A NEW ANTIARRHYTHMIC COMPOUND POTENT CLASS III IBUTILIDE: AN OVERVIEW

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ABSTRACT

This article reviews the safety and efficacy of ibutilide for use in patients with atrial fibrillation and flutter. Ibutilide, a methanesulfonamide derivative is a class III antiarrhythmic drug that was approved by the Food & Drug Administration for 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. The drug is indicated for the rapid restoration of normal sinus rhythm in patients with atrial fibrillation or atrial flutter of recent onset who are hemodynamically stable. The ibutilide effects is dependent on concentration. Clinical trials have established ibutilide's efficacy in converting sustained atrial flutter and atrial fibrillation to normal sinus rhythm. 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. Comparative studies have reported that ibutilide was a more effective intravenous agent than amiodarone, DL-sotalol, procainamide for conversion of atrial flutter and atrial fibrillation. The present review describe 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.

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INTRODUCTION
Atrial arrhythmias after cardiac surgery occur in 15% to 40% of patients\(^1\)\(^-\)\(^3\). Atrial fibrillation (AF) is a disturbance of the normally rhythmical beating of the cardiac atria, characterized by rapid (e.g., 400–600 beats/min), irregular electrical and mechanical activation of the atrial muscle. It is the most common cardiac arrhythmia encountered in clinical practice, and has multiple causes, such as coronary artery disease, heart failure, valve disease and hypertension. Patients with AF have an increased risk of death from stroke due to embolisation of atrial thrombi which form because the rapid and irregular activation causes uncoordinated atrial contraction and hence disturbed and reduced atrial blood flow. AF can be treated with electrical cardioversion, tissue ablation, and pharmacological therapy; the latter being the mainstay, particularly in the expanding elderly population. However, currently available antiarrhythmic drugs are only moderately effective in preventing or terminating AF or maintaining sinus rhythm after it is restored, and may also exert adverse effects such as ventricular pro-arrhythmia, organ toxicity, or both\(^4\). Anti-arrhythmic drugs are conventionally grouped according to their broad mechanism of action (Vaughan Williams, 1984), namely, Na\(^+\) channel blockade (class I), \(\beta\)-adrenoceptor antagonism (II), action potential prolonging (III), and Ca\(^{2+}\) channel blockade (IV). Many drugs that prevent AF possess activity in more than one class, and some in none. Although different classification schemes have been proposed, the first scheme (Vaughan-Williams) is still the one that most physicians use for antiarrhythmic drugs.

Table 1: Vaughan-Williams classification scheme of antiarrhythmic drugs.

