The effect of oral magnesium, alone or as an adjuvant to sotalol, after cardioversion in patients with persistent atrial fibrillation

M. Frick¹, B. Darpo², J. Östergren³ and M. Rosenqvist²

¹Department of Cardiology, South Hospital, and Departments of ³Medicine and ²Cardiology, Karolinska Hospital, Stockholm, Sweden

Aims To determine whether magnesium given orally decreases the recurrence rate of atrial fibrillation after elective direct current cardioversion of persistent atrial fibrillation.

Methods and Results Consecutive outpatients were randomized to treatment with oral magnesium (10·3 mmol) or placebo twice daily in a double-blind fashion. Two groups were studied; magnesium study: 170 patients with atrial fibrillation persistent for >1 month, scheduled for their first direct current cardioversion. No concomitant antiarrhythmic drugs of class I or III were allowed. Sotalol and magnesium study: 131 patients with recurrence of persistent atrial fibrillation after previous direct current cardioversion, or a history of paroxysmal atrial fibrillation, treated with sotalol. Patients were followed until recurrence of atrial fibrillation or for at least 6 months. Magnesium study: at cardioversion 67 of 85 (79%) in the placebo group and 64 of 85 (75%) in the magnesium group had converted to sinus rhythm. At the end of the study, with a follow-up of 6 to 42 months, 15% of patients in the placebo group and 19% of patients in the magnesium group remained in sinus rhythm (Log rank test: P=0·37). Sotalol and magnesium study: pharmacological conversion to sinus rhythm, after oral treatment, was achieved in 34 of 131 (26%) patients. Sinus rhythm, with or without cardioversion, was restored in 89% and 85% of the patients in the placebo and magnesium groups, respectively. At the end of the study, with a follow-up of 6 to 42 months, 37% of patients in the placebo group and 30% of patients in the magnesium group remained in sinus rhythm (Log rank test: P=0·64).

Conclusion In patients with persistent atrial fibrillation, oral treatment with magnesium alone or as an adjuvant to sotalol, does not influence the recurrence rate of atrial fibrillation after elective cardioversion.

(Eur Heart J 2000; 21: 1177–1185)
© 2000 The European Society of Cardiology

Key Words: Atrial fibrillation, cardioversion, magnesium, sotalol, arrhythmias.

See page 1116 for the Editorial comment on this article

Introduction

Atrial fibrillation is the most commonly sustained arrhythmia in the elderly population. Atrial fibrillation is associated with thromboembolic events and increased mortality[1]. In patients with persistent atrial fibrillation, restoring sinus rhythm has several potential benefits: improved haemodynamic status, relief of symptoms and reduced embolic risk. Direct current cardioversion remains the technique of choice for restoring sinus rhythm[2]. Because of adverse effects and risks of proarrhythmias[3], treatment with antiarrhythmics of class I and III are not advised after a first direct current cardioversion[4]. Without prophylactic treatment, 60–80% of patients relapse into atrial fibrillation within 12 months[3,4]. However, even with use of these drugs the recurrence rate of atrial fibrillation after direct current cardioversion is about 50% after 6 months[5,6]. Randomized trials have not demonstrated any significant difference among class I and III antiarrhythmics regarding maintenance of sinus rhythm[5,6].

Magnesium, given intravenously, affects atrial and atrioventricular conduction electrophysiologically[7–9] and in some trials it has reduced the number of supraventricular arrhythmias[10,11]. Magnesium deficiency has been reported in patients with atrial fibrillation[12,13], and magnesium deficiency in the heart muscle has been

Revision submitted 18 October 1999, and accepted 20 October 1999.

This study was supported by the Swedish Heart and Lung Foundation.

Correspondence: Mats Frick, MD, Department of Cardiology, South Hospital, S-118 83 Stockholm, Sweden.
shown to be associated with an increased rate of arrhythmias after heart surgery\textsuperscript{10}. Several studies have shown a decrease of postoperative supraventricular tachycardia/atrial fibrillation with prophylactic magnesium treatment\textsuperscript{16,17}, but other studies have failed to confirm this observation\textsuperscript{18}.

