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Intravenous magnesium sulfate versus diltiazem in paroxysmal atrial fibrillation☆

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Abstract

Background: Drugs currently available for the acute treatment of paroxysmal atrial fibrillation have significant limitations. We assessed the safety and effectiveness of intravenous magnesium sulfate versus diltiazem therapy in patients with prolonged episodes of paroxysmal atrial fibrillation. *Methods*: In a prospective randomized trial, 46 symptomatic patients presenting with paroxysmal atrial fibrillation were given intravenous magnesium sulfate ($n=23$) or diltiazem ($n=23$) therapy. Primary outcome measures were effects on ventricular rate control and proportion of patients restored to sinus rhythm at 6 h after initiation of treatment. *Results*: There were no differences in baseline characteristics between the two groups. Both forms of treatment were well tolerated, with no adverse clinical events. Both drugs had similar efficacy in reducing the ventricular rate at the first hour of treatment ($P<0.05$) with a tendency toward a further decrease during infusion times of 2 ($P<0.01$), 3, 4, 5 and 6 h, respectively ($P<0.001$). However, at the end of the 6-h treatment period, restoration of sinus rhythm was observed in a significantly higher proportion of patients in the magnesium group compared with the diltiazem group [13 of 23 patients, (57%), versus five of 23 patients, (22%), $P=0.03$]. *Conclusions*: Magnesium sulfate favorably affects rate control and seems to promote the conversion of long lasting episodes of paroxysmal atrial fibrillation to sinus rhythm, representing a safe, reliable and cost-effective alternative treatment strategy to diltiazem.

Keywords: Paroxysmal atrial fibrillation; Magnesium sulfate; Diltiazem

1. Introduction

Recurrent paroxysmal atrial fibrillation (PAF) predisposes, especially when associated with structural heart disease, to disabling symptoms, thromboembolic complications, increased mortality and considerable expenses [1–3]. Attention is primarily focused on acute pharmacologic control of heart rate and early restoration of sinus rhythm. Digoxin, calcium channel blockers and β-adrenergic blockers provide control of atrioventricular conduction during atrial fibrillation, while class I or III antiarrhythmic agents may additionally restore sinus rhythm. Still, drugs that effectively control the heart rate are often initially preferred because of a more favorable side-effect profile. However, there are well known contraindications to the use of β-blockers, whereas verapamil has limited usefulness because of its negative inotropic effect, and digoxin has a slow onset of action to achieve heart rate control [4–7]. Moreover, digoxin, calcium- and β-blockers are no more effective than placebo in reverting atrial fibrillation to sinus rhythm. On the contrary, digoxin may prolong duration of PAF [8]. Nowadays, intravenous

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diltiazem is increasingly used for acute management of rapid attacks of PAF.

Magnesium sulfate ($MgSO_4$), capable of increasing conduction time and refractoriness at the atrium and the atrioventricular nodal level while suppressing atrial automaticity, has been found useful for treating various atrial tachyarrhythmias [9–14], but there are few if any data on its use in PAF. Furthermore, no prospective controlled trial directly comparing $MgSO_4$ with diltiazem has been so far conducted. Thus, the aim of the present prospective randomized study was to compare the safety and efficacy of intravenous $MgSO_4$ vs. diltiazem in the management of persistent episodes of PAF during the first 6 h of therapy.

2. Population and methods

Forty-six consecutive patients (25 men and 21 women, aged 19–90 years) admitted for therapy of a long symptomatic episode of PAF were randomly assigned to $MgSO_4$ or diltiazem therapy. Informed written consent was obtained from all participants. Only patients with prolonged and continuous paroxysms of atrial fibrillation of <12 h duration, with a mean ventricular response >100 beats/min, were included in the study. The time of onset of arrhythmia was documented either electrocardiographically during hospitalization or by a well-defined clinical history of onset of palpitations with subsequent electrocardiographic evidence of rapid atrial fibrillation. All patients underwent a physical examination and evaluation of functional status before therapy. Exclusion criteria were acute myocardial infarction, severe circulatory failure requiring inotropic agents, hypotension with a systolic blood pressure <90 mmHg, electrocardiographic evidence of high-degree atrioventricular block or ventricular preexcitation, a history of sick sinus syndrome or known thyroid disease, pacemaker dependence, severe metabolic disturbances and women in pregnancy. Patients already receiving β-blockers, calcium channel blockers, digitalis and antiarrythmic drugs were also excluded. Supplemental potassium was given in patients with hypokalemia before entry into the study. Conjunctive therapy included heparin with a bolus of 5000 IU, followed by infusion of 1000 IU/h further adjusted as required to keep the activated partial thromboplastin time at twice the upper normal limit.

