Antiarrhythmic Actions of Intravenous \textbf{Ibutilide} Compared With \textbf{Procainamide} During Human Atrial Flutter and Fibrillation: Electrophysiological Determinants of Enhanced Conversion Efficacy

[Clinical Investigation And Reports: Ventricular Arrhythmias/Heart Block]

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\textbf{Abstract}

Background The selective class III antiarrhythmic agent ibutilide prolongs action potential duration and terminates atrial flutter (AFL) and fibrillation (AF), but the mechanism of its antiarrhythmic efficacy in humans has not been fully characterized. This study compared the antiarrhythmic effects of ibutilide with the class IA agent procainamide in humans during AFL and AF. Antiarrhythmic drug actions and electrophysiological characteristics of AFL and AF that enhanced pharmacological termination were investigated.

Methods and Results Right atrial monophasic action potentials were recorded during 148 episodes of AFL (n = 89) or AF (n = 59) in 136 patients treated with intravenous ibutilide (n = 73) or placebo (n = 22) as participants in randomized double-blinded comparative studies or intravenous procainamide (n = 53) in a concurrent open-label study. The conversion rates in AFL with ibutilide, procainamide, and placebo were 64% (29 of 45 patients), 0% (0 of 33), and 0% (0 of 11), respectively, whereas in AF the rates were 32% (9 of 28), 5% (1 of 20), and 0% (0 of 11), respectively. In AFL, ibutilide increased atrial monophasic action potential duration (MAPD) more (30% versus 18%, P < .001) and prolonged atrial cycle length (CL) less (16% versus 26%, P < .001) than procainamide. Ibutilide shortened and procainamide prolonged action potential diastolic interval during AFL (-12% versus 51%, P < .001). Ibutilide increased MAPD/CL ratio, whereas procainamide tended to decrease this ratio (13% versus -6%, P < .01). In AFL, ibutilide and procainamide induced similar increases in atrial CL (48% versus 45%), but ibutilide induced a greater increase in MAPD (52% versus 37%, P < .05). Independent electrophysiological predictors of pharmacological arrhythmia termination were increase in MAPD/CL ratio (P = .005) in AFL and longer baseline mean MAPD (P = .011) in AF. Termination of AFL with ibutilide was characterized by significant increases in beat-to-beat atrial CL, MAPD, and diastolic interval variability. Ibutilide was significantly more effective in converting AF when the mean atrial CL was $\geq$ to 160 ms (64% versus 0%, P < .001) or MAPD was $\geq$ to 125 ms (57% versus 0%, P = .002) at baseline.

Conclusions Enhanced conversion efficacy of ibutilide compared with procainamide in AFL is correlated with a relatively greater prolongation of atrial MAPD than atrial CL, and termination of AFL by ibutilide is characterized by oscillations in atrial CL and MAPD. Conversion of AF by ibutilide is enhanced by a longer baseline mean atrial CL or MAPD. (Circulation. 1997;96:4298-4306.)

\textbf{Key Words} antiarrhythmia agents; action potentials; fibrillation; electrophysiology

Experimental studies of atrial fibrillation (AF) and atrial flutter (AFL) in animal models have provided knowledge of the antiarrhythmic mechanism of action of pharmacological agents and the vulnerable parameters of reentrant circuits. [1-18] Investigations in humans, however, often have focused on the electrophysiological properties of antiarrhythmic drugs rather than on determinants of antiarrhythmic action during atrial arrhythmias. Thus the mechanisms responsible for acute pharmacological conversion of atrial arrhythmias in humans remain incompletely understood. Clinical predictions of whether particular electrophysiological properties will be antiarrhythmic are far from ideal and at times have resulted in unexpected and proarrhythmic responses.

Ibutilide is an intravenous, selective class III antiarrhythmic agent that prolongs action potential duration and refractoriness by enhancing slow inward Na$^+$ plateau current and blocking delayed-rectifier outward K$^+$ current. [18-20]
Several clinical trials have demonstrated that ibutilide is effective in terminating AF or AFL, but the mechanism of its antiarrhythmic action in humans has not been fully characterized. In contrast, procainamide is a class IA drug that slows conduction velocity but also has other important pharmacological actions including action potential and refractory period prolongation. Procainamide blocks fast inward Na\(^{+}\) current and outward K\(^{+}\) current. Although data to support its efficacy are limited, intravenous procainamide is used clinically to terminate AF or AFL.

The objectives of this study were (1) to compare the atrial antiarrhythmic actions of intravenous ibutilide with procainamide during acute pharmacological conversion of AF and AFL, (2) to use atrial monophasic action potential recordings during AF and AFL to determine antiarrhythmic drug actions that favor tachyarrhythmia termination, and (3) to identify specific electrophysiological characteristics of AF and AFL that make a drug with particular electrophysiological properties antiarrhythmic.

