Electrophysiological Effects of Ibutilide in Patients With Accessory Pathways

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Background—Atrial fibrillation (AF) may cause life-threatening ventricular arrhythmias in patients with Wolff-Parkinson-White syndrome. We prospectively evaluated the effects of ibutilide on the conduction system in patients with accessory pathways (AP).

Methods and Results—In part I, we gave ibutilide to 22 patients (18 men, 31±13 years of age) who had AF during electrophysiology study, including 6 pediatric patients ≤18 years of age. Ibutilide terminated AF in 21 of 22 patients (95%) during or 8±5 minutes after infusion and prolonged the shortest preexcited R-R interval during AF. Successful ablation was performed in all patients. In part II, ibutilide was given to 18 patients (14 men, 28±21 years) to assess its effects on the AP and conduction system. Ibutilide prolonged the antegrade atrioventricular node effective refractory period (ERP) (from 252±60 to 303±70 ms; P<0.02). Ibutilide caused transient loss of the delta wave in 1 patient and abolished inducible tachycardia in 2 patients, although retrograde mapping still allowed for successful AP ablation. The antegrade AP ERP prolonged from 275±40 to 320±60 ms (P<0.01), as did the antegrade AP block cycle length; the retrograde AP ERP and block cycle length similarly prolonged with ibutilide. The relative and effective refractory period of the His-Purkinje system increased in 61% of patients after ibutilide. There were no adverse side effects.

Conclusions—We report the use of ibutilide in terminating AP-mediated AF, including the first report in the pediatric population. Ibutilide prolonged refractoriness of the atrioventricular node, His-Purkinje system, and AP. (Circulation. 2001;104:1933-1939.)

Key Words: Wolff-Parkinson-White syndrome • fibrillation • antiarrhythmia agents

Ibutilide is a class III antiarrhythmic drug useful in patients with atrial fibrillation (AF) or atrial flutter.1,2 Its actions as a potassium channel (I Kr) blocker and its effects on the sodium channel prolong atrial repolarization and restore sinus rhythm.3-5 AF occurs in patients with atioventricular reentrant tachycardia (AVRT) and may produce life-threatening ventricular arrhythmias in patients with Wolff-Parkinson-White (WPW) syndrome.6,7 Additionally, recurrent AF may interrupt attempts at catheter ablation during electrophysiology (EP) study in patients with either manifest or concealed accessory pathways (APs).

Currently, intravenous procainamide is the only drug approved for emergent treatment of patients with WPW and AF.8 However, procainamide has a relatively slow onset of action, may cause severe hypotension, and is inferior to ibutilide for acute cardioversion of atrial arrhythmias.9,10 Limited case reports have suggested that ibutilide may terminate AF in patients with AP.11,12 However, to our knowledge, no prior study has undertaken a detailed analysis of the mechanism of action by ibutilide on the atrioventricular node (AVN), AP, or His-Purkinje system (HPS), all of which are critical components in AP-mediated tachycardia circuits.

The purpose of this study was to assess the electrophysiological effects of ibutilide in patients with AP-mediated tachycardia. In addition, we present the first description on the use of ibutilide in the pediatric population.

Methods
We designed a 2-part, prospective study to determine the effectiveness of ibutilide in terminating AF during invasive EP study and to assess the mechanism of action by ibutilide on both antegrade and retrograde conduction and refractoriness of the AVN, AP, and HPS.

Study Protocol Part I

Patients
Twenty-two patients with 23 APs, who had AF during EP study, were treated with ibutilide. There were 18 male patients with a mean age of 31±13 years (range, 9 to 54 years), with 6 patients (27%) 18 years or younger. The APs were located in the left free wall (n=10),

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right free wall (n=5), and septum (n=8). Fourteen pathways (61\%) were manifest. One patient had Ebstein’s anomaly, but the remaining patients had no structural heart disease.

