Role of Ibutilide in Atrial Fibrillation

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Introduction

Ibutilide is an anti-arrhythmic drug belonging to Class III of the Vaughan-Williams classification primarily used for acute termination of atrial tachyarrhythmias. The drug is uncommonly used, especially in India despite its efficacy, possibly because of non-availability, risk of proarrhythmia and lack of awareness among physicians. The current review discusses its role in patients with atrial fibrillation.

Ibutilide – Clinical Pharmacology and Mechanism of Action

Ibutilide fumarate is given intravenously and acts by blocking the rapid component of the cardiac delayed rectifier potassium current (IKr) resulting in prolongation of repolarization in atrial and ventricular myocardium. It increases the action potential duration and lengthens the refractory period of myocardial cells. It affects not only the atrial and ventricular myocardium but also the atrioventricular node, His-Purkinje system and accessory pathway. Also, it activates a slow delayed inward sodium channel promoting the influx of sodium during early repolarization.

The drug is not used orally due to its extensive first-pass metabolism. With intravenous route, it has a half-life of 6 hours (2 to 12 hours). It is metabolized by liver to produce at least eight metabolites of which only one exhibits anti-arrhythmic action. However, the clinical efficacy of this metabolite is negligible as its serum level is less than 10% of the parent drug level. The native drug and its metabolites are primarily excreted by the renal route.

Ibutilide – Clinical and Electrocardiographic Effects

Ibutilide is primarily used for the acute termination of atrial fibrillation and atrial flutter especially of recent onset. Its efficacy for ventricular arrhythmias is unknown and is not approved for their treatment. Also, since it can’t be used orally, it has no role in long-term prevention of recurrence of atrial arrhythmias.

The ECG effects of the drug are the same as seen with other class III anti-arrhythmic drugs and include mild slowing of the sinus rate and QT prolongation. The PR interval and QRS duration remain unaffected. The degree of QT prolongation is influenced by the dose given, rate of drug infusion and the serum concentration. The QT interval prolongation is responsible for the proarrhythmia associated with Ibutilide i.e., torsade de pointes. The return of QT interval to baseline may take up to 4 hours after stopping the drug infusion. Hence, the patients need to be monitored for at least 4 hours after stopping the drug to enable detection of possible proarrhythmia.

Ibutilide – Indications for Use in Atrial fibrillation

Ibutilide can be used as the drug of first choice for termination of atrial fibrillation or flutter as a means of chemical cardioversion in selected patients. The guidelines for anticoagulation before and after conversion remain same as for electrical cardioversion and should be strictly adhered to in order to significantly reduce the risk of stroke. The efficacy of Ibutilide is greatest when the arrhythmia is of recent duration.

Though, Ibutilide is highly effective when AF has been present of less than 7 days, it is also efficacious when the AF duration is longer. The rates of conversion of AF of less than 90 days duration to sinus rhythm varies from 31% to 44% with Ibutilide (dose 0.015 mg/kg or 2 mg) in various studies and is higher compared to placebo, sotalol (1.5 mg/kg) or procainamide (1200 mg).

The efficacy of Ibutilide for converting arrhythmias of recent onset (3 hours to 48 hours) is higher for atrial flutter (87%) compared to AF (77%). The same study also showed that efficacy of Ibutilide is higher than that of intravenous amiodarone (80% vs. 57%) though its sub-analysis showed that superior efficacy of Ibutilide over amiodarone was limited to atrial flutter (conversion rate 87% vs. 29%, p 0.003) whereas in AF their efficacy was similar (77% vs. 69%, p non-significant).

The efficacy of Ibutilide in converting recent onset AF or flutter to sinus rhythm is 53% with a single dose and increases to 75% when the second dose is also used. Some studies have shown that apart from shorter duration of AF, female gender and younger age predict
flutte with ibutilide is more compared to atrial fibrillation conversion irrespective of the clinical setting – recent onset, persistent of longer duration or postoperative. Also, intravenous ibutilide enhances the termination of atrial flutter by atrial overdrive pacing, an clinical effect also shared with intravenous procainamide although by a different electrophysiological mechanism.14

**Ibutilide in Combination with Other Anti-Arrhythmic Drugs**

An interesting feature of use of ibutilide for conversion of atrial fibrillation is its concomitant use with other anti-arrhythmic drugs. It can be safely used in patients who are already on class IC drugs like flecainide and propafenone.15 In fact, there is possibly lower risk of proarrhythmia in this setting since the class IC drugs induced slow conduction by blocking sodium channels has exert somewhat protective effect. Also, these drugs do not prolong the QT interval. Similarly, ibutilide has been found to be safe and effective in patients who are already taking oral amiodarone, although amiodarone is known to prolong the QT interval.17 Ibutilide use should be avoided in patients on other drugs that prolong the QT interval.

Another potentially useful combination is use of intravenous esmolol and ibutilide. A randomized study comparing esmolol and ibutilide alone in patients with recent onset AF with rapid ventricular rate showed that the combined therapy has a higher rate of conversion to sinus rhythm (67% vs. 46%), reduced rate of immediate recurrence and a lower risk of proarrhythmia.18

**Ibutilide in Post-operative AF and Atrial Flutter**

Ibutilide is usually safe and effective in terminating AF and atrial flutter that develops after cardiac surgery. In one dose ranging study of ibutilide in this setting, the conversion rates increased (dose of 0.25 mg – 40%, 0.5 mg – 47% and 1 mg – 57%) and time to conversion decreased with increasing doses of ibutilide.19

Another randomized study that compared propafenone (oral, single dose of 600 mg), ibutilide (intravenous 1 mg, up to 2 doses) or rate control only in stable patients with postoperative AF, showed that at 24 hours no patient in ibutilide group was in AF compared to 65% of patients in propafenone group and 34% in rate control group.20 However, there was no difference in the hospital length of stay or rhythm at discharge among the three groups. The authors suggested that stable patients with postoperative AF need not necessarily be administered drugs for pharmacological cardioversion.