We have studied whether treatment with magnesium, given orally, decreased the recurrence rate of atrial fibrillation after elective cardioversion: in patients with persistent atrial fibrillation, scheduled for their first direct current cardioversion, without concomitant anti-arrhythmic drugs of class I or III (magnesium study), and in patients with recurrence of persistent atrial fibrillation after previous direct current cardioversion, or a history of paroxysmal atrial fibrillation, randomized to treatment with magnesium or placebo in addition to sotalol (sotalol and magnesium study).

**Methods**

**Study group**

From 1 September 1995 to 30 September 1998, patients with persistent atrial fibrillation referred to the arrhythmia services of the South Hospital and Karolinska Hospital, Stockholm, were selected for inclusion if they met the following inclusion criteria: persistent atrial fibrillation, of either unknown or continuous duration between 1 and 12 months, and a clinical indication for direct current cardioversion. In the magnesium study, only patients scheduled for their first direct current conversion were included; patients with previous electric or pharmacological cardioversion were excluded. Furthermore, in this study, treatment with drugs known to influence the success rate of cardioversion or maintenance of sinus rhythm (e.g. Vaughan Williams class I and III, including sotalol) were not allowed. Treatment with digoxin, diltiazem, verapamil or β\textsubscript{i}-blockers for ventricular rate control were allowed.

In the sotalol and magnesium study, only patients with recurrence of persistent atrial fibrillation after previous direct current cardioversion or a history of self terminating paroxysmal atrial fibrillation were included. In patients with early relapse after previous cardioversion (i.e. <1 month), duration of atrial fibrillation was defined as the sum of the total atrial fibrillation duration. Patients with >2 previous direct current cardioversions were excluded.

At baseline, patients underwent a physical examination, echocardiography, Holter electrocardiogram, and blood samples were drawn for assay of serum electrolytes. Patients with atrial flutter for more than 6 out of 24 h on a Holter electrocardiogram, were excluded. Other exclusion criteria were: heart rate <55 beats . min\textsuperscript{-1} (defined as a mean rate during a Holter electrocardiogram), a history of atrioventricular block II or III, left atrial dimension <50 mm (echocardiographic parasternal long axis view), uncorrected thyroid disease, serum potassium <3.7 mmol . l\textsuperscript{-1}, chronic renal insufficiency (serum creatinine >145 mmol . l\textsuperscript{-1}) and myocardial infarction or cardiac surgery within the last 2 months. In the sotalol and magnesium study, the following exclusion criteria were added: contraindications for sotalol, bifascicular block, sick sinus syndrome, hypotension (<90 mmHg), uncompensated congestive heart failure.

All patients were treated with warfarin, with an international normalized ratio of 2.0 to 3.0 for at least 3 weeks before and 4 weeks after cardioversion.

**Cardioversion**

Direct current cardioversion was started at 200 J and, if necessary, repeated at increased energy levels with at least one attempt at 360 J. In patients with a rapid ventricular rate or high blood pressure, selective β\textsubscript{i}-blockers were given intravenously according to the clinician’s decision. Successful cardioversion was defined as the maintenance of sinus rhythm for more than 1 h after cardioversion. Treatment with digoxin, if present, was withdrawn in patients who converted to sinus rhythm.

**Treatment protocol**

Patients were randomly assigned to therapy with magnesium or placebo in a double-blind fashion. Identical treatment packs for magnesium and placebo, identified by number, were manufactured according to a randomization schedule kept securely by the South Hospital pharmacy. The packs either contained T Emgesan 250 mg (10.3 mmol magnesium hydroxide, Pharmacia and Upjohn\textsuperscript{16}) or identical placebo tablets. The study treatment, and sotalol treatment in the sotalol and magnesium study, was initiated at least 1 week before cardioversion. Study treatment was initiated with one tablet a day for 7 days, and thereafter one tablet twice daily (20.6 mmol magnesium, day\textsuperscript{-1}). Treatment with sotalol was initiated with 80 mg twice daily. Thereafter, the dose was titrated to 160 mg twice daily in patients with a mean heart rate of >60 beats . min\textsuperscript{-1} at rest. Dosages were reduced in patients with drug-related side effects or a mean heart rate <50 beats . min\textsuperscript{-1}.