**EP Study**
All patients underwent EP study in the postabsorptive, fasting state. Antiarrhythmic agents were discontinued ≥5 half-lives before the study. The basic EP study protocol has been described previously. Patients with left-sided pathways underwent transseptal catheterization for left atrial access. A 12-lead surface ECG and bipolar intracardiac electrograms were simultaneously recorded from the high right atrium, coronary sinus, His bundle region, right ventricular apex, and left atrium (where appropriate) and were recorded on optical disk with a Prucka recording system computer. Electrical stimulation was performed with both atrial and ventricular overdrive and programmed extrastimulus pacing. AP location was confirmed by successful pathway ablation.

In this study, AF occurred either in response to catheter movement or during cardiac pacing. No specific efforts were made to induce AF.

**Drug Infusion**
Patients with sustained AF during EP study were given 2 mg of ibutilide intravenously over 15 minutes for patients older than 18 years. Weight-based dosing (0.03 mg/kg) was used for patients under age 18 years (up to 2 mg). The infusion was discontinued when AF terminated or maximal drug dose was given.

**Atrial Fibrillation**
The entire recorded episode of AF was analyzed. During AF, consecutive R-R intervals were measured for 1 minute before drug infusion and for the 1 minute immediately before termination of the AP to obtain average R-R intervals.

**Study Protocol Part II**

**Patients**
Eighteen patients with APs undergoing EP study gave written informed consent to a protocol approved by the Committee on Human Research at the University of California, San Francisco. Two of these patients who had AF after baseline measurements were obtained were also included in study protocol part I. There were 14 male patients, and their mean age was 28±21 years (range, 4 to 49 years), with 7 patients (39\%) under age 18 years. Eleven pathways (61\%) were manifest, and their locations were right free wall (n=5), left free wall (n=8), and septal (n=5). No patient had structural heart disease, abnormal electrolytes, or heart failure before study enrollment.

**Drug Infusion**
After measurements were made in the baseline state (“control” measurements), 2 mg ibutilide was infused into a peripheral vein over 15 minutes for patients older than 18 years of age and 0.03 mg/kg for patients younger than 18 years (up to 2 mg total). The same protocol at the same drive cycle length was then performed (“ibutilide” measurements).

**QT Measurements**
Ten consecutive QT and R-R intervals were measured before and immediately after ibutilide infusion. The QTc interval (corrected QT interval) was calculated by Bazett’s formula.

**Statistical Analysis**
The change from baseline to after ibutilide infusion for all variables was tested with the paired t test. For selected variables, the difference between the pre-ibutilide (control) infusion value was subtracted from the post–ibutilide infusion value. This difference value was then tested between different sets of patients with the unpaired t test.

**Results**

**Study Protocol Part I**

**Development of AF**
Twenty-two patients had sustained (>10 minutes) AF during invasive EP study before ibutilide infusion. Nine patients (41\%) had a history of AF. Six patients had a history of syncope, aborted sudden death, or rapidly conducting AF over an AP. External cardioversion was attempted initially in 3 patients (average 2 shocks per patient, 200 to 360 J), but AF recurred.

**Cardioversion of AF**
Two milligrams of ibutilide was infused intravenously over 15 minutes during AF. AF terminated in 21 of 22 patients (95\%) either during or 8±5 minutes (mean±SD) after infusion was completed. The remaining patient with persistent AF after ibutilide underwent successful external cardioversion with a single application of 360 J. Two patients in whom the ablation procedure was prolonged had recurrent AF >1 hour after ibutilide infusion. For the group as a whole, the QTc intervals prolonged after ibutilide from 404±30 to 502±30 ms (mean±SD; P<0.001).

**Effects on Ventricular Response During AF**
The shortest preexcited R-R interval during AF could be compared before and after ibutilide infusion in 14 patients with manifest conduction over the AP. The mean shortest preexcited R-R interval during AF increased from 269±54 to 318±47 ms with ibutilide for the 14 patients (P<0.001; mean±SD; Figure 1). Additionally, the shortest preexcited R-R interval during AF prolonged in every patient. In 7 patients with baseline shortest preexcited R-R interval in AF <260 ms, this value prolonged to >260 ms in 5 patients after ibutilide.