In another randomized double-blind study of postoperative AF comparing ibutilide or intravenous amiodarone, both had similar time to conversion and conversion rates, though significant hypotension was not seen with ibutilide.21

**Ibutilide in Preexcited AF in WPW Syndrome**

Though, the drug of choice for termination of preexcited AF has traditionally been intravenous procainamide, ibutilide is also highly effective in this regard. Ibutilide successfully terminated AF in 95% of patients (including children) during electrophysiology study of accessory pathways that were subsequently ablated.22 This strikingly high success rate may be because of very short duration of AF in this study. Thus, ibutilide may be used as an alternative to procainamide of electrical cardioversion in stable patients with preexcited AF as was seen in a case report.23

**Ibutilide in Children and those with Congenital Heart Disease**

In a case series of 19 patients,
Aged 6 months to 34 years, with many having congenital heart disease, ibutilide converted 71% of arrhythmia episodes overall with 63% success in first dose itself. It was not only highly efficacious but also safe with only one episode of polymorphic and monomorphic VT seen among the 19 patients. Thus, ibutilide can be a safe and effective drug for children and those with congenital heart disease for pharmacological conversion of AF and flutter.

Ibutilide for Atrial Fibrillation or Flutter during an Electrophysiology Study

AF occurring during an electrophysiology study can be a nuisance as it hinders with the progress of the study and ablation procedure for supraventricular arrhythmias, ablation of accessory pathway or pulmonary vein isolation for AF itself. It often needs electrical cardioversion and if recurrent can increase the risk of the procedure and require sedation or anesthesia. Ibutilide can be very useful in this regards. In one report of 3 patients with concealed accessory pathways, ibutilide permitted successful catheter ablation by converting and controlling AF mediated by atrioventricular reentry.

In another study, amiodarone and ibutilide were equally effective in suppressing immediate recurrences of AF after electrical cardioversion during a pulmonary vein isolation procedure for AF. The performance of the ablation procedure for AF is often easier during sinus rhythm as it allows better recognition of pulmonary vein potentials and performance of atrial pacing.

Ibutilide – Dosing and Administration

Ibutilide is only available for intravenous use. The recommended doses are based on the patient’s weight.

Weight < 60 kg – 0.01 mg/kg infused over 10 min. A second infusion of same dose over 10 min can be repeated if the arrhythmia does not terminate within 10 min.

Weight > 60 kg – 1 mg over 10 min infusion. A repeat dose can be given after 10 min, if required.

Few studies have shown that concurrent administration of intravenous magnesium along with ibutilide increases the chances of restoration of sinus rhythm and also reduces the risk of polymorphic VT.

Among responders of Ibutilide, the arrhythmia usually terminates within 40-60 minutes of initiation of its infusion. The infusion should be prematurely stopped if the arrhythmia terminates, VT occurs or marked QTc prolongation develops.

Ibutilide – Adverse Effects, Cautions and Precautions

The Ibutilide is usually safe and the reported common non-cardiac side effects like nausea, headache and acute kidney injury are transient &self limited. The more serious side effect is cardiac proarrrhythmia in the form of polymorphic ventricular tachycardia (VT) or torsades de pointes. Monomorphic VT also can sometimes occur. The incidence of polymorphic VT is 4-8% in several studies, though those requiring DC shock occur in less than 2% and non-sustained monomorphic VT occur in 3-4%. The majority of episodes of polymorphic VT occur within 10 min of the first dose of Ibutilide, though they can occur even up to 4 hours or longer. Hence, continuous ECG monitoring is recommended for at least 4 hours after finishing Ibutilide dose or till return of QT interval to baseline. Also, concurrent administration of other drugs that also prolong the QT interval should be avoided. Interestingly, however, the risk of proarrhythmia with Ibutilide has not been shown to be higher when it is administered in patients on long term oral amiodarone.

The risk of torsades is higher in women, in patients with heart failure and in those with baseline prolonged QT interval. Use of Ibutilide in patients who are on class IC antiarrhythmic drugs (flecainide or propafenone) has been seen to have lower risk of polymorphic VT.

Non-arrhythmic cardiac side effects of Ibutilide are usually minimally symptomatic and transient and include hypotension, sinus tachycardia or bradycardia, bundle branch block and atrioventricular block. Each of these has been reported in less than 2% of patients.

In view of serious arrhythmic side effects of Ibutilide, it should not be used in patients with severe structural heart disease, heart failure, prolonged QT interval or sick sinus syndrome in absence of pacemaker.

Conclusions

Ibutilide is an intravenous class III antiarrhythmic drug that has been shown to be efficacious and safe for pharmacological cardioversion of AF and atrial flutter in a wide variety of clinical settings and situations. Its safety can be enhanced by appropriate dosing, avoidance of concomitant QT prolonging drugs, clinical and ECG monitoring for at least 4-6 hours and restriction of its use in certain patients and situations. Also, the anticoagulation during its use should be strictly followed based on the guidelines during electrical cardioversion.


References