<table>
<thead>
<tr>
<th>Class</th>
<th>Known as</th>
<th>Examples</th>
<th>Mechanism</th>
<th>Clinical uses in cardiology</th>
</tr>
</thead>
</table>
| Ia    | Fast-channel blockers-affect QRS complex | Quinidine, Procainamide, Disopyramide | (Na\(^+\)) channel block (intermediate association/dissociation) | • Ventricular arrhythmias  
• Prevention of paroxysmal recurrent atrial fibrillation (triggered by vagal overactivity)  
• Propranolol in Wolff-Parkinson-White syndrome |
| Ib    | Do not affect QRS complex | Lidocaine, Phenytoin, Mexiletine, Tocainide | (Na\(^+\)) channel block (fast association/dissociation) | • Treatment and prevention during and immediately after myocardial infarction, though this practice is now discouraged given the increased risk of a systole  
• ventricular tachycardia  
• atrial fibrillation |
| Ic    | | Flecaínide, Propafenone, Moricizine | (Na\(^+\)) channel block (slow association/dissociation) | • Prevents paroxysmal atrial fibrillation  
• Treats recurrent tachyarrhythmias of abnormal conduction system.  
• Contraindicated immediately post-myocardial infarction.  
• Decrease myocardial infarction mortality  
• Prevent recurrence of tachyarrhythmias |
| II    | Beta-blockers | Propranolol, Esmolol, Timolol, Metoprolol, Atenolol, Bisoprolol | Beta blocking | • In Wolff-Parkinson-White syndrome  
• (sotalol:) ventricular tachycardias and atrial fibrillation  
• (Ibutilide:) atrial flutter and atrial fibrillation |
| III   | K\(^+\) channel blocker | Amiodarone, Sotalol, Ibutilide, Dofetilide, Dronedarone, E-4031 | Sotalol is also a beta blocker  
Amiodarone has Class I, II, III & IV activity | • Prevent recurrence of paroxysmal supraventricular tachycardia  
• Reduce ventricular rate in patients with atrial fibrillation  
• Used in supraventricular arrhythmias, especially in Heart Failure with Atrial Fibrillation, contraindicated in ventricular arrhythmias. Or in the case of Magnesium Sulfate, used in Torsades de Pointes |
| IV    | Slow-channel blockers | Verapamil, Diltiazem | Ca\(^{2+}\) channel blocker | • Prevent recurrence of paroxysmal supraventricular tachycardia  
• Reduce ventricular rate in patients with atrial fibrillation  
• Used in supraventricular arrhythmias, especially in Heart Failure with Atrial Fibrillation, contraindicated in ventricular arrhythmias. Or in the case of Magnesium Sulfate, used in Torsades de Pointes |
| V     | | Adenosine, Digoxin, Magnesium Sulfate | Work by other or unknown mechanisms (Direct nodal inhibition). |
Nevertheless, this classification serves as a useful basis for assessing and comparing electrophysiological effects of drugs with broadly related activities. These arrhythmias, although not lethal, predispose to cerebrovascular accidents can cause disabling symptoms (especially in patients with significant cardiac dysfunction) and are responsible for a prolonged length of stay and an increased hospital cost. Thus, measures to terminate these arrhythmias acutely would be clinically useful. The purpose of the present review is to extend the awareness about the safety and efficacy profile of ibutilide which is superior to most of the other antiarrhythmic agents. Ibutilide fumarate is a class III antiarrhythmic drug recently approved for the acute termination of atrial fibrillation (AF) and flutter (AF).

Chemistry:
Common Name: Ibutilide fumarate
Chemical Name: Methanesulfonamide, N-{4-[4-(ethylheptylamino)-1-hydroxybutyl]phenyl, (+) (-), (E)-2-butenedioate (1:0.5) (hemifumarate salt)
Description: Ibutilide fumarate: White to off-white powder with an aqueous solubility of over 100 mg/mL at pH 7 or lower. Ibutilide fumarate (racemate) melts over the range of 117 to 121°C.
Chemical Structure:

![Chemical Structure of Ibutilide Fumarate]

It is a potent blocker of the rapid component of the cardiac-delayed rectifier potassium current and also activates the slow inward sodium current. Ibutilide has been shown to be modestly effective in terminating both atrial flutter and atrial fibrillation, particularly if the arrhythmia is relatively short-lived, and may be more effective than other anti-arrhythmic drugs for this purpose. This drug, however, never enjoyed mainstream success because of modest efficacy, a potentially high risk of torsade-de-pointes in some patients, and the time commitment for physicians and other personnel. Older drugs, such as quinidine and procainamide, are not as effective as ibutilide and carry additional risks so that they have faded from the scene. Other drugs, including intravenous b-blockers, terminate atrial fibrillation rarely, and most conversions noted after administration are probably spontaneous reversions. The only exception to this is post-operative atrial fibrillation, where adrenergic activation plays an important role, and intravenous esmolol was associated with superior conversion rates when compared with diltiazem. Newer drugs such as vernakalant hydrochloride, a multi-channel and partially specific atrial potassium channel blocker, also available as an intravenous infusion, but not yet approved for use in many countries, can terminate atrial fibrillation (but not atrial flutter) with similar efficacy and perhaps with a lower risk of developing torsade-de-pointes. Given these limitations, improved conversion rates and reduction in proarrhythmic risks with current pharmacological agents or newer agents are of significant interest. Though ibutilide is similar to sotalol in chemical structure, it has a unique class III action by prolonging the APD not only via HERG channel block (human cardiac delayed rectifier K+ channel) but also via activation of a slow inward current carried by Na+. This dual mode of action is associated with QT prolongation and enhanced risk of torsades-de-pointes arrhythmias. When used intravenously for pharmacological conversion of AF the risk can be greatly reduced by administering simultaneously the short acting β-adrenoceptor blocker esmolol.

