

## CLINICAL REVIEW

# Safety and Efficacy of Ibutilide in Cardioversion of Atrial Flutter and Fibrillation

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This article reviews the safety and efficacy of ibutilide for use in patients with atrial fibrillation and flutter. Ibutilide, a class III antiarrhythmic agent, is primarily used for conversion of atrial flutter and fibrillation and is a good alternative to electrical cardioversion. Ibutilide has a conversion rate of up to 75% to 80% in recent-onset atrial fibrillation and flutter; the conversion rate is higher for atrial flutter than for atrial fibrillation. It is also safe in the conversion of chronic atrial fibrillation/flutter among patients receiving oral amiodarone therapy. Ibutilide pretreatment facilitates transthoracic defibrillation and decreases the energy requirement of electrical cardioversion by both monophasic and biphasic shocks. Pretreatment with ibutilide before electrical defibrillation has a conversion rate of 100% compared with 72% with no pretreatment. Ibutilide is also safe and efficient in the treatment of atrial fibrillation in patients who have had cardiac surgery, and in accessory pathway-mediated atrial fibrillation where the conversion rate of ibutilide is as high as 95%. There is up to a 4% risk of torsade de pointes and a 4.9% risk of monomorphic ventricular tachycardia. Hence, close monitoring in an intensive care unit setting is warranted during and at least for 4 hours after drug infusion. The anticoagulation strategy is the same as for any other mode of cardioversion. (J Am Board Fam Med 2011;24:86–92.)

**Keywords:** Antiarrhythmics, Arrhythmia, Atrial Fibrillation, Cardiovascular Disorders, Cardioversion, Drug Therapy, Ibutilide, Patient Safety, QT Prolongation

In selected patient populations, cardioversion still remains the preferred management for atrial fibrillation and flutter, even though data suggest no survival advantage for rhythm control over rate control.<sup>1</sup> Electrical cardioversion has been the most widely used and the most effective method to restore sinus rhythm in these atrial arrhythmias. However, chemical cardioversion is a good alternative for use in certain patient groups. Chemical cardioversion is less invasive, more cost-effective, and, unlike electrical cardioversion, it does not require sedation.<sup>2–4</sup> The various drugs commonly

used for pharmacologic cardioversion are ibutilide, procainamide, propafenone, flecainide, amiodarone, and dofetilide. Among these drugs, ibutilide, dofetilide, flecainide, and propafenone have class I (level of evidence A) indication for their use in pharmacologic cardioversion of atrial fibrillation.<sup>5</sup> This corresponds to the Strength of Recommendation Taxonomy (SORT) level 1 recommendation. Amiodarone has class IIa (SORT level 2 recommendation), whereas procainamide and quinidine have class IIb (SORT level 3 recommendation) indication for their use in cardioversion of atrial fibrillation.<sup>5</sup> Digoxin and sotalol do not have proven efficacy when used for this purpose.<sup>5</sup>

Ibutilide—despite its efficacy, which is comparable or superior to other agents—is not widely used, mainly because of physician's lack of awareness about its safety and efficacy profile. This article reviews the safety and efficacy data of ibutilide and also compares it with other antiarrhythmics used for atrial fibrillation and flutter.

Ibutilide, a class III antiarrhythmic drug that was approved by the Food and Drug Administration for

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use on December 28, 1995, is available only for intravenous use because of its extensive first-pass metabolism. It prolongs repolarization time, action potential duration, and refractory period of atrial and ventricular myocardium through its action as a potassium channel blocker, affecting the rapid component of the cardiac delayed rectifier potassium current.<sup>6</sup> In addition to this action, ibutilide also activates the slow delayed inward sodium current that occurs early during repolarization.<sup>6</sup> Ibutilide also increases the refractory period of the accessory pathway, the His-Purkinje system, and the atrioventricular node.<sup>6</sup>

The most common electrocardiography changes caused by ibutilide are mild slowing of the sinus rate and prolongation of QT interval, similar to most other class III antiarrhythmic drugs. The degree of prolongation of QT interval is related to the dose, the rate of infusion, and serum concentration.<sup>7</sup> The QT interval returns to baseline within 2 to 4 hours after stopping the infusion<sup>8,9</sup>; however, PR or QRS intervals are not affected.<sup>10</sup>