All patients had a 24-h Holter monitor applied before $MgSO_4$ or diltiazem administration. Mean ventricular rates were obtained at intervals of 2 min at baseline, and thereafter at the end of hourly intervals during treatment. Blood pressure was measured at 15-min intervals or more frequently if clinically indicated. Magnesium sulfate was administered as a bolus of 2.5 g over 15 min, followed by continuous infusion of 7.5 g over 6 h, and diltiazem was given as a bolus of 25 mg over 15 min, followed by continuous infusion of 12.5 mg/h over 6 h. Conversion to sinus rhythm with $MgSO_4$ or diltiazem was considered successful if it occurred within the initial 6-h treatment period. Additional antiarrhythmic therapy was started thereafter in patients remaining in atrial fibrillation. An M-mode and two-dimensional echocardiographic examination was performed after restoration of sinus rhythm to determine the left atrial dimension and the left ventricular ejection fraction using the Simpson's method.

The results are expressed as mean±S.D. Differences in the distribution of characteristics between groups were analyzed by Fischer's exact test and Student's *t* test for discrete and continuous variables, and multiple comparisons were estimated by the Tukey–Kramer test, respectively. A probability value of <0.05 was considered significant.

3. Results

The clinical and echocardiographic data of the 46 study patients are listed in Table 1. All patients had normal baseline serum magnesium concentrations before treatment and proved to have normal thyroid function. No patient was under warfarin therapy. Between the two groups there were no significant differences with respect to arrhythmia characteristics and echocardiographic variables after reversion to sinus rhythm. In one patient, PAF was associated with excessive intake of alcohol. Drug-related adverse reactions necessitating treatment discontinuation did not occur. Short-lasting flushing after the bolus injection of $MgSO_4$ was seen in three patients (13%). Clinically significant hypotension, defined as a decrease in systolic blood pressure to <80 mmHg, or

Table 1
Patients' demographic, clinical and arrhythmia characteristics

	$MgSO_4$ (n=23)	Diltiazem (n=23)	P value
Mean age (years)	61±6	64±4	NS
No. of men (%)	12 (52%)	13 (57%)	NS
Underlying disease			
Coronary artery disease	2 (9%)	5 (22%)	NS
Hypertension	8 (35%)	12 (52%)	NS
Pulmonary disease	1 (4%)	1 (4%)	NS
Alcohol consumption	1 (4%)	0	NS
Gastrointestinal disease	6 (26%)	5 (22%)	NS
NYHA I-II	21 (91%)	21 (91%)	NS
Arrhythmia characteristics			
Heart rate at presentation (bpm)	142±20	136±21	NS
Time from first paroxysm (years)	1.0±3.0	1.4±2.0	NS
Number of prior paroxysms	1.6±2.0	1.3±2.0	NS
Duration of prior paroxysms (h)	5.0±4.0	4.5±3.0	NS
Echocardiography			
LA (cm)	3.7±0.6	3.8±0.5	NS
LVEF (%)	59.6±8.8	59.2±10	NS

LA, left atrium; LVEF, left ventricular ejection fraction.

an exacerbation of congestive heart failure was not observed. Asymptomatic long pauses >3 s were noted in two patients (9%) treated with diltiazem (of 3.3 s and 5.7 s duration, respectively).

The mean baseline heart rate during PAF was 142±20 beats/min for the $MgSO_4$ group and 136±21 beats/min for the diltiazem group. In both groups there was a similar significant slowing in heart rate at the first hour of treatment ($P<0.05$) with a tendency toward a further decrease during infusion times of 2 ($P<0.01$), 3, 4, 5 and 6 h, respectively ($P<0.001$). The effect of $MgSO_4$ infusion over time in reducing the ventricular rate did not differ from that of the diltiazem group (Fig. 1). At the end of the initial 6-h treatment period, restoration of sinus rhythm was observed in a total of 18 patients (39%): in 13 of 23 patients (57%) in the $MgSO_4$ group and in five of 23 patients (22%) in the diltiazem group ($P=0.03$). Between the two groups, there was no significant difference noted in the sinus heart rate after PAF was terminated with $MgSO_4$ (60±11 beats/min; $n=13$) or diltiazem therapy (56±10; $n=5$). Administration of antiarrhythmic agents resulted in restoration of sinus rhythm in all those 28 patients remaining in atrial fibrillation after the initial 6-h treatment period.

4. Discussion

To our knowledge, the present study is the first one to directly compare in a prospective randomized fashion the safety and efficacy profiles of intravenous therapy with $MgSO_4$ or diltiazem in patients with PAF. Although both modes of treatment provided