**Methods**

**Study Patients**

The study population consisted of 136 patients (120 men and 16 women; mean +/- SD age, 67 +/- 8 years; range, 42 to 86) with 148 episodes of spontaneous, sustained AFL or AF referred between October 1991 and December 1994 to the McGuire Veterans Affairs Medical Center or the Medical College of Virginia electrophysiology laboratory for elective cardioversion. Patients received ibutilide or placebo as participants in one of two multicenter, double-blinded, randomized, placebo-controlled trials in which our center was a participating site. Patients received procainamide as participants in a concurrent open-label study conducted at our institution if they had previously received ibutilide (n = 9) or placebo (n = 2), if they were unwilling to receive an investigational agent or placebo (n = 17), if ibutilide was not available at the time of cardioversion (n = 9), or if they had specific exclusion criteria defined in the ibutilide investigational protocol (participants in another investigational study within the previous 30 days [n = 2], cardiac surgery within the previous 30 days [n = 4], serum potassium < 4.0 mEq/L [n = 2], serum creatinine > 2.0 mg/dL [n = 3], heart rate < 60 bpm [n = 5]).

Patients were excluded if any of the following were present: atrial tachyarrhythmia duration < 24 hours or > 90 days, hemodynamic instability (systolic blood pressure < 90 mm Hg or diastolic blood pressure > 105 mm Hg), unstable angina or congestive heart failure symptoms, acute myocardial infarction within the previous 30 days, lack of adequate anticoagulation if AF was present for > 2 days, age < 18 or > 90 years, weight > 300 lbs, history of torsade de pointes, QTc > 440 ms on ECG, concurrent or within five half-lives before enrollment treatment with class I or III antiarrhythmic drugs, or inability or unwillingness to give informed consent. Patients were treated with digoxin, beta-adrenergic blocking agents, or calcium antagonists for heart rate control. All patients gave written informed consent, and the study protocol was approved by the Committee on the Conduct of Human Research of Virginia Commonwealth University.

**Electrophysiology Study**

A steerable catheter (EPT) with a pair of silver/silver chloride electrodes at the distal tip and a pair of platinum ring electrodes located adjacent to the tip was used for recording atrial monophasic action potentials and bipolar electrograms, respectively, and for attempting overdrive pace termination of the atrial arrhythmia if conversion was not achieved with the drug infusion. This catheter was inserted through the femoral vein into the right atrium in a position where a stable monophasic action potential recording was obtained, usually in the lateral right atrium or appendage, and in patients with AF where relatively organized atrial electrical activity was observed and was not moved during the course of the study. Monophasic action potential signals obtained with a direct current-coupled preamplifier, bipolar atrial electrograms and > or = to 3 ECG leads (I, aVF and V\(_1\)) were displayed simultaneously and recorded at speeds of 100 to 200 mm/s.

**Drug Studies**

Seventy-three patients (45 with AFL, 28 with AF) were treated with ibutilide, 53 (33 with AFL, 20 with AF) received procainamide, and 22 (11 with AFL, 11 with AF) were given placebo (Table 1). Nine patients who previously received ibutilide (5 of whom converted with ibutilide) and 2 patients previously given placebo were treated with procainamide for a separate episode of AFL (n = 7) or AF (n = 4). One patient received procainamide twice on separate occasions, once for AFL and once for AF.
Patients given ibutilide received one of several dosing regimens as determined by the randomization code of the multicenter study in which they were participants. As part of a single-dose study, patients were randomly assigned to receive a 10-minute intravenous infusion of placebo (n = 7) or ibutilide (n = 28) with one of the following doses: 0.005 mg/kg (n = 8), 0.010 mg/kg (n = 4), 0.015 mg/kg (n = 7), or 0.025 mg/kg (n = 9) body weight. [22] As part of a repeat-dose study, patients were randomized to receive up to two 10-minute intravenous infusions, separated by 10 minutes, of placebo (n = 15) or ibutilide (n = 45) with one of the following dosing regimens: placebo followed by placebo, 1.0 mg followed by 0.5 mg ibutilide, or 1.0 mg followed by 1.0 mg ibutilide. [21] Patients who converted with the first 10-minute infusion did not receive the second dose. Fourteen patients each received 1.0 mg and 1.0 + 0.5 mg ibutilide and 17 received 1.0 + 1.0 mg ibutilide. Patients treated with procainamide were given an intravenous infusion at a dose of 15 mg/kg (mean dose, 1202 +/- 241 mg) at a rate not exceeding 50 mg/min. Drug infusions were discontinued when the arrhythmia terminated or the total dose was given. Patients were observed for arrhythmia termination for 1 hour after completion of the last infusion. A blood sample was obtained for measurement of ibutilide serum concentrations 5 (single dose study) or 10 (repeat dose study) minutes after the last ibutilide infusion or at the moment of conversion and for procainamide and N-acetylprocainamide (NAPA) serum concentrations 5 minutes after completion of the procainamide infusion. The mean serum concentration of ibutilide, was 4.9 +/- 4.5 ng/mL and of procainamide and NAPA were 10.7 +/- 3.9 and 1.4 +/- 0.6 [micro sign]g/mL, respectively.

**Definitions and Data Analysis**

Atrial flutter was defined as a regular atrial tachyarrhythmia with a stable atrial cycle length (< 20 ms difference in cycle length of 20 to 30 consecutive beats) and characteristic flutter wave sawtooth appearance in the inferior ECG leads. Atrial fibrillation was defined as a tachyarrhythmia demonstrating irregularity in the surface ECG baseline, ventricular response, and atrial electrogram activity. On the basis of bipolar atrial electrograms and monophasic action potential recordings from a single lead at baseline and using the criteria of Wells et al, [26] type I AF was present in 27 ibutilide, 19 procainamide, and 9 placebo-treated patients, type II AF in 1 ibutilide, 1 procainamide, and 2 placebo-treated patients, and type III AF in no patients.