### Use of Ibutilide in Chemical Cardioversion in Acute Atrial Fibrillation and Flutter

Ibutilide can be used as a first-line agent in chemical cardioversion of recent-onset atrial fibrillation and flutter. Its rapid onset of action can be especially beneficial for patients with depressed left ventricular function, and these patients tolerate the drug well.<sup>10</sup> It has been seen in various studies that the cardioversion rate in atrial fibrillation of <90 days' duration was higher (31% to 44%) with ibutilide (a dose of 0.015 mg/kg or 2 mg) compared with placebo,<sup>11</sup> sotalol (1.5 mg/kg),<sup>12</sup> or procainamide 1200 mg.<sup>13–15</sup> In acute episodes with onset of 3 to 48 hours, ibutilide has a higher efficacy in atrial flutter (87%) compared with atrial fibrillation (77%). More than 80% of patients with recent-onset atrial flutter are converted to sinus rhythm within 30 minutes of drug administration.<sup>16</sup> The same study<sup>16</sup> compared the efficacy of intravenous ibutilide to intravenous amiodarone in the conversion of atrial fibrillation or atrial flutter, and the conversion rate was found to be significantly higher with ibutilide (80% vs 57%;  $P = .0054$ ). A subanalysis of the same study showed no significant difference in the conversion rate between these drugs in patients with atrial fibrillation (77% vs 69%;  $P = \text{NS}$ ); however, when used for atrial

flutter, ibutilide was superior to amiodarone (87% vs 29%;  $P = .003$ ). It was concluded that ibutilide was more effective than amiodarone in converting recent-onset atrial flutter to sinus rhythm, but both drugs are equally effective in converting recent-onset atrial fibrillation to sinus rhythm.<sup>16</sup> In new-onset arrhythmia, a single dose of ibutilide successfully converted 53% patients' fibrillation or flutter into sinus rhythm, and an additional 22% patients converted with the second dose, which resulted in an overall conversion rate of 75%.<sup>17</sup> Female sex and younger age were independent predictors of successful cardioversion with ibutilide.<sup>18</sup>

### Use of Ibutilide in Postoperative Atrial Fibrillation and Flutter

Ibutilide is safe and effective when used to terminate atrial fibrillation and flutter in the period after cardiac surgery. There was an incremental increase in the overall conversion rate with increasing doses of ibutilide (40% with a dose of 0.25 mg, 47% with a dose of 0.5 mg, and 57% with 1.0-mg dose). The time to conversion also decreased with increasing doses of ibutilide.<sup>19</sup> The conversion rates were higher in all doses for atrial flutter compared with atrial fibrillation. Ibutilide's efficacy and safety profile was compared with those of amiodarone and propafenone in terminating postoperative atrial fibrillation<sup>20,21</sup> (Table 1). It was as effective as amiodarone in converting postoperative atrial fibrillation; however, the time to cardioversion was significantly lower in patients receiving ibutilide. In a study that randomized patients in a double-blind fashion to either ibutilide or amiodarone, these drugs had comparable conversion rates at 4 hours.<sup>20</sup> Ibutilide was superior in terms of hemodynamic and systemic side effects; hypotension was seen more often in patients receiving amiodarone.<sup>20</sup>

Another study, in which 42 stable patients with new atrial fibrillation after cardiac surgery were randomized to oral propafenone (600 mg, single dose), ibutilide (1 mg up to 2 doses if necessary), or rate control with, preferably, a  $\beta$ -blocker, ibutilide was significantly superior to propafenone in terminating the arrhythmia. At 24 hours, none of the patients in the ibutilide group were in atrial fibrillation, compared with 65% of patients in propafenone.<sup>21</sup> However, none of these drugs affected the length of hospital stay or the rhythm at

**Table 1. Comparison of the Conversion Rates of Ibutilide, Amiodarone, Propafenone, Procainamide, Dofetilide, and Flecainide in Recent-Onset Atrial Fibrillation, Persistent Atrial Fibrillation, and Recent-Onset Atrial Flutter**

Pharmacological Agent	Conversion Rates (%)		
	Recent-Onset Atrial Fibrillation	Persistent Atrial Fibrillation/Flutter	Recent-Onset Atrial Flutter
Ibutilide	31–77 <sup>11,16,18</sup>	48 <sup>12</sup>	63–76 <sup>17,22</sup>
Amiodarone	34–69 (with bolus regimen) <sup>23</sup> 55–95 (with bolus followed by continuous infusion)	15–48 <sup>24–29</sup>	29 <sup>16</sup>
Propafenone	56–87.5 <sup>30,31</sup>	37.5–40 <sup>31,32</sup>	40 <sup>33</sup>
Procainamide	20–60 <sup>34,35</sup>		14 <sup>36</sup>
Dofetilide	24 <sup>37</sup>	20 (dose of 125 mcg bid) 44 (250 mcg bid) 85 (500 mcg bid) <sup>38</sup> 66.7 atrial flutter <sup>39</sup>	64 <sup>37</sup>
Flecainide	57–68 (at 2–4 hr) <sup>18,40</sup> 75–91 (at 8 hr) <sup>40</sup>		13 (with intravenous administration) <sup>41</sup>

discharge when compared with rate control. Therefore, it was suggested that, because of the transient nature of the arrhythmia, routine attempts to cardiovert with antiarrhythmic agents is not necessary in stable patients with postoperative atrial fibrillation.