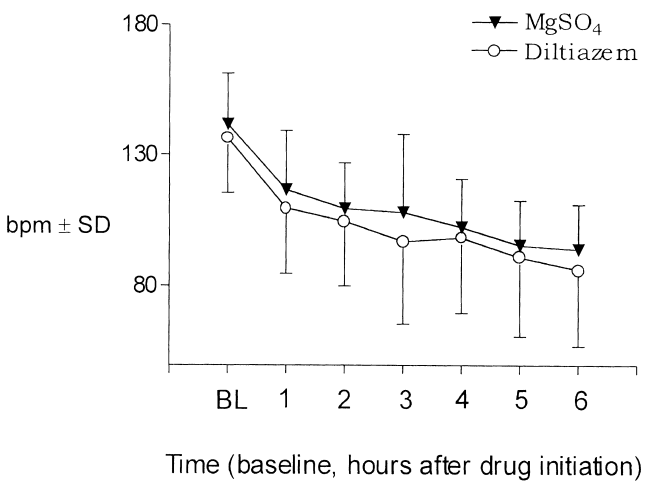

Fig. 1. Heart rate response to magnesium and diltiazem infusion over 6 h of treatment. There was a similar significant decrease in ventricular rate over time within each treatment group ($P<0.05$ at 1 h, $P<0.01$ at 2 h, and $P<0.001$ at times of 3, 4, 5 and 6 h, respectively). There were no significant heart rate changes over time between the two groups.

quick and sustained control of heart rate in our patients, the beneficial effects of $MgSO_4$ therapy have apparently received inadequate attention in the acute management of prolonged episodes of PAF. Therapy with $MgSO_4$ seems to control the ventricular rate but also promote the conversion to sinus rhythm.

Electrophysiologic mechanisms to account for the antiarrhythmic effects of $MgSO_4$ primarily suggest significant increases of conduction time and refractoriness in the atrium and the atrioventricular node, which may be explained by changes in calcium channel kinetics and reduced sympathetic influences [9,10]. Although these actions are generally of low potency and short duration, it is most likely the doses of $MgSO_4$ used in our study which account for the drug's higher efficacy in converting PAF to sinus rhythm, compared to diltiazem. Moreover, this therapy may emerge as a cost-effective approach, due to the low cost of the drug [12] and the shorter length of hospital stay [3,4], implying that magnesium may even be used as single first-line agent in patients with PAF. It could be argued that choosing patients with long-lasting arrhythmia attacks might have resulted in a selection bias. However, this is a way to handle the inherent limitation of the great variations in duration of the arrhythmia episodes, by examining prolonged paroxysms which might have a lower probability to be spontaneously converted to sinus rhythm. We chose a limited observation period of PAF of 6 h which justifies short-term postponing of pharmacologic or electrical conversion to sinus rhythm, which, if not effected with this mode of therapy, can then be safely performed within the generally accepted 48-h time window from onset of the arrhythmia.

Both $MgSO_4$ and diltiazem demonstrated similar therapeutic efficacy in ventricular rate control and proved to be well tolerated without causing hemodynamic deterioration. However, there are other reports [5,6] of significant reduction in blood pressure in up to 13% of patients receiving intravenous diltiazem for treating atrial fibrillation. Some concern has also been raised about the scarce occurrence of asymptomatic long pauses which were observed in two patients in our study who were receiving diltiazem. Underscoring the latter point, a combined administration of $MgSO_4$ or diltiazem with other agents that exert a synergistic action on the atrioventricular node should be viewed with caution.

Ideally, a drug that controls the ventricular rate response should also promote early conversion to sinus rhythm. In this regard, strategies for the acute management of PAF should certainly consider the high spontaneous conversion rates in up to 50% within 24 h [14,15], especially when atrial fibrillation is associated with a short duration of <24 h. However, in view of the scarce efficacy of rate-controlling medications to convert atrial fibrillation to sinus rhythm, the percentage of patients in our diltiazem group who converted to sinus rhythm corresponds with the spontaneous conversion rate. Although the value of 22% in the diltiazem group seems low, it could have been as high as in the other reports, if we had followed our patients for longer than 6 h, before proceeding to other antiarrhythmic drug treatment. Thus, the significantly higher percentage of patients in the $MgSO_4$ group who converted to sinus rhythm (57%) might truly reflect the potential of magnesium therapy to achieve higher conversion rates in patients with PAF, or at least do so earlier than diltiazem.

We conclude that $MgSO_4$ favorably affects rate control and seems to promote the conversion of long-lasting persistent episodes of PAF to sinus rhythm, representing a reasonable safe, reliable and cost-effective alternative treatment strategy to intravenous diltiazem.

4.1. Study limitations

The major limitation of the study is the absense of a double-blind evaluation of the effects of $MgSO_4$ versus diltiazem in the control of heart rate and early restoration of sinus rhythm. In fact, our study was randomized in a single-blind fashion (blind to the patient). We feel that we could not include a non-treated placebo group, since according to our methodology, we assessed the efficacy of the drugs only in symptomatic patients with PAF.

Although we did not obtain magnesium or diltiazem serum concentrations during the infusion period, we administered stable doses of these drugs which have been found to have a safe toxic–therapeutic ratio [5,13]. It could be also argued that the efficient cardiac depressant effects of $MgSO_4$ on the atrial and atrioventricular node function seem to be exerted independently of plasma concentrations of

magnesium in patients with hypomagnesemia as well in patients with normal electrolyte levels [11,16].

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