ECG and continuous ECG monitoring beginning at −10 minutes. Patients in atrial flutter or fibrillation at the end of the baseline period proceeded to the treatment phase of the protocol. The infusion period lasted from the beginning of the first infusion (0 min) to the end of the third infusion (30 min). During the infusion period, blood pressure and heart rate were recorded every 5 min, and the patient's rhythm was continuously monitored. A 12-lead ECG was obtained at 30 min and at the time of conversion or on development of a significant rhythm change. The study medication was infused according to schedule until atrial flutter or fibrillation was converted or a medical event occurred that necessitated termination of treatment. Pacing or direct current cardioversion was permitted if the patient experienced a significant adverse rhythm change, remained in atrial flutter or fibrillation past 90 min or reverted to atrial flutter or fibrillation after initial successful conversion.

The postinfusion period lasted from the end of the infusion period (30 min) to 24 h. A 12-lead ECG was obtained at the time of arrhythmia conversion, on the appearance of a significant rhythm change during the 1-h period after the infusions, at 90 min for patients whose arrhythmia had not yet terminated and on the appearance of a significant adverse rhythm change occurring from 90 min through 24 h. One-lead ECG monitoring was continued for 24 h. Vital signs were recorded at 35 and 40 min and at 1, 1.5, 2, 4, 6, 8, 16 and 24 h after the start of the first infusion. Blood and urine specimens for laboratory assays were obtained at 24 h.

Safety evaluations. Safety of the study infusions was evaluated by calculating the mean change from baseline for systolic and diastolic blood pressures and pulse rate, plus any significant changes from baseline in the 12-lead ECG. Adverse medical events and their relation to the study drug were noted or volunteered by the patients during the 72 h after infusion, and events were graded as mild, moderate or severe per the patient. Patients who left the hospital were contacted by telephone to obtain follow-up information through 72 h. All adverse events were followed until they resolved. A serious medical event was defined as that requiring hospital admission

or prolonging the hospital stay, requiring intervention to prevent permanent incapacity or damage, producing significant disability, immediately threatening the patient's life or resulting in death.

Statistical methods. Comparability of treatment groups with respect to age, height, weight and duration of arrhythmia was assessed using the Scheffé F test derived from one-way analysis of variance. Gender and history of cardiovascular disease were examined for comparability of treatment groups, using the chi-square test for two-way contingency tables. In addition, efficacy—the proportion of patients converting—was compared using the chi-square test for two-way contingency tables. The efficacy analyses were conducted for patients with atrial flutter and fibrillation (as determined by baseline ECGs) both separately and combined.

For pulse rate and systolic and diastolic blood pressure, assessment of the significance of the mean change from baseline to each follow-up reading was made within treatment groups using paired *t* tests. Comparisons between treatment groups were made using the mean change from baseline and the Scheffé *F* test derived from the usual one-way analysis of variance fixed-effects model. The proportion of medical events was assessed using the chi-square test for two-way contingency tables. Statistical findings were deemed significant at $p \leq 0.05$.

Results

Comparability of treatment groups. The study enrolled 127 patients, but only 120 were evaluated for efficacy. All patients were evaluated for safety of the drugs. Seven patients were found to have violated the protocol and were not included in the final evaluation. There were 60 patients in each group whose data were evaluated. There were fewer patients with atrial flutter (33%) than with atrial fibrillation (67%), and the two drug groups were comparable in this regard. The two groups were also comparable with respect to age, height, weight, gender and cardiovascular disease history, as well as duration of arrhythmias (Table 1). A broad spectrum of other cardiovascular medications was in use in the 7 days before infusion, and the two treatment groups were comparable in this regard, as well.

Conversion rates. Conversion rates of atrial fibrillation or flutter were higher in the ibutilide group (58%) than in the procainamide group (18%) ($p < 0.0001$); this was true for both atrial flutter (76% vs. 14%, $p = 0.0001$) and atrial fibrillation (51% vs. 21%, $p = 0.005$) (Fig. 1). Patients who converted did so in a mean of 31.2 min with ibutilide and 34.4 min with procainamide. The analysis of variance for successes versus failures indicated no differences in prolongation of the QTc interval at 90 min between successes and failures in the ibutilide group or the procainamide group.