USES:
a) 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. 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\textsuperscript{19}, sotalol (1.5 mg/kg)\textsuperscript{20}, or procainamide 1200 mg\textsuperscript{21-23}. In acute episodes with onset of 3 to 48 hrs, 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\textsuperscript{24}. The same study\textsuperscript{24} 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%; \(P = 0.0054\)). A sub-analysis 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%; \(P = 0.003\)). 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\textsuperscript{24}. 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% \textsuperscript{25}. Female sex and younger age were independent predictors of successful cardioversion with ibutilide\textsuperscript{26}.

\textbf{b) 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\textsuperscript{27}. 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\textsuperscript{28,29}. 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 hrs\textsuperscript{28}. Ibutilide was superior in terms of hemodynamic and systemic side effects; hypotension was seen more often in patients receiving amiodarone\textsuperscript{28}.

\textbf{Table-2: 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.}

<table>
<thead>
<tr>
<th>Pharmacological Agent</th>
<th>Recent-Onset Atrial Fibrillation</th>
<th>Persistent Atrial Fibrillation/Flutter</th>
<th>Recent-Onset Atrial Flutter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibutilide</td>
<td>31–77</td>
<td>48</td>
<td>63-76</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>34–69 (with bolus regimen)</td>
<td>15-48</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>55–95 (with bolus followed by continuous infusion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>56–87.5</td>
<td>37.5-40</td>
<td>40</td>
</tr>
<tr>
<td>Procainamide</td>
<td>20–60</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>24</td>
<td>20 (dose of 125 mcg bid)</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 (250 mcg bid)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>85 (500 mcg bid)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>85 (500 mcg bid)</td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>57–68 (at 2–4 hr)</td>
<td>-</td>
<td>13 (with intravenous administration)</td>
</tr>
<tr>
<td></td>
<td>75–91 (at 8 hr)</td>
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</table>
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 β-blocker, ibutilide was significantly superior to propafenone in terminating the arrhythmia. At 24 hrs, none of the patients in the ibutilide group were in atrial fibrillation, compared with 65% of patients in propafenone. However, none of these drugs affected the length of hospital stay or the rhythm at 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.

c) 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 (20), 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. 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 (31) 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 fibrillation 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.

Ibutilide pretreatment also has been found to facilitate successful electrical cardioversion. Ibutilide significantly facilitates cardioversion of atrial fibrillation with standard monophasic transthoracic defibrillation. 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±80 Joules vs 228±93 Joules). 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.

Ibutilide has a greater efficacy in conversion of atrial flutter compared with atrial fibrillation, especially in patients with recent-onset arrhythmia. Ibutilide causes the prolongation of atrial flutter cycle length and increases cycle length variability by fully abolishing the excitable gap. 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. Pretreatment with ibutilide also has been shown to facilitate the cardioversion of atrial flutter by atrial overdrive pacing.

d) 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 (38) 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 (21) when ibutilide was compared with procainamide, ibutilide's conversion rate to sinus rhythm in these patients was 58% versus 18% for procainamide (P<0.0001). 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.

