Intravenous Magnesium Increases the Efficacy of Ibutilide in the Conversion of Atrial Flutter and Fibrillation: A Meta Analysis

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ABSTRACT. Intravenous ibutilide is an anti-arrhythmic drug used for the acute conversion of atrial flutter and fibrillation to sinus rhythm. Supplemental magnesium improves the safety profile of ibutilide by preventing torsades de pointes. However, its effect on efficacy of ibutilide is largely unknown. We searched the PUBMED, Cochrane, and EMBASE databases for all English language articles using the phrases “atrial fibrillation,” “atrial flutter,” “ibutilide,” and “magnesium.” Dose of magnesium used, rate of successful conversion to sinus rhythm, and safety profile were collected. Data were analyzed using Revman 5.1 (Oxford, UK). Concomitant administration of intravenous magnesium with ibutilide significantly increases the efficacy of conversion to sinus rhythm compared with ibutilide alone (OR 1.66, 95% CI, 1.29–2.15, p<0.0001) with no significant side effects. The incidence of ventricular arrhythmias was significantly reduced with magnesium (3.25% versus 6.27%, p=0.03). Clinicians should consider administration of intravenous magnesium even in normomagnesemic patients who receive ibutilide for conversion of atrial flutter or fibrillation.

KEYWORDS. ibutilide, atrial flutter, atrial fibrillation, magnesium.

Introduction
Intravenous ibutilide is an anti-arrhythmic drug used for the acute conversion of atrial flutter and fibrillation to sinus rhythm by virtue of its class III antiarrhythmic properties. Its efficacy in conversion of atrial flutter is 80% and of atrial fibrillation of recent onset is close to 50%. The presence of hypokalemia and hypomagnesemia predisposes patients who receive ibutilide to torsades de pointes. The role of supplemental magnesium in improving the safety profile of ibutilide is well known. Magnesium is however a versatile anti-arrhythmic drug with documented efficacy in rate and rhythm control of atrial fibrillation. A few studies demonstrate that intravenous magnesium may improve the efficacy as well as the safety of ibutilide. We conducted a meta-analysis of the existing literature to quantify the benefit of administering magnesium with ibutilide in the conversion of atrial flutter or fibrillation to sinus rhythm.

Methods
We searched the PUBMED, Cochrane, and EMBASE databases for all English-language articles using the phrases “atrial fibrillation”, “atrial flutter”, “ibutilide”, and “magnesium.” The “related article” feature was used to identify more related studies. Abstracts of all articles were reviewed. Those that were felt to be
appropriate for inclusion were reviewed by two authors independently. The bibliography of these articles was also reviewed to identify any studies that had been missed. Since it is known that there are few data on this subject, we decided to include all studies irrespective of their design. Dose of magnesium used, rate of successful conversion to sinus rhythm, and safety profile were collected. Data were analyzed using Revman 5.1 (Oxford, UK). The results of individual studies and the overall result were expressed as an odds ratio (OR) with 95% confidence intervals (CI) and were analyzed using a random-effect model. A two-sided p-value less than 0.05 was considered statistically significant. The $I^2$ test was used as a measure of heterogeneity.

**Results**

Figure 1 details the study identification process, after which four studies were included in the analysis. Table 1 describes the study characteristics. A total of 1,143 patients were analyzed. Compared with ibutilide alone, concomitant administration of intravenous magnesium with ibutilide significantly increases the efficacy

**Table 1**: Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Dose of magnesium used</th>
<th>Incidence of ventricular arrhythmias (Mg + ibutilide vs. ibutilide alone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalus 2003</td>
<td>Multicenter cohort</td>
<td>2.2 ± 1.0 g</td>
<td>2.8% vs. 4.2% (p=0.553)</td>
</tr>
<tr>
<td>Tercius 2007</td>
<td>Retrospective</td>
<td>1–4 g</td>
<td>Only torsades de pointes reported 0 vs. 1 case</td>
</tr>
<tr>
<td>Patsilinakos 2010</td>
<td>Single center cohort</td>
<td>10 g (5 g before and 5 g after ibutilide)</td>
<td>1.2% vs. 7.4% (p=0.002)</td>
</tr>
<tr>
<td>Steinwender 2010</td>
<td>Unblinded</td>
<td>4 g</td>
<td>20% vs. 17% (p non-significant)</td>
</tr>
</tbody>
</table>
of conversion to sinus rhythm (OR=1.66, 95% CI, 1.29–2.15, p<0.0001) (Figure 2) with no significant heterogeneity among the studies included (I²=0%). The incidence of ventricular arrhythmias was significantly reduced with magnesium (3.25% versus 6.27%, p=0.03).

No significant side effects were identified with the use of magnesium in these studies.

Discussion
Magnesium affects the cardiac action potential through its effects on ion channels. It has been shown to antagonize both L- and T-type calcium channels in the atria, which may occur in a dose-dependent fashion as demonstrated in an animal model. This has led to its description as “nature’s physiologic calcium channel blocker.” The rapid inward rectifying potassium channel is also inhibited in a dose-dependent fashion.

In the atrial tissue, intravenous magnesium increases the conduction time and refractoriness, which may decrease the number of re-entrant circuits implicated in atrial flutter and fibrillation. In animal models, early afterdepolarizations are suppressed in ventricular and Purkinje fiber cells. Magnesium also increases action potential duration and thus may possess type III antiarrhythmic properties. Magnesium has been studied in multiple trials in the rate and rhythm control of atrial fibrillation, and its efficacy has been confirmed by two meta-analyses. In addition, it is a very safe drug, with toxic effects seen only with high doses in the presence of renal failure. These properties of magnesium form the basis of the hypothesis that magnesium and ibutilide would be more efficacious than ibutilide alone.

Clinically, serum magnesium concentrations are often used to document hypomagnesemia. Serum magnesium contributes to only 1% of total body stores and intracellular magnesium concentrations provide a better indication of the electrolyte status. There is often no correlation between measured intracellular and serum magnesium levels. Intracellular magnesium can be estimated by measurement of magnesium in oral epithelial cells but this is not routinely done in clinical practice. The improved efficacy with magnesium administration may be overstated since some patients included in these studies may have been intracellularly magnesium depleted, which may have affected the efficacy and safety of ibutilide alone. In the studies included in the current meta-analysis, magnesium was administered in patients with normal serum magnesium levels and thus was used not as a replacement for electrolyte deficiency. The combination of magnesium and ibutilide can be cost-effective as well. Magnesium is a fairly inexpensive medication. Patients who fail ibutilide often receive moderate sedation and DC cardioversion which leads to increased costs. In a pharmacoeconomic study, the combination of magnesium and ibutilide showed a statistically non-significant trend towards being more cost-effective than ibutilide alone (USD1,075 versus USD1,201, p=0.116).

Limitations
This meta-analysis included a small number of studies with varying methodologies. The dose of magnesium used varied from 1 to 10 g so no conclusion of the most efficacious dose can be made. However based on the study by Tercius et al., at least 4 g of magnesium is likely necessary to have any beneficial effect. In our practice, we routinely administer 2 g of magnesium sulfate with each dose of ibutilide. The definition of ventricular arrhythmias varied widely among these studies. Only a well-designed randomized controlled trial with measurement of intracellular magnesium levels and studying a range of doses will provide a definitive answer.

In conclusion, this meta-analysis shows that intravenous magnesium when administered with ibutilide increases its efficacy and safety profile in conversion of atrial flutter and fibrillation. Since it has an excellent safety profile, clinicians should consider administration of intravenous magnesium to even normomagnesemic patients who are receiving ibutilide for conversion of atrial flutter or fibrillation.

References