Patients were followed, by clinical investigation, blood samples and a 12-lead electrocardiogram 1 week and 1 month after cardioversion, and thereafter every 6 months. Additional examinations were performed in patients with symptoms suggestive of relapse into atrial fibrillation between scheduled appointments. The primary end-point was recurrence of atrial fibrillation verified with a 12-lead electrocardiogram. All patients who maintained sinus rhythm were followed for at least 6 months. A tablet count of the study drug was performed at each visit in order to evaluate compliance.
The side effects of study medication and sotalol were noted at each clinical examination.

**Blood sample analyses**

Serum potassium and creatinine were analysed using ion-selective electrodes, Kodak Ektachem 750 (Kodak Company, Rochester, N.Y.). Serum magnesium was analysed using a xylidyl blue method, Hitachi 917, (Roche Company, Naka, Japan).

**Statistical analysis**

Data were analysed on the basis of intention-to-treat. Continuous variables were expressed as mean values ± standard deviation. Categorical data were compared using the chi-square test or Fisher’s exact test and continuous variables by using Student’s t-test or Mann–Whitney test when appropriate. Kaplan–Meier analysis with the log-rank test was used to compare the frequency of recurrence of atrial fibrillation. On the basis of previous studies, it was anticipated that, after a successful cardioversion, 75% of patients would relapse into atrial fibrillation during follow-up in the magnesium study. On the assumption that 55% of patients with magnesium treatment would relapse into atrial fibrillation, a sample size of 122 patients was calculated to be sufficient to determine this difference in response rate at an α level of 0.05 with a power of 0.80. In the sotalol and magnesium study it was anticipated that 50% of patients would relapse into atrial fibrillation during follow-up and that 30% of patients with magnesium treatment would relapse into atrial fibrillation; in this case a sample size of 110 patients was calculated to be sufficient. A P-value of less than 0.05 was considered to indicate statistical significance. Calculations were performed with the statistical computer package STATISTICA 5.0 (StatSoft Inc., Tulsa, Oklahoma).

**Ethics**

The study was approved by the Local Ethics Committees, of South Hospital and Karolinska Hospital, and patients gave their written, informed consent to participate.

**Results**

**Magnesium study**

One hundred and seventy patients were included in this study. Eighty five patients were randomized to treatment with placebo or magnesium, respectively. Clinical characteristics for all patients are presented in Table 1. The study drug was withdrawn in one patient, randomized to placebo, after direct current cardioversion because of
transient atrioventricular block III. There were no deaths among study patients during the study. One patient, randomized to placebo, was lost to follow-up after 1 month.

Clinical characteristics for patients with sinus rhythm after cardioversion are presented in Table 1. Both treatment groups were comparable for all variables except for gender. There was a non-significant tendency towards a shorter duration of atrial fibrillation in the magnesium group.

**Success rate at cardioversion**

Sinus rhythm was restored and maintained for >1 h in 131 (77%) patients by direct current cardioversion. The success rate of cardioversion did not differ between the placebo and magnesium groups, Table 2.

### Table 2  Success rate at cardioversion, maintenance of sinus rhythm at 1 and 6 months and at the end of the magnesium, and sotalol and magnesium studies

<table>
<thead>
<tr>
<th></th>
<th>Magnesium study</th>
<th>Sotalol and magnesium study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n=170)</td>
<td>Placebo (n=85) Mg (n=85)</td>
</tr>
<tr>
<td>SR with pharmacological cardioversion</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SR after DC and pharmacological cardioversion</td>
<td>131 (77)</td>
<td>67 (79)</td>
</tr>
<tr>
<td>SR at 1 month</td>
<td>49 (37)</td>
<td>23 (34)</td>
</tr>
<tr>
<td>SR at 6 months</td>
<td>37 (28)</td>
<td>18 (27)</td>
</tr>
<tr>
<td>SR at the end of study</td>
<td>22 (17)</td>
<td>10 (15)</td>
</tr>
</tbody>
</table>

Values are expressed as number (%) of patients.