**Pharmacology**: Ibutilide is a methanesulfonamide derivative with structural similarities to the antiarrhythmic agent sotalol. This drug increases action potential duration as its primary mechanism of action, so-called class III effect, largely by blocking the rapid component of the cardiac delayed rectifier potassium current, $I_{Kr}$. In isolated cardiac myocytes, ibutilide also prolongs action potential duration, although its mechanism of action is unique among available class III drugs. At nanomolar concentrations, ibutilide appears to activate a slow inward current, largely carried by sodium ions, that is unresponsive to $I_{Kr}$ blockers. In addition, ibutilide blocks $I_{Kr}$ on the basis of both binding studies of 3H-dofetilide in guinea pig ventricular myocytes and patch-clamp studies in an atrial tumor cell line in which $I_{Kr}$ is the major repolarizing current. Over a limited range of stimulation rates, ibutilide can increase action potential duration without significant reverse use dependence or loss of effect at rapid pacing rates. In humans, ibutilide causes a dose and concentration-related increase in the uncorrected and rate-corrected QT interval in both healthy volunteers and patients with atrial fibrillation and atrial flutter. Recent studies indicate that the congenital long-QT syndrome can arise from ion channel mutations that cause either reduced $I_{Kr}$ current or enhanced inward sodium current. Therefore, it is not surprising that ibutilide administration can cause excessive QT prolongation associated with the development of triggered activity (early after depolarization) in animal models and torsade de points in patients. Action potential prolongation by ibutilide leads to an increase in atrial and ventricular refractoriness in vivo. In models of atrial flutter, this was associated with arrhythmia termination, with an increase in atrial flutter cycle length before conversion, suggesting slowed conduction in some area of the reentrant circuit.

The drug was also effective in termination of atrial fibrillation in a model of coronary occlusion with ischemic left ventricular dysfunction. In patients with atrial flutter, ibutilide caused greater prolongation of repolarization (and therefore refractoriness) than slowing of conduction, this effect would cause a reduction in the excitable gap of a reentrant circuit and likely contributes to arrhythmia termination under these circumstances. In a model of recent myocardial infarction, ibutilide was also effective at suppressing inducible ventricular arrhythmias. Additional evidence indicates that the drug can lower the energy threshold required for ventricular defibrillation. Although administration of ibutilide can cause mild slowing of sinus rate and AV nodal conduction, there was no significant effect on heart rate, PR interval, or QRS interval during a dose-response study of ibutilide in healthy volunteers. Ibutilide administration is associated with minimal hemodynamic effects both in animal models of ischemic left ventricular dysfunction and in patients.

In a study of hemodynamic function in patients with a range of ejection fractions (including 35%), intravenous ibutilide had no clinically significant effects on cardiac output, mean pulmonary arterial pressure, or pulmonary capillary wedge pressure after doses up to 0.03 mg/kg. There has been no clinically significant effect of ibutilide to lower blood pressure or worsen congestive heart failure in published clinical trials. In reproduction studies in rats, orally administered ibutilide was both teratogenic and embryocidal. The excretion of the drug into breast milk has not been studied. Ibutilide has not been shown to be genotoxic in multiple tests including the Ames assay, although no animal studies have been conducted to determine its carcinogenic potential.

**Mechanism of action**: Unlike most other Class III antiarrhythmic drugs, ibutilide does not produce its prolongation of action potential via blockade of cardiac delayed rectifier of potassium current $I_{Kr}$, nor does it have a sodium-blocking, anti-adrenergic, and calcium blocking activity that other Class III agents possess. Thus it is often referred as a “pure” Class III antiarrhythmic drug. It does have action on the slow sodium channel and promotes the influx of sodium through these slow channels. Although potassium current seems to play a role, their interactions are complex and not well understood. Ibutilide’s unique mechanism works by an activation of a specific inward sodium current, thus producing its therapeutic response in which a prolonged action potential increases myocytes’ cardiac refractoriness in case of atrial fibrillation and flutter. The Class III drugs block $I_{Kr}$,
the rapid component of the cardiac delayed rectifier potassium current. This results in prolonged repolarization, increased action potential duration, and lengthening of the refractory period\textsuperscript{56,57}. Ibutilide increases the refractoriness of atrial and ventricular myocardium, the atrioventricular node, His-Purkinje system, and accessory pathway. In addition, ibutilide activates a slow, delayed inward sodium current that occurs early during repolarization\textsuperscript{45,52-54,60}.