### Use of Ibutilide in Persistent Atrial Fibrillation and Flutter

The efficacy data of the use of ibutilide in the cardioversion of persistent atrial fibrillation is not as impressive as the data about use of ibutilide for acute atrial fibrillation. In the study by Vos et al,<sup>12</sup> the conversion rate of persistent atrial fibrillation lasting for >30 days with ibutilide was 48%. The predictors of successful cardioversion found in another study were lower duration of the arrhythmia, the presence of underlying atrial flutter, the absence of heart failure, and the absence of concomitant digoxin therapy.<sup>42</sup> Ibutilide is also safe and effective in cardioversion of patients with a history of persistent atrial fibrillation or flutter who are taking oral amiodarone treatment for the prevention of recurrences of these arrhythmias. Because of the long half-life of amiodarone it is often not feasible to discontinue it before ibutilide administration; both of these drugs are class III antiarrhythmic agents and the prolongation of the QT interval could result in proarrhythmia. Glatter et al<sup>22</sup> addressed this concern of the increased incidence of proarrhythmia. In their study, which assessed the efficacy and safety of cardioversion with combination therapy in patients with atrial fibrilla-

tion or flutter, it was found that within 30 minutes of infusion, ibutilide converted 54% of patients with atrial flutter and 39% of patients with atrial fibrillation who had been treated with long-term amiodarone. The use of ibutilide was found to be safe in these patients, with no excess occurrence of proarrhythmia.<sup>22</sup>

Ibutilide pretreatment also has been found to facilitate successful electrical cardioversion. Ibutilide significantly facilitates cardioversion of atrial fibrillation with standard monophasic transthoracic defibrillation.<sup>3</sup> There was a 100% conversion rate in patients receiving pretreatment with ibutilide compared with 72% in patients receiving no pretreatment. In pretreated patients, transthoracic electrical cardioversion was performed 10 minutes after completion of infusion of 1 mg of ibutilide given intravenously over 10 minutes. Moreover, the patients who did not convert with initial transthoracic cardioversion converted after pretreatment with ibutilide. The energy requirement for defibrillation after pretreatment was significantly reduced ( $166 \pm 80$  Joules vs  $228 \pm 93$  Joules).<sup>3</sup> Ibutilide pretreatment preceding biphasic shock defibrillation improves the efficacy of cardioversion by reducing the number of attempts and the energy requirement, thereby lowering the risk of muscle damage.<sup>2</sup>

Ibutilide has a greater efficacy in conversion of atrial flutter compared with atrial fibrillation, especially in patients with recent-onset arrhythmia.<sup>15</sup> Ibutilide causes the prolongation of atrial flutter cycle length and increases cycle length variability

by fully abolishing the excitable gap.<sup>43</sup> Studies also have shown that ibutilide increases the atrial effective refractory period that leads to significant variability in the cycle length of typical atrial flutter before termination.<sup>44,45</sup> Pretreatment with ibutilide also has been shown to facilitate the cardioversion of atrial flutter by atrial overdrive pacing.<sup>46</sup>

### **Ibutilide Use in Terminating Accessory Pathway–Mediated Atrial Fibrillation**

Ibutilide was very effective in terminating accessory pathway–mediated atrial fibrillation. In a study by Glatter et al,<sup>6</sup> it was found that the conversion rate of ibutilide to terminate such arrhythmia was as high as 95%. In this study the atrial fibrillation was treated within minutes of development. In addition, a higher drug infusion rate was used, which may have resulted in the high conversion rate. In another study by Volgman et al,<sup>13</sup> when ibutilide was compared with procainamide, ibutilide's conversion rate to sinus rhythm in these patients was 58% versus 18% for procainamide ( $P < .0001$ ). Moreover, procainamide caused hypotension whereas ibutilide infusion did not. Ibutilide was also effective in preventing the recurrence of atrial fibrillation for at least 60 minutes, which allowed successful completion of an ablation procedure.<sup>6</sup>

### **The Use of Ibutilide in Children**

The safety and efficacy of ibutilide in the cardioversion of atrial flutter and atrial fibrillation in the pediatric population and in patients with congenital heart disease is not well known. A retrospective review of the data from 19 patients (range, 6 months to 34 years; median, 16 years) who received ibutilide for atrial flutter or atrial fibrillation found that the overall conversion rate was 71%, with a 63% success rate with administration of the first dose. Fourteen episodes in 6 patients required electrical cardioversion after failure of ibutilide treatment. Ibutilide was well tolerated with no episodes of symptomatic bradycardia, but there was one episode of both torsade de pointes and unsustained ventricular tachycardia. It was concluded that, with careful monitoring, ibutilide could be an effective tool for use in pediatric patients for cardioversion of atrial flutter and fibrillation.<sup>47</sup> The approved dose of ibutilide in patients weighing  $>60$  kg is 1 mg intravenously given as a 10-minute infusion. In

patients weighing  $<60$  kg, the dose is 0.01 mg/kg given as a 10-minute infusion.

