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## FACILITATING TRANSTHORACIC CARIOVERSION OF ATRIAL FIBRILLATION WITH IBUTILIDE PRETREATMENT

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### ABSTRACT

**Background** Atrial fibrillation cannot always be converted to sinus rhythm by transthoracic electrical cardioversion. We examined the effect of ibutilide, a class III antiarrhythmic agent, on the energy requirement for atrial defibrillation and assessed the value of this agent in facilitating cardioversion in patients with atrial fibrillation that is resistant to conventional transthoracic cardioversion.

**Methods** One hundred patients who had had atrial fibrillation for a mean ( $\pm$ SD) of  $117 \pm 201$  days were randomly assigned to undergo transthoracic cardioversion with or without pretreatment with 1 mg of ibutilide. We designed a step-up protocol in which shocks at 50, 100, 200, 300, and 360 J were used for transthoracic cardioversion. If transthoracic cardioversion was unsuccessful in a patient who had not received ibutilide pretreatment, ibutilide was administered and transthoracic cardioversion attempted again.

**Results** Conversion to sinus rhythm occurred in 36 of 50 patients who had not received ibutilide (72 percent) and in all 50 patients who had received ibutilide (100 percent,  $P < 0.001$ ). In all 14 patients in whom transthoracic cardioversion alone failed, sinus rhythm was restored when cardioversion was attempted again after the administration of ibutilide. Pretreatment with ibutilide was associated with a reduction in the mean energy required for defibrillation ( $166 \pm 80$  J, as compared with  $228 \pm 93$  J without pretreatment;  $P < 0.001$ ). Sustained polymorphic ventricular tachycardia occurred in 2 of the 64 patients who received ibutilide (3 percent), both of whom had an ejection fraction of 0.20 or less. The rates of freedom from atrial fibrillation after six months of follow-up were similar in the two randomized groups.

**Conclusions** The efficacy of transthoracic cardioversion for converting atrial fibrillation to sinus rhythm was enhanced by pretreatment with ibutilide. However, use of this drug should be avoided in patients with very low ejection fractions. (N Engl J Med 1999; 340:1849-54.)

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**I**BUTILIDE is a class III antiarrhythmic agent that is used for the conversion of atrial fibrillation to sinus rhythm.<sup>1-6</sup> Ibutilide lowers the energy requirement for ventricular defibrillation, but its effect on the energy required for atrial defibrillation has not been determined.<sup>7-9</sup> We examined the effect of ibutilide on the energy requirement for atrial defibrillation and assessed whether this agent facilitates transthoracic cardioversion of atrial fibrillation that is resistant to conventional transthoracic cardioversion.

### METHODS

#### Patients

Between August 1997 and December 1998, we enrolled 100 consecutive patients referred for cardioversion for an episode of atrial fibrillation that had lasted more than six hours (mean [ $\pm$ SD] duration,  $117 \pm 201$  days). Patients were excluded if they were less than 18 years old; were pregnant; had inadequate anticoagulation, in those in whom atrial fibrillation had been present for more than 48 hours; had a corrected QT interval of more than 480 msec, unless QT prolongation was attributable to amiodarone; or were unable or unwilling to provide informed consent. Early in the course of the study, polymorphic ventricular tachycardia occurred during or after the infusion of ibutilide in two patients, each of whom had a left ventricular ejection fraction of 0.20 or less; thereafter, patients with a left ventricular ejection fraction of less than 0.30 were excluded.

Fifty patients were randomly assigned to undergo transthoracic electrical cardioversion without ibutilide pretreatment, and the other 50 were randomly assigned to undergo transthoracic cardioversion with ibutilide pretreatment. The age, sex, body weight, presence of underlying heart disease, duration of atrial fibrillation, concomitant use of antiarrhythmic drugs, left atrial size, and left ventricular ejection fraction in both groups of patients are given in Table 1. There were no significant differences between

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**TABLE 1.** CHARACTERISTICS OF 100 PATIENTS RANDOMLY ASSIGNED TO UNDERGO TRANSTHORACIC CARIOVERSION WITH OR WITHOUT IBUTILIDE PRETREATMENT.\*