**Pharmacokinetics:** Ibutilide is not available for long-term oral use because of extensive first-pass metabolism when administered by this route. After intravenous administration, the plasma concentration declines in a multiexponential manner, with a high systemic plasma clearance that approximates liver blood flow\textsuperscript{61,62}. Pharmacokinetic properties are linear with respect to dose\textsuperscript{60}.

**Table-3:** Pharmacokinetic properties of Ibutilide

<table>
<thead>
<tr>
<th>Properties</th>
<th>Ibutilide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic oxidation</td>
</tr>
<tr>
<td>Half-life</td>
<td>6 hours (2-12 hours)</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal (82%), fecal</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>40%</td>
</tr>
<tr>
<td>Dose</td>
<td>1mg</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>11L/Kg</td>
</tr>
</tbody>
</table>

Co-administration of digoxin, calcium channel blockers, or β-adrenergic receptor blockers with ibutilide has no apparent effect on the pharmacokinetics, safety, or efficacy of the drug in clinical trials\textsuperscript{62}. In healthy male volunteers, about 82% of a 0.01 mg/kg dose of ibutilide was excreted in the urine (about 7% of the dose as unchanged ibutilide) within 4 days of dosing, and the remainder (19%) was recovered in the faeces within 7 days of dosing. Clearance appears to be unaltered by either a reduction in creatinine clearance or left ventricular dysfunction. However, abnormal liver function would likely lead to reduced clearance and prolonged pharmacological effect and might necessitate longer periods of monitoring in these patients after ibutilide administration\textsuperscript{62}. In normal volunteers and patients with atrial fibrillation and atrial flutter, ibutilide pharmacokinetics are not influenced by patient age, sex, or type of arrhythmia\textsuperscript{60,62,64}.

**Safety and efficacy 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\textsuperscript{74}. 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.

**Safety and efficacy of ibutilide in 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, ≥65 years), the overall rate of successful conversion was 59%. In the same study on sub-analysis, the conversion rate for atrial fibrillation was 63% and was 54% for atrial flutter. The mean conversion time was 33 ± 45 minutes. Three fourths of the conversions occurred within 45 minutes of treatment. Ibutilide-induced lengthening of the QTc interval was 17±21 milliseconds. This data showed 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\textsuperscript{75}.
Adverse effects: 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. 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. Most episodes of torsade-de-pointes occur during the first hour of treatment with ibutilide. The half-life of ibutilide is 3 to 6 hrs; its clinical effect can be measured by the corrected QT interval, which disappears in 2 to 6 hrs. Hence, a minimum of a 4 to 6 hrs observation period is recommended after ibutilide treatment. 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. The risk is increased in patients with severe left ventricular systolic dysfunction with an ejection fraction <20%. 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.

The risk of developing torsade-de-pointes with ibutilide monotherapy is 4%. 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. The incidence of ventricular arrhythmias including torsade de pointes may also be reduced with intravenous infusion of high-dose magnesium sulfate. 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 hrs after ibutilide infusion.

The risk of un-sustained monomorphic ventricular tachycardia is 4.9%. 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 hrs 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 hrs 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.

Dosage and administration: For intravenous administration, the recommended dose of ibutilide is 1 mg over a 10-minute period in patients weighing ≥60 kg. Ten minutes after the end of the initial infusion, a second 10-minute infusion of equal strength can be given if the arrhythmia has not terminated. For patients weighing <60 kg, the recommended dose is 0.01 mg/kg initially, with a second dose of the same strength 10 minutes later if necessary. The ibutilide infusion should be stopped as soon as the arrhythmia is terminated or in the event of nonsustained/sustained ventricular tachycardia or marked prolongation of the QT/QTc interval. Patients should be monitored for at least 4 hrs after the infusion or until the QTc has returned to baseline, with a longer monitoring period if nonsustained ventricular tachycardia develops. Patients with hepatic dysfunction should also be monitored for an extended period of time given the likelihood of reduced drug clearance in this situation. It is currently recommended that therapy with antiarrhythmic drugs that prolong the QT interval (class Ia and class III) be withheld for at least 4 hrs after ibutilide administration. Ibutilide should not be administered to pregnant women unless it is determined that the clinical benefit outweighs potential risks to the fetus. The safety and efficacy of ibutilide in persons younger than 18 years of age has not been determined.
Drug interactions: No specific or formal drug interaction studies have been conducted.