The average preexcited R-R interval during AF for the 14 patients with manifest pathways prolonged with ibutilide from 345±72 ms to 442±82 ms before termination (P<0.001; Figure 2). The average R-R interval during AF also prolonged after ibutilide in the 8 patients with concealed pathways from 406±45 to 521±21 ms (P<0.001).
Ibutilide infusion did not affect subsequent successful catheter ablation in all patients. There were no adverse side effects related to the infusion.

Study Protocol Part II

Effects on Atrial and Ventricular Refractory Periods

Of the 18 patients in part II, the atrial ERP could be assessed before and after ibutilide in 17 patients. For the entire group, the atrial ERP increased from 221±29 to 266±37 ms (mean±SD; P<0.001) after infusion. The ventricular ERP could be assessed in 15 patients and increased from 228±25 to 265±32 ms after ibutilide (mean±SD; P<0.01). The atrial and ventricular ERP could not be assessed in each patient because of either tachycardia induction or for technical reasons.

Effects on AVN

The effects of ibutilide on the antegrade AVN ERP could be assessed in 12 patients and prolonged for the entire group from 252±60 to 303±70 ms (mean±SD; P<0.02; see Table 1 and Figure 3). Ibutilide also prolonged the retrograde AVN ERP in 7 patients from 241±57 to 319±78 ms (P<0.02).

The antegrade AVN BCL increased in 7 patients from 309±46 to 387±79 ms (P<0.05) after ibutilide (Table 1). There were no episodes of AV block during or after infusion.

Antegrade Conduction Over the AP

The effects of ibutilide on the antegrade AP ERP could be assessed in 8 of 11 patients with manifest AP conduction and prolonged from 275±40 to 320±60 ms (mean±SD; P<0.01, Table 2). The antegrade AP BCL prolonged with ibutilide in 7 patients in whom it was measured (Table 2) from 276±31 to 353±63 ms (P<0.01). The delta wave disappeared transiently after ibutilide in 1 patient (patient 33) but returned within 15 minutes. The delta wave persisted after ibutilide in the remaining 10 patients with preexcitation (91%). Two patients with concealed pathways (2 of 7, 29%) did not have inducible tachycardia after ibutilide infusion. However, retrograde conduction over the pathway (in 1 patient) allowed for mapping and successful ablation. In another patient (patient 24), retrograde conduction returned 1 hour after ibutilide, allowing for successful ablation.

Retrograde Conduction Over the AP

Ibutilide prolonged the retrograde AP ERP in 15 patients from 283±56 to 345±82 ms (mean±SD; P<0.001, Table 2). The retrograde AP BCL also increased in 16 patients after ibutilide from 305±52 to 389±55 ms (P<0.001; Figure 4). There was no statistical difference between the prolongation of ERP for antegrade versus retrograde AP ERP after ibutilide.

Effects on the HPS

Transient BBB or HV prolongation occurred in 23 patients (23 of 38, 61%) in response to atrial overdrive pacing. In a limited number of patients, data were available to evaluate the effects of ibutilide on HPS conduction and refractory periods. The paced cycle length at which BBB developed prolonged from 322±55 ms to 450±94 ms after ibutilide infusion in 11 patients (mean±SD; P<0.01). Three patients had intrahisian conduction delay or intrahisian block after ibutilide in response to overdrive pacing (Figure 5). The HPS RRP prolonged in 10 patients with ibutilide from 347±40 to 438±25 ms (mean±SD; P<0.001).

Safety Issues

There were no episodes of torsade de pointes or other ventricular arrhythmias associated with ibutilide. Ibutilide infusion probably prolonged the procedure time in 1 patient because of pathway conduction suppression. Ablation was successful in 16 of 18 patients (89%) in whom it was attempted after infusion. Ablation was not attempted in 2 pediatric patients who underwent EP study primarily for risk assessment. Ibutilide was given during sustained orthodromic AVRT in 3 patients and was associated with prolongation of tachycardia cycle length without arrhythmia termination.