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<table>
<thead>
<tr>
<th></th>
<th>Ibutilide</th>
<th>Procainamide</th>
<th>Placebo</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>73</td>
<td>53</td>
<td>22</td>
<td>...</td>
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<tr>
<td>Age, y</td>
<td>67±8</td>
<td>68±8</td>
<td>65±8</td>
<td>.204</td>
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<tr>
<td>Number of males</td>
<td>64 (88)</td>
<td>48 (91)</td>
<td>20 (91)</td>
<td>.841</td>
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<td>Atrial flutter/atrial fibrillation</td>
<td>45 (28)</td>
<td>33 (20)</td>
<td>11/11</td>
<td>.573</td>
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<td>Duration of arrhythmia, days</td>
<td>21±16</td>
<td>30±26</td>
<td>19±16</td>
<td>.554</td>
</tr>
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<td>Previous atrial flutter or fibrillation</td>
<td>38 (52)</td>
<td>30 (57)</td>
<td>15 (68)</td>
<td>.408</td>
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<td>Associated heart disease</td>
<td></td>
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<td></td>
<td></td>
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<td>Coronary artery disease</td>
<td>36 (49)</td>
<td>32 (60)</td>
<td>10 (45)</td>
<td>.358</td>
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<td>Hypertension</td>
<td>30 (41)</td>
<td>25 (47)</td>
<td>11 (50)</td>
<td>.683</td>
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<tr>
<td>Cardiomyopathy</td>
<td>19 (26)</td>
<td>20 (38)</td>
<td>3 (14)</td>
<td>.089</td>
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<td>Valvular disease</td>
<td>13 (18)</td>
<td>8 (15)</td>
<td>5 (23)</td>
<td>.729</td>
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<td>Conduction disease</td>
<td>6 (8)</td>
<td>5 (9)</td>
<td>3 (14)</td>
<td>.749</td>
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<td>Heart transplant</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>.724</td>
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<td>None</td>
<td>5 (7)</td>
<td>2 (4)</td>
<td>3 (14)</td>
<td>.301</td>
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<td>Concomitant cardiac medications</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Digoxin</td>
<td>31 (42)</td>
<td>24 (45)</td>
<td>11 (50)</td>
<td>.817</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>39 (53)</td>
<td>31 (58)</td>
<td>12 (55)</td>
<td>.849</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>6 (8)</td>
<td>5 (9)</td>
<td>6 (27)</td>
<td>.041</td>
</tr>
<tr>
<td>Left atrial size, cm</td>
<td>4.4±0.8</td>
<td>4.3±0.7</td>
<td>4.3±0.7</td>
<td>.645</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>43±15</td>
<td>44±11</td>
<td>45±14</td>
<td>.871</td>
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</tbody>
</table>

Values are expressed as mean±SD or number (%).
The AFL or AF cycle length (CL) and the atrial monophasic action potential duration (MAPD) were determined from an average of at least 10 (AFL) or 25 (AF) cycles at baseline and after each pharmacological intervention. Drug measurements were made either just before arrhythmia termination in converters or 5 minutes after completion of drug or placebo infusion in nonconverters. Measurements were made by one nonblinded observer (B.S.S.) with an intraobserver variability of +/- 5 ms. When analyzing AF recordings, only segments demonstrating type I AF were analyzed, that is, atrial activity was acceptable for measurement if a clear action potential upstroke was present along with a discrete electrogram separated by an isoelectric segment in the atrial bipolar recording. The MAPD was measured from the action potential upstroke to the point where repolarization was 90% back to baseline. If repolarization was not complete before the next action potential, the baseline was selected using the points of intersection of the upstroke with the preceding action potential and the repolarization phase with the next upstroke. In AFL, the diastolic interval (DI) was defined as atrial CL minus MAPD and activation time as the interval from the ECG flutter wave onset to the action potential upstroke. The MAPD and activation time were used as indices of repolarization and conduction times, respectively, and the DI was used as an estimate of the excitable gap. The fraction of the AFL CL occupied by the action potential, that is, the ratio MAPD/CL was used as a measure of relative drug-induced changes in repolarization to conduction velocity. The coefficient of variation (SD/mean times 100) was used as an index of beat-to-beat variability in AFL CL, MAPD, and DI.

Since the electrophysiological effects of the various doses of ibutilide were not significantly different, all doses of ibutilide were analyzed together, and only combined values for the ibutilide doses are presented. Chi squared analysis was used to compare variables with discrete end points such as study patient clinical characteristics. A repeated-measures ANOVA was used to evaluate electrophysiological variables within each drug group in AFL and AF and where appropriate to compare changes in other continuous, paired variables. A one-way ANOVA was used to compare variables between drug groups, between AFL and AF, and between converters and nonconverters. When significant F values were demonstrated in the ANOVA, the Bonferroni multiple comparisons test was used to determine significance of individual comparisons. Linear regression analysis was used to examine the relation between changes in atrial CL and MAPD. To assess the degree of linear association between drug efficacy and electrophysiological and clinical variables, a Spearman rank correlation test was initially performed. Those variables significantly associated with arrhythmia termination based on the univariate correlation analysis were then subjected to multivariate analysis using stepwise logistic regression to determine the independent association of these variables with arrhythmia termination. A value of P < .05 was considered statistically significant. Data are reported as mean +/- 1 SD.