**Antiarrhythmics**: Class Ia antiarrhythmic drugs (Vaughan Williams classification), such as disopyramide, quinidine and procainamide and other class III drugs, such as amiodarone and sotalol, should not be given concomitantly with ibutilide or within 4 hrs post-infusion because of their potential to prolong refractoriness. These antiarrhythmics may be administered 4 hrs after the ibutilide dosing.

**Drugs that Prolong the QT Interval**: The potential for proarrhythmia may increase with the administration of ibutilide to patients who are being treated with drugs that prolong the QT interval. These include psychoactive drugs such as phenothiazines, tricyclic antidepressants, tetracyclic antidepressants, and pimozide; antihistamine drugs (eg. terfenadine, astemizole); antimicrobials (eg. erythromycin particularly intravenously); antimalarials (eg. halofantrine); gastrointestinal prokinetic drugs (eg. cisapride).

**Digoxin**: Supraventricular arrhythmias might mask the cardiotoxicity associated with excessive digoxin levels. Therefore, it is advisable to be particularly cautious in patients whose plasma digoxin levels are above or suspected to be above the usual therapeutic range. Concomitant treatment with digoxin did not affect either serum digoxin levels or the pharmacokinetics of ibutilide in clinical trials.

**Calcium Channel Blocking Agents**: Concomitant treatment with calcium channel blocking agents did not affect the pharmacokinetics of ibutilide in clinical trials.

**Beta Adrenergic Blocking Agents**: Concomitant treatment with beta adrenergic blocking agents did not affect the pharmacokinetics of ibutilide in clinical trials.

**Comparison with other therapy**: Although ibutilide is the only drug approved in the United States for acute termination of atrial fibrillation and atrial flutter, other therapies have been used for this purpose, including intravenous administration of procainamide as well as oral loading of multiple different agents such as quinidine, procainamide, propafenone, and flecainide. It is difficult to compare the efficacy of ibutilide with other drugs using previously published studies given the differences in arrhythmia duration, drug administration, and patient characteristics that exist in the patient populations studied. Several studies have reported that intravenous procainamide can acutely terminate atrial fibrillation/flutter with moderate efficacy. One group of investigators reported a conversion rate of 58% (15 of 26 patients) after administration of procainamide 1g IV. Patients who converted had a shorter duration of arrhythmia (6±7 days) than those who did not convert (79±88 days). In another study of 21 patients who received 20 mg/kg procainamide, 43% (9 patients) converted to normal sinus rhythm.