### **Use of Ibutilide in Acute Atrial Fibrillation in the Elderly**

Ibutilide is a safe and effective antiarrhythmic agent for use in the elderly. In a study done to assess the efficacy of ibutilide in elderly patients (age,  $\geq 65$  years), the overall rate of successful conversion was 59%. In the same study on subanalysis, the conversion rate for atrial fibrillation was 63% and was 54% for atrial flutter. The mean conversion time was  $33 \pm 45$  minutes. Three fourths of the conversions occurred within 45 minutes of treatment. Ibutilide-induced lengthening of the QTc interval was  $17 \pm 21$  milliseconds. This data shows that ibutilide seems to be a safe and effective drug for conversion of recent-onset atrial fibrillation and flutter in elderly patients when monitored carefully.<sup>48</sup>

### **Adverse Effects of Ibutilide**

Ibutilide causes prolongation of the QT interval, like any other Class III antiarrhythmic agent, thus increasing the risk of fatal arrhythmias. The most common and the most serious of these arrhythmias is torsade de pointes, which is a distinct, polymorphic, ventricular tachycardia occurring in the setting of a prolonged QT interval.<sup>49,50</sup> The predictors of occurrence of torsades de pointes in patients treated with ibutilide are bradycardia, small body size, history of heart failure, nonwhite race, and female sex.<sup>50</sup> Most episodes of torsade de pointes occur during the first hour of treatment with ibutilide. The half-life of ibutilide is 3 to 6 hours; its clinical effect can be measured by the corrected QT interval, which disappears in 2 to 6 hours. Hence, a minimum of a 4- to 6- hour observation period is recommended after ibutilide treatment.<sup>8,9</sup> The rate of administration may also be important because faster rates of administration of class III agents have been shown in experimental models to increase the risk of torsade de pointes.<sup>51</sup> The risk is increased in patients with severe left ventricular systolic dysfunction with an ejection fraction  $<20\%$ .<sup>3</sup> Caution should be used in patients with ischemia, previous myocardial infarction, and uncompensated heart failure because ibutilide-induced torsade de pointes maybe difficult to treat in these patients.<sup>50</sup>

The risk of developing torsade de pointes with ibutilide monotherapy is 4%.<sup>52</sup> However, the risk is



reduced to 1% in patients who are already taking propafenone or flecainide. This reduction in risk is because of the protective effect of the sodium channel blockade of type IC drugs.<sup>53,54</sup> The incidence of ventricular arrhythmias including torsade de pointes may also be reduced with intravenous infusion of high-dose magnesium sulfate.<sup>55,56</sup> Precautions should be taken to reduce this risk of fatal arrhythmia by the appropriate selection of patients for ibutilide treatment, correction of serum potassium and magnesium abnormalities, ensuring immediate availability of resuscitation equipment, and monitoring for at least 4 hours after ibutilide infusion.

The risk of unsustained monomorphic ventricular tachycardia is 4.9%.<sup>8</sup> This rate is decreased by the infusion of intravenous magnesium before ibutilide administration. In view of the risk of ventricular arrhythmias, patients should be monitored in an intensive care unit during and for at least 4 hours after ibutilide infusion. The administration of ibutilide should be under the supervision of a cardiologist or a physician who is trained in emergent arrhythmia management and is certified in Advanced Cardiac Life Support. There is no increased risk of hypotension, conduction block, or bradycardia.

Adequate anticoagulation to reduce the risk of stroke is necessary before attempting cardioversion with ibutilide. When attempting cardioversion with ibutilide, standard guideline recommendation for electrical cardioversion should be followed. If the duration of atrial fibrillation or flutter is >48 hours or if its onset is unknown, a transesophageal echocardiogram should be performed to assess the presence of a left atrial thrombus. Presence of an intracardiac thrombus is a contraindication for cardioversion.

## Conclusion

The efficacy of ibutilide for rapid conversion of atrial fibrillation and atrial flutter to sinus rhythm is superior to most of the other antiarrhythmic agents (table 1). However, it seems to be underused in clinical practice because of a lack of awareness of its efficacy and safety profile. It is a good alternative to electrical cardioversion and also can be used to facilitate cardioversion with both monophasic and biphasic direct current shock. Ibutilide also increases the efficacy of other antiarrhythmic agents like amiodarone and propafenone. It can be safely

used in children and elderly patients. The risk of torsade de pointes with ibutilide is small and can be minimized by adequate selection of patients and careful monitoring of the patients in the peri-infusion period.

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