CHARACTERISTIC	IBUTILIDE PRETREATMENT (N=50)	NO IBUTILIDE PRETREATMENT (N=50)
Age — yr	64±15	64±11
Sex — M/F	33/17	40/10
Weight — kg	85±21	92±17
Heart disease — no. (%)		
Ischemia	12 (24)	11 (22)
Valvular disease	13 (26)	13 (26)
Nonischemic cardiomyopathy	6 (12)	5 (10)
Hypertension	10 (20)	12 (24)
None	9 (18)	9 (18)
Duration of atrial fibrillation — days	102±165	132±232
Duration of atrial fibrillation — no. (%)		
6 to 24 hr	3 (6)	1 (2)
>1 day to 1 wk	7 (14)	6 (12)
>1 wk to 3 mo	20 (40)	22 (44)
≥3 mo	20 (40)	21 (42)
Concurrent drug therapy — no. (%)†		
Beta-blocker	16 (32)	20 (40)
Calcium-channel blocker	13 (26)	17 (34)
Digoxin	13 (26)	13 (26)
Amiodarone	17 (34)	24 (48)
Sotalol	3 (6)	3 (6)
Class I agent	4 (8)	5 (10)
Size of left atrium — mm	48±10	46±6
Left ventricular ejection fraction	0.48±0.09	0.46±0.09

\*Plus-minus values are means ±SD.

†Some patients were receiving more than one type of concurrent therapy.

the two groups with regard to these variables. Of the 100 patients, 14 had been referred to our institution for internal cardioversion after transthoracic cardioversion at another hospital had failed.

### Protocol

The study protocol was approved by the institutional review board at the University of Michigan Medical Center, and all subjects provided written informed consent. For each patient, a history was obtained and physical examination, electrocardiography, and transthoracic echocardiography were performed. QT intervals were corrected for heart rate by applying Bazett's formula.<sup>10</sup> If atrial fibrillation had been present for more than 48 hours, cardioversion was preceded either by transesophageal echocardiography to rule out the possibility of intracardiac thrombi or by therapeutic anticoagulation with warfarin (to obtain an international normalized ratio of 2 to 3) for at least three weeks.

Adhesive 12-cm patch electrodes (model HP M1749A, Hewlett-Packard, Andover, Mass.) were applied to the cardiac apex and the right infraclavicular area and then connected to a conventional defibrillator that delivered direct-current shocks with a Lown-type, damped sinusoidal wave form (Codemaster XL, Hewlett-Packard). In patients who were randomly assigned to pretreatment with ibutilide, 1 mg of ibutilide (Corvert, Pharmacia & Upjohn, Kalamazoo, Mich.) was infused over a 10-minute period. If atrial fibrillation was still present after 10 minutes, midazolam hydrochloride and fentanyl citrate were administered for sedation and transthoracic cardioversion was performed. The same step-up protocol of 50, 100, 200, 300, and 360 J for cardioversion was used in all patients. For the purposes of this study, successful cardioversion was defined as the presence of sinus

rhythm after the delivery of a shock, even if the sinus rhythm was short-lived. If cardioversion was not successful in a patient who had not received ibutilide pretreatment, ibutilide was administered and transthoracic cardioversion was attempted again. An electrocardiogram was obtained after the completion of the protocol, and patients who had received ibutilide underwent continuous electrocardiographic monitoring for three to four hours.

### Follow-up

Patients who were being treated with an antiarrhythmic drug at the time of cardioversion continued the drug regimen after the restoration of sinus rhythm. Anticoagulant therapy was maintained for one month after cardioversion in patients in whom atrial fibrillation had been present for more than 48 hours. Patients were seen for follow-up examinations 1, 3, 6, and 12 months after cardioversion. The mean duration of follow-up was 218±110 days. No patients were lost to follow-up.

### Statistical Analysis

Continuous variables are expressed as means ±SD and were compared with the use of Student's t-test. Categorical variables were compared with the use of chi-square analysis or Fisher's exact test. The chi-square test for trend was used to compare energy requirements for atrial defibrillation. A Kaplan-Meier analysis with the log-rank test was used to compare the probability of freedom from recurrent atrial fibrillation. The end point for this analysis was a recurrence of atrial fibrillation, assessed on the basis of either the patient's self-report or, if the patient was asymptomatic, a documented episode. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

### Restoration of Sinus Rhythm before Crossover

Of the 50 patients randomly assigned to undergo transthoracic cardioversion without ibutilide pretreatment, cardioversion was successful in 36 (72 percent). Of the 50 patients who were given ibutilide initially, 10 (20 percent) had restoration of sinus rhythm after receiving ibutilide, and in all 40 remaining patients (80 percent) sinus rhythm was restored by subsequent transthoracic cardioversion. The efficacy of transthoracic cardioversion was therefore significantly higher with ibutilide pretreatment than without it (100 percent vs. 72 percent,  $P<0.001$ ).