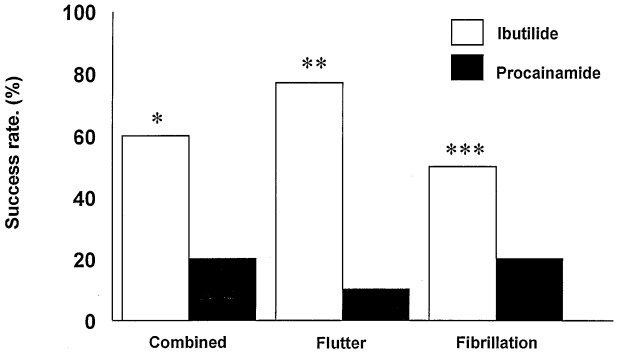
Safety evaluations. Adverse events were generally more common in the procainamide-treated group (46.2%) than in the ibutilide-treated group (29.0%, $p = 0.047$). Headache (10.8%), hypotension (10.8%), flushing (3.1%), dizziness (3.1%) and hypesthesia (3.1%) occurred in the procainamide group but not in the ibutilide group. Extrasystole (4.8%) occurred in the ibutilide group but not in the procainamide group. Figure 2 illustrates the mean change in blood pressure and pulse rate for all patients receiving either ibutilide or procainamide. In the procainamide-treated group, there was a statistically significant decrease from baseline in mean systolic and mean diastolic blood pressure beginning at the start of infusion and lasting through 24 h, except for mean diastolic blood pressure at 1.5 and 2 h; this was not evident in the ibutilide-treated group, except at 4, 6 and 16 h for mean systolic blood pressure and 2 through 24 h for mean diastolic blood pressure. The decrease in mean systolic and mean diastolic pressure seen in the procainamide group corresponded in time to the period of infusion of procainamide. Blood pressure began to drop immediately after administration, and a maximal decrease in mean systolic blood pressure was noted at 30 and 35 min. This differed from the ibutilide

Table 1. Patient Characteristics*

Characteristics	Ibutilide Group (n = 60)	Procainamide Group (n = 60)
Age (years)	64.3	67.7
Height (in.)	68.6	67.9
Weight (lb)	197.1	189.0
Gender (%)		
Male	75.0	70.0
Female	25.0	30.0
Cardiovascular history		
Coronary artery disease	38.3	53.3
Myocardial disease	18.3	15.0
Valvular disease	23.3	25.0
Arrhythmia	65.0	58.3
Other (hypertension, hypercholesterolemia and peripheral vascular disease)	66.1	60.0
Duration of arrhythmia (days)	22.3 ± 24.7	17.0 ± 23.0
Median	9.4	4.6
Range	0.2–84.5	0.2–89.5

*p = NS for all comparisons. Data presented are mean value ±SD, unless otherwise indicated.

Figure 1. Rate of successful conversion of atrial fibrillation and flutter in the ibutilide and procainamide groups. *$p < 0.0001$. **$p = 0.0001$. ***$p = 0.005$.



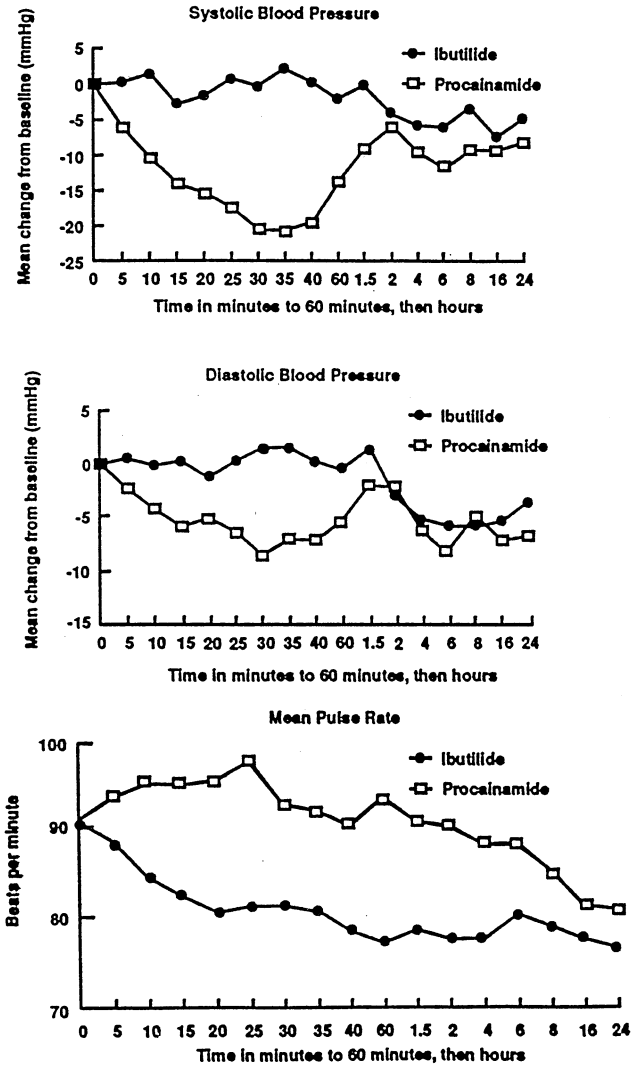


Figure 2. Mean change from baseline in systolic and diastolic blood pressure and in pulse rate in ibutilide- and procainamide-treated patients.