Discussion

Ibutilide Effects During AP-Associated AF

We report the first prospective study to examine the ability of ibutilide to terminate AF in patients with APs. We found that
Ibutilide caused a prompt decrease in ventricular response in patients with preexcited AF. This finding was due to prolongation of both preexcited and nonpreexcited R-R intervals during AF. In 5 of 7 patients with the shortest preexcited R-R intervals during AF (260 ms), this value increased to 260 ms after ibutilide. In addition, we found reversion to sinus rhythm in 21 of 22 patients during or 5 minutes after the infusion. Furthermore, the increase in ventricular ERP after ibutilide should provide additional protection against the development of ventricular fibrillation in those patients with short AP ERPs.

Atrial fibrillation complicates catheter ablation of accessory pathways, and repetitive cardioversions may be necessary. We found that pathway function usually persisted after ibutilide infusion, and all patients subsequently underwent successful ablation. No patient had AF up to 1 hour after ibutilide treatment. However, 2 patients with poor AP conduction had transient loss of antegrade AP function after ibutilide infusion.

Ibutilide Effects on the Conduction System

Consistent with previous studies, ibutilide prolonged both the atrial and ventricular ERPs. Additionally, we found that ibutilide markedly increased the AVN ERP in both the antegrade and retrograde directions as well as the antegrade BCL over the AVN. The I_{Kr} current is “the primary repolarizing current in most nodal cells.” Also, a recent report confirmed the presence of I_{Kr} channels in rabbit AVN and that ibutilide affects these channels. Thus, the actions of ibutilide to prolong refractoriness in the AVN are not surprising. However, previous clinical studies of the efficacy of ibutilide in terminating AF have not necessarily shown slowing of the ventricular rate during drug infusion. Minor changes in ventricular rate after ibutilide infusion for AF may be missed. Additionally, we infused ibutilide more rapidly than the previous studies, which may give higher peak tissue doses.

To our knowledge, our study is the first to prospectively examine the effects of ibutilide on the HPS. The RRP of the HPS prolonged in 61% of patients, as manifested by transient development of either HV prolongation or BBB with atrial

### Table 1. Effects of Ibutilide on AVN

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C indicates control; IB, ibutilide; SVT, supraventricular tachycardia; AP, conduction only over AP; AVN, conduction only over AVN; and AP/AVN, conduction over both AP and AVN. Comparisons for statistical purposes were performed only when conduction was over same route (AP or AVN) before and after ibutilide. Antegrade measurements not obtained for patient 28 because atrial pacing induced SVT.
overdrive pacing. However, none had complete AV block. On the basis of our data, we believe that ibutilide should be used with caution in patients who have preexisting BBB. Additionally, wide-complex beats after ibutilide during AF may represent functional BBB and not ventricular ectopy.

**Ibutilide Effects on the AP**

We systematically evaluated for the first time the effects of ibutilide on AP conduction and refractoriness. Ibutilide markedly increased both the antegrade and retrograde AP ERP and antegrade AP BCL. Although several patients exhibited transient loss of preexcitation during ibutilide infusion, retrograde conduction over the pathway was still present that permitted successful ablation.

**Comparison With Other Drugs Used for Preexcited AF**

Currently the only drug approved in the United States for patients with AF and WPW is procainamide. Our study was not designed to compare these two drugs, although other studies have demonstrated the superiority of ibutilide over

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<th>Patient</th>
<th>Antegrade AP BCL, ms</th>
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Comparisons for statistical purposes done only when conduction was over same route (AP or AVN) before and after ibutilide. Only retrograde AP measurements were obtained in patient 1 because atrial fibrillation developed early in protocol and was treated with ibutilide. Antegrade measurements not obtained for patient 28 because atrial pacing induced SVT.
intravenous procainamide at terminating atrial arrhythmias in patients without APs.9,10 Volgman et al9 found that 58% of those treated with ibutilide converted to sinus rhythm versus 18% for procainamide (P<0.0001). Also, ibutilide infusion does not cause hypotension, which is a well-recognized side effect of procainamide. Infusion of procainamide at the recommended rate (20 mg/min) would not be expected to produce therapeutic blood levels for at least 40 to 60 minutes. We found that ibutilide infusion prevented AF recurrence for at least 60 minutes, which allowed successful completion of the procedure.