### Energy Requirement for Atrial Defibrillation

The mean energy required for atrial defibrillation was significantly greater in patients who did not receive ibutilide pretreatment than in patients who received ibutilide ( $228±93$  vs.  $166±80$  J,  $P<0.001$ ). Concomitant therapy with antiarrhythmic drugs was not associated in either group of patients with the amount of energy required for defibrillation.

### Restoration of Sinus Rhythm after Crossover

Atrial fibrillation persisted in 14 of the 50 patients who underwent transthoracic cardioversion without having first received ibutilide. These patients then received 1 mg of ibutilide intravenously. In none of these 14 patients was sinus rhythm restored by the administration of ibutilide alone. Each of these patients then underwent successful transthoracic car-

dioversion to sinus rhythm with the application of a mean of  $238 \pm 87$  J.

#### Variables Associated with Successful Cardioversion

Among the 50 patients who did not receive ibutilide pretreatment, the 36 patients in whom cardioversion was successful and the 14 in whom it failed did not differ significantly in terms of age, weight, duration of atrial fibrillation, presence of structural heart disease, concomitant drug therapy, left atrial size, or left ventricular ejection fraction (Table 1).

Among the 50 patients who did receive pretreatment with ibutilide, there was a trend toward a shorter duration of atrial fibrillation in those in whom sinus rhythm was restored with ibutilide alone than in those in whom it was not ( $24 \pm 43$  vs.  $122 \pm 179$  days,  $P=0.09$ ). There were no significant differences between these two subgroups of patients with regard to age, weight, presence of structural heart disease, concomitant drug therapy, left atrial size, or left ventricular ejection fraction.

#### Complications

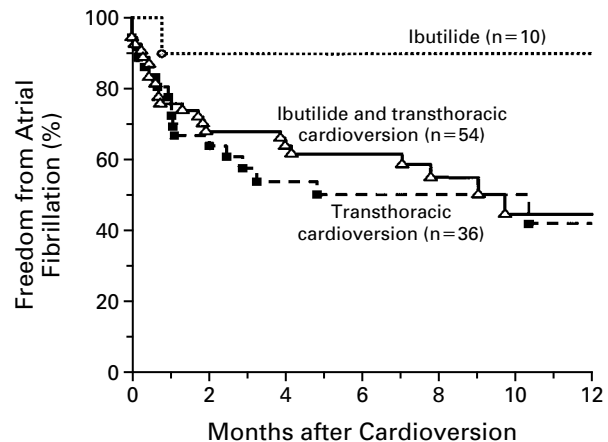
In 2 of the 64 patients who received ibutilide (3 percent), sustained polymorphic ventricular tachycardia developed and required transthoracic cardioversion. These episodes of ventricular tachycardia occurred within 15 minutes after the infusion of ibutilide. One of the two patients also had an episode of ventricular tachycardia, again requiring transthoracic cardioversion, 30 minutes after the completion of the infusion. The left ventricular ejection fractions in these two patients were 0.10 and 0.20. One of them was being treated with digoxin, and the other was not receiving any antiarrhythmic drugs. A third patient had a single episode of unsustained polymorphic ventricular tachycardia 10 minutes after the completion of the ibutilide infusion. No other patients had complications associated with the ibutilide infusion or transthoracic cardioversion.

#### Effect of Ibutilide on the QT Interval

In the group of 50 patients who did not receive ibutilide pretreatment, the mean corrected QT intervals measured before cardioversion did not differ significantly from those measured afterward ( $440 \pm 28$  vs.  $451 \pm 46$  msec,  $P=0.28$ ). In the group that did receive ibutilide pretreatment, the mean corrected QT interval after cardioversion was significantly longer than that before cardioversion ( $482 \pm 49$  vs.  $432 \pm 37$  msec,  $P<0.001$ ).

#### Freedom from Recurrent Atrial Fibrillation

By Kaplan–Meier analysis, 57 percent of the patients who were randomly assigned to undergo transthoracic cardioversion without first receiving ibutilide were free of recurrent atrial fibrillation at the six-month follow-up examination, as compared with



**Figure 1.** Kaplan–Meier Analysis of the Percentage of Patients Remaining Free of Recurrent Atrial Fibrillation after the Restoration of Sinus Rhythm with Ibutilide, Transthoracic Cardioversion Alone, or Transthoracic Cardioversion with Ibutilide Pretreatment.

There were no significant differences among the three groups ( $P=0.13$  by the log-rank test). The number of patients in each treatment group is shown in parentheses.

64 percent of the patients who were randomly assigned to receive pretreatment ( $P=0.39$ ).