group, whose mean blood pressure remained steady through 1.5 h. There was a statistically significant difference between the treatment groups in both mean systolic and mean diastolic blood pressure until 1.5 h. Severe hypotension occurred in seven patients treated with procainamide, with decreases in diastolic blood pressure up to 67 mm Hg, and three patients necessitated discontinuation of infusion. In six of seven patients, the hypotension was classified by investigators as being moderate or severe in intensity. Intervention with IV fluids or dopamine, or both, was necessary for three patients, and in one patient, blood pressure was unrecordable until after IV fluid replacement. All but one of these events occurred during or immediately after the infusion of procainamide. There was a steady and statistically significant decrease in mean heart rate in the ibutilide group through 24 h, whereas there was a statistically significant increase in mean heart rate in the procainamide group at 25 min, and then a statistically significant decrease from 6 through 24 h. Although there was a statistically significant difference in mean heart rate between the treatment groups throughout the 24-h period, the magnitude of change within each group or between groups was not clinically significant.

Three patients discontinued ibutilide because of adverse events (one each for extrasystole, nonsustained monomorphic ventricular tachycardia and QT interval prolongation). Four patients discontinued procainamide for medical events (three for hypotension [i.e., a decrease in systolic blood pressure >20 mm Hg or to a level <80 mm Hg] and one catheter site reaction). Three medical events in the ibutilide group were reported as serious. One patient developed sustained polymorphic ventricular tachycardia after 30 min of ibutilide infusion. Electrical cardioversion was successful with a single application of 200 J, and the patient alternated between atrial fibrillation and normal sinus rhythm for the remainder of the 24-h observation period. It was determined that the patient was in violation of the protocol, because the patient's predose serum magnesium level was 1.7 mg/dl and potassium level 3.8 mEq/liter, and the patient is therefore not included in the group that was evaluable.

There were two other serious medical events: presyncope in an 80-year old patient who felt presyncopal while standing at 23 h. He was in normal sinus rhythm with no orthostatic changes. The patient never lost consciousness. This patient had a history of hypertension, hypercholesterolemia, peripheral vascular disease with angioplasty of the left iliac artery and pacemaker placement in 1991 for bradycardia. These underlying conditions are all risk factors for presyncope. The investigator reporting the medical event did not believe the event was related to exposure to ibutilide. Another patient who had a history of multiple infarct dementia experienced acute delirium at 8 h. The patient required sedation and safety restraints. The patient had multiple sclerosis. The event was regarded by the investigator as unrelated to exposure to ibutilide. Both patients required prolongation of their hospital stay.

Discussion

This comparison study of intravenous ibutilide versus procainamide establishes that ibutilide is significantly more effective than procainamide (58% vs. 18%) in the acute conversion of patients with atrial fibrillation and atrial flutter of up to 90 days' duration. Although the number of patients with atrial flutter was small, ibutilide was superior to procainamide in converting this rhythm (76% vs. 14%). For the larger number of patients with atrial fibrillation, ibutilide was also more effective than procainamide (51% vs. 21%). A low incidence of major proarrhythmia was the main adverse event seen with administration of ibutilide, whereas hypotension was caused by infusion of intravenous procainamide.

Previous studies. Previous studies using ibutilide to convert atrial fibrillation have shown that ibutilide was effective in the rapid conversion of new-onset atrial fibrillation with a duration up to 37 days (1,2).

Previous studies using procainamide for the rapid termination of atrial fibrillation demonstrated that IV procainamide was highly effective (5–7). However, these studies had small numbers of subjects and were largely uncontrolled, using patients with atrial fibrillation of short duration, in some cases <24 h. An extensive review of these studies, recently summarized by Ellenbogen et al. (1) showed that procainamide was much more successful if the duration of the atrial fibrillation was <7 days, especially <24 h. The success of conversion was markedly lower in patients with atrial fibrillation lasting >10 days.

In the present study, the mean durations of atrial fibrillation and atrial flutter were 22 days for the ibutilide group and 17 days for the procainamide group. This longer duration of arrhythmia may account for the lower efficacy of procainamide in this study compared with the efficacy previously reported in the published data.