The arrhythmia duration was ≤5 days in 19 of the 21 patients. In a comparative study with intravenous flecainide, procainamide at a dose of 1 g converted 25 (65%) of 40 patients with atrial fibrillation/flutter of <24 hrs duration. Although these studies indicate that intravenous procainamide is useful in this clinical setting, particular caution should be used when conversion rates are compared with other drugs such as ibutilide, because most patients in these trials had arrhythmias of relatively recent onset. Substantial clinical data now indicate that probably the most important predictor of successful pharmacological conversion of atrial fibrillation/flutter with any agent is the pretreatment duration of the arrhythmia. Therefore, data regarding comparative efficacy can only be obtained in randomized clinical trials in which drugs are compared in the same patient population. More limited data are also available from noncomparable clinical studies for sotalol and amiodarone. A group of 48 patients having atrial fibrillation/flutter for <7 days were randomized to receive either placebo or sotalol at a dose of either 1.0 or 1.5 mg/kg IV. Patients who received placebo initially could subsequently receive 1.0 or 1.5 mg/kg sotalol in an open-label phase. In total, 5 (19%) of 26 patients receiving placebo converted to normal sinus rhythm compared with 4 (17%) of 23 and 4 (18%) of 22 patients receiving sotalol at doses of 1.0 and 1.5 mg/kg, respectively. The success rate of acute conversion with intravenous amiodarone has been similarly disappointing. In a comparative trial with intravenous dofetilide, administration
of amiodarone (5 mg/kg) led to a conversion rate of 4% compared with 4% for placebo and 35% for dofetilide (8 mg/kg). Finally, a recent study reported on the success of oral loading regimens of propafenone (400 to 600 mg), propafenone plus digoxin (0.75 to 1.0 mg in 24 hrs), and quinidine (1100 mg) plus digoxin for atrial fibrillation/ flutter of <24 hrs duration. Not surprisingly, a high rate of conversion was seen not only with propafenone plus digoxin (89%) and quinidine plus digoxin (84%) but also with placebo (77%) at 24 hrs. In studies (which have appeared in abbreviated form) that directly compare the efficacy of ibutilide to other therapies, the drug was found to be superior to intravenous administration of either sotalol or procainamide in terminating atrial fibrillation and atrial flutter. In a double-blind study, 319 patients with an arrhythmia duration of 3 to 45 days were randomized to receive either ibutilide (1 or 2 mg) or sotalol (1.5 mg/kg). In patients with atrial flutter, 53% and 70% of patients who received 1 and 2 mg of ibutilide, respectively, converted to normal sinus rhythm compared with 18% receiving sotalol.

For patients with atrial fibrillation, the rates of conversion were 22% and 43% for 1 and 2 mg of ibutilide versus 10% for sotalol. Ibutilide has also been compared with intravenous procainamide in a double-blind, placebo-controlled trial of 127 patients with atrial fibrillation/flutter lasting 3 hrs to 90 days. Intravenous administration of ibutilide (2 mg) led to conversion of 76% and 51% of patients with atrial flutter and atrial fibrillation, respectively, compared with 12% and 20% for patients given intravenous procainamide (1200 mg). In a nonrandomized comparison with intravenous procainamide in 67 patients, ibutilide (0.005 to 0.025 mg/kg) converted 42% and 37% of patients with atrial fibrillation and flutter, respectively, versus 9% and 0% for procainamide (12 to 15 mg/kg). The efficacy of ibutilide in that study was attributed to greater prolongation of monophasic action potential duration relative to slowing of conduction; the resultant increase in refractoriness would tend to close the excitable gap to facilitate arrhythmia termination. In contrast, procainamide caused a greater change in conduction than repolarization, which could account for its lack of success relative to ibutilide. In a separate study, both intravenous ibutilide and procainamide enhanced termination of drug-refractory atrial flutter by atrial overdrive pacing.

Clinical studies: Two full-length, peer-reviewed articles have been published to support the clinical efficacy of ibutilide, whereas other data have appeared in abstract form or from the pharmaceutical sponsor. The first major clinical study was a double-blind, randomized, placebo-controlled, dose-response trial that evaluated the efficacy and safety of ibutilide in 200 patients with atrial flutter or fibrillation from 3 hrs to 90 days in duration. Patients were randomized to receive a single intravenous dose of either placebo or ibutilide at 0.005, 0.010, 0.015, or 0.025 mg/kg. The study population consisted of patients who were hemodynamically stable without uncontrolled heart failure or angina. In the group, 72% of patients had structural heart disease, with a similar percentage having significant left atrial enlargement. The rates of successful arrhythmia termination were 3% for placebo and 12%, 33%, 45%, and 46%, respectively, for the doses of ibutilide administered. The overall success rate of ibutilide-treated patients with atrial flutter (38%) tended to be higher than for those with atrial fibrillation (29%).