Freedom from atrial fibrillation was also analyzed according to the treatment that restored sinus rhythm, regardless of the initial group assignment. At the six-month follow-up, 50 percent of the 36 patients in whom sinus rhythm had been restored with transthoracic cardioversion alone remained free of recurrent atrial fibrillation, as compared with 90 percent of the 10 in whom sinus rhythm had been restored with ibutilide alone and 62 percent of the 54 in whom sinus rhythm was restored with transthoracic cardioversion after ibutilide pretreatment. The percentage of patients remaining free of atrial fibrillation did not differ significantly among these three groups ( $P=0.13$ ) (Fig. 1). Fifty percent of the 36 patients in whom sinus rhythm had been restored with transthoracic cardioversion alone had had no recurrence of atrial fibrillation at six months of follow-up, as compared with 71 percent of the 14 patients in whom transthoracic cardioversion alone had failed but in whom it was successful after ibutilide administration ( $P=0.56$ ).

#### Variables Associated with Recurrent Atrial Fibrillation

When the 59 patients who had no recurrence of atrial fibrillation were compared with the 41 who had a recurrence, there were no significant differences with regard to age, duration of atrial fibrillation, presence of structural heart disease, concomitant drug therapy, left atrial size, or left ventricular ejection fraction (Table 2).

## DISCUSSION

We found that pretreatment with ibutilide before transthoracic cardioversion significantly improved the success of cardioversion and lowered the energy requirement for atrial defibrillation by approximately 30 percent. Furthermore, in all the patients in whom conventional transthoracic electrical cardioversion failed, conversion to sinus rhythm was successful when electrical cardioversion was repeated after the administration of ibutilide. The rate of recurrence of atrial fibrillation was essentially the same whether or not transthoracic cardioversion was preceded by ibutilide administration. Therefore, the use of ibutilide to facilitate transthoracic cardioversion resulted in a clinically meaningful return to sinus rhythm that was as likely to be long-lived as when sinus rhythm was restored by conventional transthoracic cardioversion alone.

Transthoracic electrical cardioversion alone restored sinus rhythm in 72 percent of patients. In previous studies, the efficacy of transthoracic cardioversion ranged from approximately 67 to 94 percent.<sup>11-13</sup> There are two possible reasons why the success rate of transthoracic cardioversion in our study was at the low end of this range. First, 14 of the 100 patients had been referred for internal electrical cardioversion (i.e., transcatheter cardioversion) specifically because transthoracic cardioversion had already failed. Second, 48 percent of the patients who were randomly assigned to undergo transthoracic cardioversion without ibutilide pretreatment were also receiving amiodarone. Amiodarone increases the amount of energy required for ventricular defibrillation, and therefore it may also increase the energy required for atrial defibrillation.<sup>14-18</sup>

In patients with persistent atrial fibrillation that does not respond to transthoracic cardioversion, the efficacy of internal cardioversion for restoring sinus rhythm has been reported to be 72 to 94 percent.<sup>13,19-27</sup> However, internal cardioversion requires expertise in the placement of specialized catheters within the heart. Transthoracic cardioversion after pretreatment with ibutilide is associated with a success rate similar to or higher than that associated with internal cardioversion but has the substantial advantages of simplicity and widespread feasibility in standard clinical practice.

Previous studies have reported that ibutilide may precipitate polymorphic ventricular tachycardia in 3.6 to 8.3 percent of patients.<sup>3,4</sup> Three percent of patients in our study had this complication. A feature common among these patients was marked impairment of left ventricular function, with a left ventricular ejection fraction of 0.20 or less. Therefore, it is likely that the risk of ventricular tachycardia can be minimized by limiting the administration of ibutilide to patients who have a left ventricular ejection fraction of more than 0.30.

**TABLE 2.** COMPARISON OF PATIENTS WITH AND THOSE WITHOUT RECURRENT ATRIAL FIBRILLATION DURING FOLLOW-UP AFTER CARDIOVERSION.\*

VARIABLE	ATRIAL FIBRILLATION (N=41)	NO ATRIAL FIBRILLATION (N=59)	P VALUE
Age — yr	66±11	63±14	0.26
Duration of atrial fibrillation — days	142±239	101±171	0.32
Structural heart disease — no. (%)	24 (59)	36 (61)	0.80
Concurrent drug therapy — no. (%)†			
Beta-blocker	14 (34)	22 (37)	0.75
Calcium-channel blocker	14 (34)	16 (27)	0.45
Digoxin	9 (22)	17 (29)	0.44
Class I or III agent	21 (51)	34 (58)	0.53
Size of left atrium — mm	47±8	47±9	0.81
Left ventricular ejection fraction	0.48±0.08	0.47±0.09	0.62

\*Plus-minus values are means ±SD.