Figure 1

![Figure 1](attachment:image.jpg)

**Figure 1.** Conversion efficacy of ibutilide, procainamide, and placebo in atrial flutter (AFL) and atrial fibrillation (AFIB). From: Stambler: Circulation, Volume 96(12).December 16, 1997.4298-4306.
Results

Clinical Characteristics of Study Patients

The mean arrhythmia duration was 23 +/- 20 days, and 56% of patients had a previous episode of AF or AFL. More than 90% had heart disease other than atrial arrhythmias, with coronary artery disease, hypertension, and cardiomyopathy being the most common. The mean left atrial diameter and left ventricular ejection fraction were 4.3 +/- 0.7 cm and 44 +/- 14%, respectively. Most patients were receiving atrioventricular nodal-blocking drugs, and the mean baseline heart rate and systolic and diastolic blood pressures were 85 +/- 22 bpm and 134 +/- 24 and 81 +/- 13 mm Hg, respectively. A higher proportion of patients in the placebo group were receiving beta-adrenergic-blocking drugs (P = .041), but there were no other significant differences in clinical characteristics between drug groups (Table 1).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Baseline</th>
<th>Ibutilide</th>
<th>Baseline</th>
<th>Procaainamide</th>
<th>Baseline</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial CL</td>
<td>242±27</td>
<td>281±35†</td>
<td>238±38</td>
<td>300±55†</td>
<td>213±36</td>
<td>215±37</td>
</tr>
<tr>
<td>Atrial MAPD</td>
<td>164±23</td>
<td>213±32‡</td>
<td>169±29</td>
<td>199±36‡</td>
<td>154±27</td>
<td>148±25</td>
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<tr>
<td>Diastolic interval</td>
<td>78±25</td>
<td>67±25‡</td>
<td>69±25</td>
<td>100±37‡</td>
<td>59±15</td>
<td>67±21</td>
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<tr>
<td>MAPD/CL</td>
<td>0.68±0.09</td>
<td>0.76±0.08*</td>
<td>0.72±0.09</td>
<td>0.67±0.09</td>
<td>0.73±0.05</td>
<td>0.69±0.07</td>
</tr>
<tr>
<td>Activation time</td>
<td>63±33</td>
<td>78±39†</td>
<td>65±33</td>
<td>93±43‡</td>
<td>69±32</td>
<td>72±34</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>163±18</td>
<td>240±28‡</td>
<td>168±29</td>
<td>241±38‡</td>
<td>158±12</td>
<td>158±14</td>
</tr>
<tr>
<td>Atrial MAPD</td>
<td>126±18</td>
<td>192±29‡</td>
<td>124±20</td>
<td>169±32‡</td>
<td>131±13</td>
<td>127±12</td>
</tr>
</tbody>
</table>

CL indicates cycle length; MAPD, monophasic action potential duration.
*P<.05, †P<.01, ‡P<.001 vs baseline.


Termination of AFL and AF

Of 89 patients with AFL, ibutilide converted 29 of 45 patients (64%), whereas procaainamide and placebo converted 0 of 33 and 11 patients, respectively. Of 59 patients with AF, conversion was achieved in 9 of 28 patients (32%) who received ibutilide, in 1 of 20 patients (5%) who received procaainamide, and in 0 of 11 patients who received placebo. Ibutilide was significantly (P < .05) more likely to convert AFL than AF (64% versus 32%). The mean time to arrhythmia termination after initiation of ibutilide was 23 +/- 17 minutes (range, 5 to 30 minutes) in AFL and 16 +/- 9 minutes (range, 8 to 64 minutes) in AF. On the basis of surface ECG and intracardiac electrogram criteria, conversion of AF to AFL was not observed in any patient during or after drug infusion. See Figure 1.

Electrophysiological Effects of Ibutilide in AFL and AF

(Table 2) summarizes the electrophysiological effects of ibutilide, and Figure 2A and Figure 3A illustrate the effects of ibutilide in patients with AFL and AF, respectively. In patients with AFL, ibutilide significantly prolonged the AFL CL by 39 +/- 20 ms (P < .01; 16% increase from baseline), the atrial MAPD by 49 +/- 20 ms (P < .001; 30%), and the activation time from the flutter wave to the action potential upstroke by 15 +/- 14 ms (P < .01; 30%). The ibutilide-induced increase in atrial CL was less (P < .001) than the increase in MAPD. Thus ibutilide shortened the action potential DI by 10 +/- 15 ms (P < .01; -12%) and increased the MAPD-to-atrial CL ratio (MAPD/CL) by 0.08 +/- 0.05(P < .05; 13%). The ibutilide induced increase in AFL CL was significantly correlated (r = .72, P < .0001) with the change in MAPD. In patients with AF, ibutilide prolonged atrial CL by 77 +/- 22 ms (P < .001; 48%) and MAPD by 65 +/- 21 ms (P < .001; 52%). The ibutilide-induced increase in AF CL was significantly correlated (r = .78, P < .0001) with change in MAPD. Comparison of the electrophysiological effects produced by ibutilide in patients with AF with those produced by ibutilide in patients with AFL (Figure 4) revealed significantly greater increases in atrial CL and MAPD in AF than in AFL (P < .001 and P < .01, respectively).
Electrophysiological Effects of Procainamide in AFL and AF

(Table 2) summarizes the effects of procainamide and Figure 2B and Figure 3B illustrate the effects of procainamide in patients with AFL and AF, respectively. In patients with AFL, procainamide significantly increased AFL CL by 62 +/- 22 ms (P < .001; 26%), MAPD by 30 +/- 20 ms (P < .05; 18%), and activation time by 28 +/- 16 ms (P < .001; 49%). The procainamide-induced increase in atrial CL was significantly greater (P < .0001) than the increase in MAPD.