The mean time to termination of the arrhythmia from beginning of infusion was 19±15 minutes (range, 3 to 70 minutes), with conversion in nearly 80% of patients within 30 minutes from the start of the infusion. The duration of the arrhythmia was a predictor of successful conversion to normal sinus rhythm, with success in 42% of patients having atrial flutter/fibrillation for ≤30 days compared with 16% of those with an arrhythmia duration >30 days. Both QT and QTc intervals were significantly prolonged from baseline by ibutilide in all dose groups, although the degree of prolongation did not predict efficacy of arrhythmia termination. Polymorphic ventricular tachycardia developed in 6 patients (3.6%) receiving ibutilide. It occurred in patients receiving doses ≥0.010 mg/kg and did not correlate with plasma ibutilide concentration. All 6 patients had reduced left ventricular function, and 3 had a baseline QTc interval that was >440 ms. On the basis of these results, a second clinical trial was conducted in which 266 patients with atrial fibrillation or flutter with an arrhythmia duration of 3 hrs to 45 days were randomized to receive up to two 10 minute infusions of ibutilide (1.0 and 0.5 mg or 1.0 and 1.0 mg) or placebo. Patients at high risk for proarrhythmia, that is, those with preexisting QT prolongation (QTc >440 ms), hypokalemia (<4.0 mEq/L), and previous torsade-de-pointes, were...
excluded. As in the previous trial, most patients had a history of heart disease and an enlarged left atrium. Ibutilide administration resulted in arrhythmia conversion in 47% of patients compared with 2% of patients receiving placebo. The two ibutilide dosing regimens did not differ with respect to conversion efficacy. Conversion occurred in a higher percent of patients with atrial flutter than those with atrial fibrillation (63% versus 31%). The average time for arrhythmia termination was 27 minutes (range, 5 to 88 minutes) after the start of the first infusion. After adjustment for dose, there was a significant effect of arrhythmia duration on efficacy in the atrial fibrillation but not the atrial flutter group, with a mean duration of 10±13 days for those who were successfully converted compared with 18±15 days for those who did not convert. In addition, there was a significant correlation between left atrial diameter and success in patients with atrial fibrillation but not in those with atrial flutter. Once again, the change in QT or QTc interval with ibutilide administration did not predict arrhythmia termination. Polymorphic ventricular tachycardia developed in 8.3% of ibutilide-treated patients. In 1.7%, this arrhythmia was sustained and required DC cardioversion. The risk of torsade de pointes was higher in patients with atrial flutter (12.5%) than in those with atrial fibrillation (6.2%). Episodes of late polymorphic VT occurred in 1 patient at 2 to 2.5 hrs; this patient had a prior episode of nonsustained VT at the end of initial drug infusion.

Plasma concentrations were not obtained in this patient, and therefore the relationship of late events to ibutilide concentration could not be determined. Logistic regression analysis indicated that female sex, nonwhite race, presence of heart failure, and low pulse rate were significant risk factors for the development of proarrhythmia. Together, these two clinical trials demonstrate that ibutilide administration is superior to placebo in terminating atrial fibrillation and flutter, with most patients converting within 30 minutes of the start of drug infusion. The drug is more effective in patients with atrial flutter but with an increased risk of torsade de pointes. Predictors of successful arrhythmia conversion include the duration of arrhythmia before treatment as well as left atrial size. For atrial flutter, additional data suggest that development of variation in the flutter cycle length predicts successful termination85. Initial clinical results from a randomized, double-blind, placebo-controlled trial indicate that ibutilide is also effective in terminating atrial fibrillation and flutter after cardiac surgery.86 Although it is not approved for this indication, preliminary results indicate that ibutilide can also prevent reinduction of sustained ventricular tachycardia in patients with coronary artery disease undergoing electrophysiological study87.

Conclusion: Ibutilide is an effective agent for use in the termination of atrial fibrillation and atrial flutter. 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. In the new language of patient rights, close monitoring by a physician is required during administration of this drug due to the relatively high incidence of torsade-de-pointes. However alternative strategies are available, the risks and benefits of ibutilide administration should be carefully considered for each patient to minimize proarrhythmic adverse events. Future work on this drug may be extended because of ibutilide efficacy, which is comparable or superior to other agents it is not widely used due to lack of awareness about its safety and efficacy profile.

REFERENCES


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