Although other class III antiarrhythmic agents act on potassium channels, ibutilide delays repolarization by the activation of a slow, inward, predominantly sodium current that increases the duration of the action potential. Furthermore, in animal studies, ibutilide has been shown to prolong not only action potential duration, but also the atrial effective refractory period. In these studies, ibutilide was found to be significantly more potent than sotalol and encainide (8–14).

Procainamide, when administered by the oral route, affects two phases of the cardiac action potential, because the metabolite produced by hepatic metabolism, *N*-acetylprocainamide, has class III effects. Thus, when given by this route, procainamide blocks both fast sodium channels and transient outward potassium channels. However, when given intravenously, procainamide acts mostly on conduction velocity, not on the refractory period, and this was evidenced by the lack of QT prolongation in patients who received procainamide in this study.

As such, prolongation of the effective refractory period would seem to be a determining factor in the increased efficacy of ibutilide over procainamide seen in this study.

Clinical significance. The current anticoagulation guidelines recommend a minimum of 3 weeks of anticoagulation in patients with atrial fibrillation lasting 48 h (15). This anticoagulation period prolongs the duration in which the patient is in atrial fibrillation. In patients in whom pharmacologic conversion is chosen over electrical cardioversion as an initial therapy, ibutilide may be a better alternative than procainamide because it is more effective in atrial fibrillation of both short and longer duration, as demonstrated in this study, whereas IV procainamide has been shown to have efficacy only in atrial fibrillation of very short duration.

Adverse effects. There were no deaths in the study and only three serious medical events. Medical events such as ventricular extrasystoles, QT prolongation and polymorphic ventricular tachycardia have all been observed to occur with the administration of ibutilide in previous studies (1–3). In the present study, proarrhythmia was also seen with the administration of ibutilide. The major proarrhythmic effect of ibutilide was observed within 30 min of the start of infusion of ibutilide. It was found that the one patient who developed sustained polymorphic ventricular tachycardia had lower than acceptable levels of potassium and magnesium. Although IV procainamide did not cause proarrhythmia, its hypotensive effects may limit its use in certain patients.

The lower incidence of proarrhythmia in this study compared with the dose-response study (1) may be due to stricter inclusion and exclusion criteria than in previous studies using ibutilide. In the dose-response study of ibutilide, all the patients who had proarrhythmia had decreased left ventricular function, one with class III congestive heart failure (1). This comparison study did not specifically address ventricular function by echocardiography, and therefore no conclusion can be made regarding the effects of left ventricular dysfunction on the adverse effects found in this study. The occurrence of one episode (1.6%) of sustained polymorphic ventricular tachycardia is comparable with the overall incidence of 1.7% (10 of 586 patients) observed in a pooled sample of ibutilide-treated patients from previous studies (4).

Conclusions. This study establishes the superior efficacy of ibutilide over procainamide when administered to patients to convert either atrial fibrillation or flutter. Hypotension was the major adverse effect seen with procainamide. A low incidence of serious proarrhythmia was seen with the administration of ibutilide occurring at the end of infusion.

Appendix

Investigators and Study Sites

Ochsner Clinic, New Orleans, Louisiana: Freddy Abi-Samra, MD; **University of Rochester Medical Center, Rochester, New York**: Toshio Akiyama, MD; **McGuire Veterans Medical Center, Richmond, Virginia**: Kenneth Ellenbogen, MD; **Highline Community Hospital, Seattle, Washington**: Bert Green, MD; **Hahnemann University Hospital, Philadelphia, Pennsylvania**: Scott Hessen, MD; **University of California at Davis Medical Center, Sacramento, California**: William R. Lewis, MD; **Lankenau Hospital, Wynnewood, Pennsylvania**: Peter Kowey, MD; **Shelby Medical Center, Birmingham, Alabama**: Michael McKinney, MD; **Loyola University Medical Center, Maywood, Illinois**: Brian Olshansky, MD; **Providence Medical Center, Portland, Oregon**: Ronald Petersen, MD; **Memphis Veteran's Medical Center, Memphis, Tennessee**: John Riddle, MD; **Louisiana State University Medical Center, New Orleans, Louisiana**: Gary Sander, MD; **McGuire Veterans Medical Center, Richmond, Virginia**: Bruce Stambler, MD; **Northwest Hospital, Seattle, Washington**: Fredric Tobis, MD; **Rush–Presbyterian–St. Luke's Medical Center, Chicago, Illinois**: Annabelle Volgman, MD; **Borgess Hospital, Kalamazoo, Michigan**: Lawrence Weston, MD

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