Figure 3. Surface ECG and monophasic action potential recordings from the right atrium during atrial fibrillation from two patients (A and B) at baseline (left side) and during ibutilide or procainamide (right side). The mean atrial cycle length (CL) and monophasic action potential duration (MAPD) are shown above and below the action potential recording, respectively. In patient A, ibutilide (top right) increased mean atrial CL (Delta 118 ms) and MAPD (Delta 104 ms), and in patient B, procainamide (bottom right) increased mean atrial CL (Delta 56 ms) and MAPD (Delta 16 ms), but atrial fibrillation failed to terminate in either patient. From: Stambler: Circulation, Volume 96(12).December 16, 1997.4298-4306.
Thus in contrast to ibutilide, procainamide prolonged DI during AFL by 32 +/- 23 ms (P < .001; 51%) and tended to decrease MAPD/CL by 0.05 +/- 0.06 (P = NS; -6%), but the ratio was not significantly different from baseline during procainamide. The increase in AFL CL induced by procainamide was significantly but modestly correlated (r = .44, P = .01) with the change in MAPD. In patients with AF, procainamide prolonged atrial CL by 72 +/- 31 ms (P < .001; 45%) and MAPD by 45 +/- 27 ms (P < .001; 37%). The procainamide-induced increase in AF CL was significantly correlated (r = .81, P < .0001) with the change in atrial MAPD. Changes in atrial CL and MAPD induced by procainamide were not significantly different in AF than AFL (Figure 4).

**Figure 4**

Comparison of the electrophysiological effects of ibutilide with procainamide during atrial flutter (A) and atrial fibrillation (B). MAPD indicates atrial monophasic action potential duration; CL, atrial cycle length. *P < .05 vs ibutilide, [dagger] P < .05 vs atrial flutter. From: Stambler: Circulation, Volume 96(12). December 16, 1997.4298-4306.

**Comparison of Electrophysiological Effects of Ibutilide With Procainamide in AFL and AF**

In patients with AFL, ibutilide increased atrial MAPD significantly more (P < .001) and prolonged AFL CL and activation time significantly less (P < .001 and P < .01, respectively) than procainamide. Ibutilide shortened whereas procainamide prolonged the action potential DI during AFL (P < .001 ibutilide versus procainamide). Ibutilide increased whereas procainamide tended to decrease the MAPD/CL ratio (P < .01, ibutilide versus procainamide). In patients with AF, ibutilide and procainamide induced similar increases in atrial CL, but ibutilide induced a significantly greater (P < .05) increase in atrial MAPD than procainamide. See Figure 4.

Among the 6 patients who received ibutilide and procainamide on separate occasions for AFL, ibutilide converted 3 patients, increased atrial CL and MAPD by 45 +/- 18 and 56 +/- 22 ms, decreased DI by 9 +/- 8 ms, and increased MAPD/CL ratio by 0.08 +/- 0.04, whereas procainamide converted no patients, increased atrial CL and MAPD by 66 +/- 35 and 35 +/- 16 ms, increased DI by 31 +/- 18 ms, and decreased MAPD/CL by 0.03 +/- 0.05. Among the 3 patients who received ibutilide and procainamide for AF, ibutilide converted 2 patients and increased atrial CL and MAPD by 87 +/- 19 and 70 +/- 20 ms, whereas procainamide converted no patients and increased atrial CL and MAPD by 86 +/- 56 and 51 +/- 42 ms.

**Comparison of Converters With Nonconverters**

In AFL, correlation of electrophysiological variables in the pooled ibutilide and procainamide groups with antiarrhythmic drug efficacy for arrhythmia termination revealed significant correlations with changes in DI (r = -.471, P < .0001), MAPD/CL ratio (r = .459, P < .0001), atrial CL (r = -.334, P = .003), and activation time (r = -.299, P = .016) but no correlation with change in MAPD (r = .174, P = .136) or with baseline atrial CL (r = -.022, P = .850), MAPD (r = .125, P = .285), MAPD/CL ratio (r = .064, P = .588), DI (r = .010, P = .930), or activation time (r = -.131, P = .302). In AF, baseline atrial CL (r = .448, P = .001) and MAPD (r = .439, P = .002) were significantly correlated with arrhythmia...
termination; however, changes in atrial CL (r = .-017, P = .911) and MAPD (r = .162, P = .278) were not correlated with termination. Examination of the association between clinical variables in the pooled ibutilide and procainamide groups with arrhythmia termination revealed significant correlation with left atrial size (r = .288, P = .017) in AFL patients and with arrhythmia duration (r = -.331, P = .027) and left ventricular ejection fraction (r = .300, P = .039) in AF patients. Thus univariate predictors of arrhythmia termination in AFL specifically included reduction in DI, increase in MAPD/CL ratio, smaller increases in atrial CL and activation time and larger left atrial size, and in AF longer mean baseline atrial CL and MAPD, shorter arrhythmia duration and higher ejection fraction. Multivariate analysis of these univariate predictors indicated that independent predictors of arrhythmia termination were left atrial size (P = .044) and increase in MAPD/CL ratio (P = .005) in AFL and baseline MAPD (P = .011) in AF.