We found a high conversion rate to sinus rhythm (95%) compared with other reports. Several large studies have shown a conversion rate with AF of only 35% with ibutilide.1–3 This discrepancy may be related to two factors. First, in our study, the AF was treated within minutes of development as compared with earlier reports, in which AF was maintained for days. In addition, we used a higher drug infusion rate, which may have influenced the conversion rate.

Comparison With Previous Ibutilide Studies
On review of the English literature, we found only two case reports in which intravenous ibutilide was used for patients with WPW and AF. Varriale et al11 found that 1 mg of ibutilide successfully terminated AF in an 81-year-old woman with WPW syndrome. Sorbera et al12 gave ibutilide during EP study to 3 patients with AF and AVRT (2 with concealed pathways) to successfully terminate AF.

Therapeutic Implications
In our current study, we first documented the effectiveness and safety of ibutilide in terminating AF that developed during EP study in patients with APs. We then defined its precise mechanism of action on both the AP and AVN. Ibutilide significantly prolongs the refractory period of both the AVN and the AP, as demonstrated by prolongation of the preexcited cycle length during AF.

The American Heart Association (AHA) Guidelines recommend intravenous procainamide as the only pharmacological agent to treat patients with WPW and AF; DC cardioversion is preferred if the patient is hemodynamically unstable.8 Additionally, the recent Advanced Cardiovascular Life Support (ACLS) Guidelines recommend amiodarone and procainamide as treatment choices for hemodynamically stable wide-complex tachycardia, which includes WPW and AF.18 Previous large-scale studies have shown that risk factors to develop torsade de pointes after ibutilide infusion include female sex, heart failure, and prolonged baseline QTc interval.1,4–9 Because most patients with APs have structurally normal hearts, their risk of torsade with ibutilide should be low. On the basis of our current study, we propose that intravenous ibutilide be considered as an alternative drug to treat patients with WPW and AF, particularly in the emergency room or EP laboratory.

Pediatric Experience With Ibutilide
We are unaware of any prior published reports in the English language using ibutilide in the pediatric population. Indeed, most large clinical studies with ibutilide specifically excluded patients under the age of 18 years.2–4,9,10 Our study included 13 pediatric patients ≤18 years of age, none of whom had adverse effects with ibutilide infusion. It is known that fundamental functional and anatomic differences exist in the AVN and APs between adults and children.19 Such studies are of great importance to identify additional antiarrhythmic drugs that may prove useful (and safe) to treat children with preexcited AF.

Safety Concerns
The primary concern with ibutilide use is the development of torsade de pointes, which can occur in up to 8.3% of patients.1,2,3,9 However, most patients who have proarrhythmia with ibutilide have depressed myocardial function, which is generally not the case in patients with APs. Our data apply only to those with structurally normal hearts. An additional concern was that ibutilide might abolish AP conduction and thus delay the study. This finding was never observed in patients with AF and AP conduction, and only 1 patient (without AF) had study delay as the result of effects of ibutilide.

Limitations
Our study included patients with normal cardiac function and should not be extrapolated to patients with structural cardiac disease. We used a more rapid administration of the drug (2 mg IV over 15 minutes) compared with previous studies, for logistical reasons, so as not to unduly prolong the ablation procedure. The mode of ibutilide administration used in our study may result in higher blood levels (due to less time for tissue redistribution) than in previous studies. In prior studies, there was a correlation between drug effect (conversion efficacy or degree of QTc prolongation) and drug dose infused.1,2 We demonstrated the remarkable utility of this dosage regimen in patients with life-threatening arrhythmias.

Conclusions
We noted that ibutilide appears to be very effective and safe in patients with preexcited AF, including children. Also, our data suggest that intravenous ibutilide at least be considered as a suitable alternative to intravenous procainamide in patients with preexcited AF.

Acknowledgments
This study was supported in part during Dr Glatter’s tenure as the Merck Fellow of the American College of Cardiology. We gratefully acknowledge the support of the McIwown Foundation. Dr Glatter was named a Finalist for the Samuel A. Levine Young Investigator’s Award at the Scientific Sessions of the American Heart Association, which will be held in Anaheim, Calif, November 13, 2001.

References


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Circulation. 2001;104:1933-1939
doi: 10.1161/hc4101.097538

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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