†Some patients were receiving more than one type of concurrent therapy.

Ibutilide-induced ventricular tachycardia is associated with a prolongation of the QT interval that is typical of torsade de pointes. Therefore, concomitant treatment with antiarrhythmic drugs that prolong the QT interval might increase the risk of ibutilide-induced ventricular tachycardia. However, our results indicate that this is not the case: neither of the two patients in whom ibutilide induced sustained ventricular tachycardia was being treated with another drug capable of prolonging the QT interval. In addition, of the 29 patients in this study who were being treated with sotalol or amiodarone at the time of ibutilide administration, none had polymorphic ventricular tachycardia. However, the number of patients in this study is inadequate to establish whether it is safe to administer ibutilide in combination with other antiarrhythmic drugs.

Previous studies have shown that ibutilide lowers the threshold for ventricular defibrillation.<sup>7-9</sup> Wesley et al. reported that ibutilide decreases the energy threshold for ventricular defibrillation in dogs by activating the plateau sodium current.<sup>7</sup> Whether this is the mechanism by which ibutilide lowers the energy requirement for atrial defibrillation in humans is unknown.

Few data are available on the effects of other antiarrhythmic drugs on the energy required for atrial defibrillation. In an uncontrolled study, flecainide was associated with a higher energy requirement for atrial defibrillation.<sup>28</sup> Sotalol decreased the energy requirement for internal atrial defibrillation, but only when atrial fibrillation had been present for less than one month.<sup>29</sup> In contrast, in our study the ability of

ibutilide to facilitate atrial defibrillation did not depend on the duration of atrial fibrillation.

We used a step-up protocol to determine the energy required for atrial defibrillation. However, because the threshold for defibrillation is a probability function, there is not a discrete, minimal energy requirement for atrial defibrillation. Accurate determination of the energy required for atrial defibrillation requires multiple shocks at a variety of energy levels. The simple step-up cardioversion protocol, with five energy levels, that we used in this study yielded only a rough estimate of the required energy; a more extensive evaluation of the energy requirement for defibrillation would not have been clinically feasible.

A second limitation is that only one technique for transthoracic cardioversion was used. The efficacy of transthoracic cardioversion in a given patient may be influenced by several variables, including the location of the electrodes, the size and type of electrodes, the phase of respiration, the use or nonuse of serial shocks, and the interval between shocks.<sup>30-38</sup> Therefore, it could be argued that some of the patients in whom transthoracic cardioversion failed might have had a successful outcome with a variation in technique, such as cardioversion with an anterior-posterior configuration of electrodes. However, no single method for transthoracic cardioversion has been shown to yield clearly superior results in a large group of patients, and the technique that we used was representative of those used in typical clinical practice.<sup>31,38</sup>

A third limitation is that many patients were concurrently being treated with antiarrhythmic drugs. Therefore, a synergistic effect with ibutilide cannot be ruled out.

Fourth, the number of patients in whom sinus rhythm was restored after the administration of ibutilide without transthoracic cardioversion was small. Although there was a trend toward a lower rate of recurrence of atrial fibrillation during follow-up in these patients, a larger study will be needed to determine whether this trend is statistically significant.

In current clinical practice, patients with persistent atrial fibrillation that is resistant to transthoracic cardioversion may be considered to have permanent atrial fibrillation, or internal cardioversion may be attempted. Our results demonstrate that the administration of ibutilide before cardioversion provides another option. Although patients with very poor left ventricular function are at risk for polymorphic ventricular tachycardia when ibutilide is administered, this risk is minimal if the left ventricular ejection fraction exceeds 0.30, even with concomitant use of an antiarrhythmic drug associated with prolongation of the QT interval, such as sotalol or amiodarone.

The value of ibutilide should be considered in terms of the cost of the drug and the cost of the subsequent three to four hours of continuous elec-

trocardiographic monitoring for adverse effects. Because transthoracic cardioversion by itself restores sinus rhythm in a majority of patients, routine pretreatment with ibutilide could unnecessarily increase the cost of cardioversion. It may be that pretreatment with ibutilide is appropriate only for patients in whom transthoracic cardioversion has already been attempted and has failed. On the other hand, pretreatment with ibutilide will at times result in successful pharmacologic cardioversion, thereby eliminating the need for transthoracic electrical cardioversion. Further studies are required to determine the most cost-effective way to use ibutilide as a pretreatment in conjunction with transthoracic cardioversion.

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