Comparison of electrophysiological variables in patients with AFL that converted with ibutilide (n = 29) with those not converted by ibutilide (n = 17) revealed no significant differences in mean AFL CL, MAPD, DI, MAPD/CL ratio, or activation time at baseline. Furthermore, because the magnitude of changes in these electrophysiological variables was similar whether AFL terminated or persisted after ibutilide, there were no significant differences in these variables between converters and nonconverters after ibutilide. Ibutilide prolonged the mean atrial CL and MAPD by 40 +/- 21 and 47 +/- 20 ms in converters compared with increases of 38 +/- 19 and 54 +/- 20 ms in nonconverters (P = .70, P = .25, respectively) and shortened DI by 7 +/- 10 and 17 +/- 20 ms in converters and nonconverters (P = .1). Patients with AFL who converted with ibutilide developed significant increases in beat-to-beat atrial CL, MAPD, and DI variability just before arrhythmia termination compared with baseline (CL: 1.5 +/- 0.9 to 8.3 +/- 5.6, P < .001; MAPD: 4.6 +/- 2.3 to 8.0 +/- 4.2, P < .05; DI: 12.9 +/- 8.6 to 30.3 +/- 15.1, P < .001) (Figure 2). The beat-to-beat AFL CL, MAPD, and DI variability that preceded AFL conversion by ibutilide was significantly greater than the beat-to-beat variability in these parameters observed in patients with AFL who failed to convert after ibutilide (CL: 1.3 +/- 0.6, P < .001; MAPD: 4.7 +/- 2.7, P < .05; DI: 14.2 +/- 7.4, P < .01) and was significantly greater than the AFL CL and DI variability observed after procainamide (CL: 1.3 +/- 1.0, P < .001; MAPD: 5.8 +/- 3.3, P = NS; DI: 12.1 +/- 5.8, P < .001).

Comparison of electrophysiological variables in patients with AF that converted with ibutilide (n = 9) with those whose AF failed to terminate (n = 19) revealed significantly longer mean AF CLs at baseline (180 +/- 15 versus 155 +/- 12 ms, P < .001) and after ibutilide (259 +/- 27 versus 231 +/- 25 ms, P < .05) and longer mean atrial MAPDs at baseline (143 +/- 19 versus 119 +/- 12 ms, P < .001) and after ibutilide (216 +/- 31 versus 181 +/- 22 ms, P < .01) in converters than nonconverters. The magnitude of the increases in atrial CL and MAPD in AF induced by ibutilide were similar, however, whether AF was or was not terminated (79 +/- 28 versus 76 +/- 20 ms, P = .82 and 73 +/- 27 and 62 +/- 18 ms, P = .22). The conversion rate with ibutilide in patients with AF was significantly higher in those with a baseline mean AF CL >or= to 160 ms or MAPD >or= to 125 ms (ie, median AF CL and MAPD for all ibutilide-treated patients). The conversion rate with ibutilide was 64% (9 of 14 patients) in those with a baseline mean atrial CL >or= to 160 ms compared with 0% (0 of 14 patients) in those with an atrial CL < 160 ms (P < .001). In those with a baseline mean atrial MAPD >or= to 125 ms, the conversion rate with ibutilide was 57% compared with 0% in those with an atrial MAPD < 125 ms (P = .002). The baseline AF CL and MAPD were not significantly correlated with arrhythmia duration (r = -.053, P = -.794; r = -.163, P = .426, respectively) or with any other clinical variable, and arrhythmia duration was not significantly different between ibutilide converters and nonconverters (19 +/- 9 versus 22 +/- 18 days, P = .660) with AF.

Adverse Effects

Ibutilide produced no significant changes in systolic or diastolic blood pressure and slightly decreased heart rate by 7 +/- 22 bpm (P < .05, -5%). Three patients (4%) who received ibutilide for AFL developed nonsustained, polymorphic ventricular tachycardia during or shortly after the infusion, which did not require electrical cardioversion. Procainamide reduced systolic blood pressure by 25 +/- 20 mm Hg (P < .001, -18%) and diastolic pressure by 9 +/- 14 mm Hg (P < .05, -10%) and produced no significant change in heart rate.

Discussion

This study demonstrated that the differing electrophysiological effects of intravenous ibutilide compared with procainamide during atrial arrhythmias correlated with the enhanced conversion efficacy of ibutilide. Pharmacological termination of AFL by ibutilide compared with procainamide was characterized by relatively greater prolongation of atrial MAPD than atrial CL and by oscillations in atrial CL and MAPD just before arrhythmia termination. Conversion of AF by ibutilide was enhanced by a longer mean atrial CL or MAPD at baseline during AF.

Atrial Arrhythmia Conversion Efficacy
Although this study was not a randomized comparison of intravenous ibutilide with procainamide, or placebo, the atrial arrhythmia conversion rates were consistent with several previous randomized, double-blinded, multicenter, efficacy studies. These previous studies demonstrated that ibutilide is significantly more effective than placebo or procainamide for conversion of AFL or AF and for conversion of AFL than AF. [21-23] In a multicenter, randomized trial that compared the conversion efficacy of intravenous ibutilide (2 mg total dose) with procainamide (1200 mg), ibutilide converted 76% of patients with AFL and 51% with AF, whereas procainamide converted 12% with AFL and 20% with AF. [23] The lack of significant conversion efficacy of intravenous procainamide contrasts with several previous reports in which the AF conversion rates were in the 40% to 60% range. [27-30] Arrhythmia duration, however, is a potent predictor of pharmacological conversion of AF. [21,27] Previous reports that demonstrated significant efficacy of procainamide evaluated patients with recent-onset AF with arrhythmia durations < 1 to 2 days. In contrast in the present study, patients had chronic established AF, with a median arrhythmia duration of 30 days. In a previous study, procainamide (1.0 g IV) terminated AF in 9 of 10 patients (90%) with an arrhythmia duration <or= to 1 day but converted only 5 of 15 patients (33%) with a duration > 1 day. [27]

Antiarrhythmic Drug Actions and AFL Conversion Efficacy

Ibutilide and procainamide produced electrophysiological effects during AFL consistent with class III and IA antiarrhythmic drug action, respectively. Because the procainamide infusion was completed within 30 minutes, minimal NAPA, a metabolite with class III antiarrhythmic properties, [2-4] was generated as demonstrated by the very low serum levels. During AFL, ibutilide prolonged right atrial MAPD more than CL (30% versus 16%), whereas procainamide increased atrial CL more than MAPD (26% versus 18%). Importantly, these significantly different antiarrhythmic class actions produced opposing effects on DI and MAPD/CL ratio. Ibutilide shortened DI and increased MAPD/CL, whereas procainamide-prolonged DI and tended to decrease MAPD/CL. Examination of the pooled ibutilide and procainamide data revealed that antiarrhythmic drug efficacy for termination of AFL was significantly correlated in the univariate analysis with increase in MAPD/CL ratio, reduction in DI, and relatively smaller increases in atrial CL and activation time. The magnitude of the increase in MAPD alone was not correlated significantly with arrhythmia termination. Thus ibutilide may have been more effective than procainamide in terminating AFL because ibutilide, in contrast to procainamide, prolonged atrial MAPD more than atrial CL.

Experimental studies suggest that wavelength (ie, product of refractory period and conduction velocity) is a critical determinant of antiarrhythmic drug effects on reentrant arrhythmias. [5,15-17] Theoretically, in a reentrant circuit with a fixed path length, wavelength is proportional to refractory period divided by CL. Although tachycardia wavelength was not directly measured in this study, the MAPD/CL ratio provided a relative measure of drug-induced changes in repolarization to conduction velocity. An increase in this ratio that reflected a relatively greater drug-induced prolongation of atrial MAPD than CL provided the most significant independent predictor of AFL termination. Ibutilide prolonged action potential duration and thus refractory period during AFL more than it slowed conduction (ie, atrial CL and activation time), resulting in a 13% increase in MAPD/CL. In contrast, procainamide slowed conduction more than it prolonged action potential duration and thus decreased MAPD/CL by 6%. These effects are consistent with an ibutilide-induced increase and procainamide-induced decrease in wavelength. In support of these conclusions, the selective class III agent dofetilide was more effective than the class IA drug quinidine in terminating AFL in a canine crush-injury model. [14] Dofetilide significantly increased wavelength by 11%, but quinidine tended to reduce wavelength by 2%. Efficacy was correlated with prolongation of wavelength and not with changes in refractoriness or conduction velocity alone. Thus the enhanced efficacy of ibutilide compared with procainamide in terminating AFL may be related in part to drug-induced changes in wavelength mediated by alterations in action potential duration and conduction.

In this study, termination of AFL with ibutilide was associated with an increase in beat-to-beat variability in atrial CL, MAPD, and DI, as previously described in animal models of reentrant arrhythmia termination. [6,11,13,31,32] These oscillations were not observed in patients with AFL that was not terminated by ibutilide or procainamide. These findings extend our previous observations regarding AFL termination with ibutilide to a larger group of patients and further suggest that oscillatory termination is an important mechanism by which ibutilide but not procainamide results in AFL termination. [33] In human AFL, there is a large, fully excitable gap that ranges in width from 14% to 25% of the AFL CL. [34,35] On the basis of this study, it seems unlikely that action potential prolongation by ibutilide was sufficient to close the total excitable gap and extinguish the circuit. The increases in MAPD were partially offset by increases in CL, which would tend to maintain excitable gap. Thus DI was reduced by only 12% despite a 30% mean increase in MAPD. The size of the excitable gap, however, can vary throughout the AFL circuit. A local excitable gap might have been eliminated or reduced by the relatively greater increases in atrial MAPD than CL produced by ibutilide. This would result in CL-dependent alterations in conduction, action potential duration, and refractory period, which could produce transient oscillations in CL, MAPD, and DI and arrhythmia termination. [11,13,31,32]
Because ibutilide does not directly slow conduction velocity, the mechanism of AFL CL prolongation by ibutilide may be explained by conversion from a fully to a partially excitable gap. In a reentrant circuit with a fully excitable gap, tachycardia CL is proportional to conduction velocity and does not depend directly on action potential duration. Prolongation of action potential duration by a class III agent may slow conduction velocity and prolong tachycardia CL by propagation of the impulse in incompletely repolarized tissues. In contrast, by directly slowing conduction velocity, procainamide would tend to maintain the fully excitable gap with propagation of impulses in completely repolarized tissues.

**Electrophysiological Characteristics of AF and Antiarrhythmic Drug Efficacy**

To our knowledge, the finding of this study that the baseline atrial CL and MAPD are electrophysiological determinants of antiarrhythmic drug efficacy for termination of AF in humans has not been previously reported. The conversion efficacy of ibutilide in AF was significantly determined by whether patients had a short or long mean atrial CL or MAPD at baseline. No patient with AF and a mean right atrial CL < 160 ms or MAPD < 125 ms was converted by ibutilide, whereas conversion was achieved in 64% and 57% of those with a mean atrial CL > or = to 160 ms or MAPD > or = to 125 ms, respectively. Although the duration of AF is a powerful predictor of drug efficacy in terminating AF and may be an important determinant of AF CL and MAPD, in this study a significant correlation between arrhythmia duration and these electrophysiological variables was not found. This may have been related to inclusion of only a relatively small number of patients with recent-onset AF and to the analysis of only recording segments demonstrating type I AF.

A correlation between the median AF interval and the complexity of AF has been demonstrated with the use of high-density mapping in humans. A longer median AF interval is associated with a smaller number of fibrillatory wavelets, and pharmacological termination of AF in animal models is preceded by an increase in mean AF CL, which is an index of local atrial refractoriness. Thus it is possible to speculate that patients in this study with a long mean AF CL had a long wavelength and a small number of wavelets, whereas those with a short mean AF CL had a short wavelength and multiple wavelets. In the group with a long mean AF CL, prolongation of AF CL and MAPD by ibutilide may have increased wavelength and critically reduced the number of wavelets that could coexist in the atria. This increased the statistical chance that all wavelets might extinguish simultaneously and the fibrillatory process would terminate spontaneously. Mapping studies in animal models indicate that antiarrhythmic drugs terminate experimental AF by this mechanism. In contrast, in the group with a short mean AF CL, although ibutilide increased AF CL, wavelength may not have prolonged sufficiently to critically reduce the number of wavelets and allow the arrhythmia to terminate. Because ibutilide induced similar increases in AF CL and MAPD in nonconverters as in converters, the AF CL and MAPD remained shorter after ibutilide in nonconverters than in converters. Finally, although the absence of a frequency-dependent effect of ibutilide on human AF has not been excluded, a previous study in dogs found no reverse use-dependent effect of ibutilide on atrial effective refractory period at paced cycle lengths from 150 to 400 ms.

Despite inducing a similar increase in AF CL as ibutilide, procainamide was ineffective in terminating AF even in patients with long AF CLs at baseline. Procainamide prolonged atrial MAPD during AF less than did ibutilide; however, the mechanism of enhanced efficacy of ibutilide in terminating AF compared with procainamide will require further evaluation.

These data may provide insight into the greater efficacy of ibutilide in terminating AFL than AF: Prolongation of action potential duration and refractoriness by class III antiarrhythmic action may be effective for termination of atrial arrhythmias that have either a single broad wavefront (ie, AFL) or a relatively small number of circulating wavelets (ie, AF with a long mean CL). Whether greater prolongation of action potential duration with higher doses of ibutilide can reliably terminate AF with a short CL without prohibitively increasing the proarrhythmia risk may warrant further study. Measurement of AF CL might be used clinically to determine the likelihood of arrhythmia conversion by ibutilide.

**Limitations**

In the present study, only single-site recordings during the atrial arrhythmias were obtained and the tachycardia wavelength was not directly measured. Therefore, the specific mechanisms of atrial arrhythmia termination could not be evaluated. Recordings during AFL were obtained from presumably normal atrial tissues that were not located in critical areas of the circuit. The findings are valid only if the measurements were representative of antiarrhythmic drug effects on the circuit. Only recordings with type I AF were analyzed, and signals from other atrial areas with more complex types of AF were not evaluated. Refractoriness and conduction velocity cannot be measured directly during AF and because programmed stimulation might have terminated the arrhythmia were not measured directly during AFL.
This study was not a randomized comparison, and the results of this study may not apply to all patients with atrial arrhythmias treated with these drugs. Procainamide was given in open-label, nonrandomized fashion, and some patients who received procainamide had previously received ibutilide. Including patients in the procainamide group who previously received ibutilide allowed a comparison of the two drugs in the same patients and did not appear to create a bias in the procainamide group by including patients who failed to respond to ibutilide. More than 50% of the procainamide patients who previously received ibutilide were ibutilide responders. The effects of only short-term intravenous drug administration were studied and because all ibutilide doses were analyzed together and only one dose of procainamide was examined, the possibility of differential electrophysiological effects of these drugs at escalating doses cannot be excluded. The electrophysiological effects and antiarrhythmic actions of intravenous procainamide may be modified during a longer infusion or observation period or by oral administration during which the class III antiarrhythmic agent NAPA would accumulate. Relatively few patients in this study had recent-onset AF in which the conversion rate of procainamide may be higher than placebo and electrophysiological effects may be altered.

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REFERENCES