†P-value=ns, comparing placebo and magnesium groups. SR=sinus rhythm; DC=direct current.

Recurrence of atrial fibrillation

As shown in Table 2, there was no difference in the ability to maintain sinus rhythm at 1 or at 6 months between the placebo and magnesium groups. In addition, the cumulative proportion of patients in sinus rhythm did not differ between the two groups (Log rank test: P=0·37), Fig. 1. At the end of the study, with a follow-up of 6 to 42 months (mean 21 months), only 10 (15%) patients in the placebo group and 12 (19%) in the magnesium group remained in sinus rhythm.

Most patients relapsed into atrial fibrillation early after cardioversion. Of all patients who relapsed into atrial fibrillation (n=109), the recurrence rate was 60%, 76% and 85% within 1 week, 1 month and 6 months, respectively.

The magnesium group tended to have a higher mean heart rate at recurrence of atrial fibrillation;
Table 3  Sotalol and magnesium study: baseline clinical characteristics for all patients and for patients with sinus rhythm after pharmacological and DC cardioversion

<table>
<thead>
<tr>
<th></th>
<th>Total  (n=131)</th>
<th>Placebo (n=57)</th>
<th>Magnesium (n=57)</th>
<th>P-value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>90 (69)</td>
<td>40 (70)</td>
<td>36 (63)</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years), mean (range)</td>
<td>67 ± (37–85)</td>
<td>68 ± (45–83)</td>
<td>65 ± (37–83)</td>
<td>ns</td>
</tr>
<tr>
<td>AF duration, months, mean (range)</td>
<td>4–8 (1–12)</td>
<td>5–3 (1–12)</td>
<td>4–3 (1–12)</td>
<td>ns</td>
</tr>
<tr>
<td>AF, unknown duration</td>
<td>32 (24)</td>
<td>13 (23)</td>
<td>10 (18)</td>
<td>ns</td>
</tr>
<tr>
<td>Previous DC</td>
<td>113 (86)</td>
<td>48 (84)</td>
<td>53 (93)</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43 (33)</td>
<td>14 (25)</td>
<td>22 (39)</td>
<td>ns</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>10 (8)</td>
<td>5 (9)</td>
<td>3 (5)</td>
<td>ns</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>59 (45)</td>
<td>25 (44)</td>
<td>27 (47)</td>
<td>ns</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>23 (18)</td>
<td>8 (14)</td>
<td>11 (19)</td>
<td>ns</td>
</tr>
<tr>
<td>HCMP</td>
<td>8 (6)</td>
<td>3 (5)</td>
<td>5 (9)</td>
<td>ns</td>
</tr>
<tr>
<td>COPD</td>
<td>4 (3)</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (3)</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>ns</td>
</tr>
<tr>
<td>Corrected thyroid disease</td>
<td>7 (5)</td>
<td>1 (2)</td>
<td>5 (9)</td>
<td>ns</td>
</tr>
<tr>
<td>Lone AF†</td>
<td>59 (45)</td>
<td>31 (45)</td>
<td>20 (35)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sotalol dose, mg, mean, (range)</td>
<td>189 (40–320)</td>
<td>185 (60–320)</td>
<td>190 (40–320)</td>
<td>ns</td>
</tr>
<tr>
<td>Digoxin</td>
<td>4 (3)</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Verapamil/diltiazem</td>
<td>5 (4)</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Calcium antagonist‡</td>
<td>11 (8)</td>
<td>4 (7)</td>
<td>5 (9)</td>
<td>ns</td>
</tr>
<tr>
<td>Diuretics</td>
<td>36 (27)</td>
<td>17 (30)</td>
<td>13 (23)</td>
<td>ns</td>
</tr>
<tr>
<td>Left atrial size, parasteral view (mm)</td>
<td>42.6 ± 4.0</td>
<td>42.6 ± 3.9</td>
<td>42.5 ± 3.7</td>
<td>ns</td>
</tr>
<tr>
<td>LVEDd (mm)</td>
<td>48.3 ± 5.6</td>
<td>48.1 ± 5.4</td>
<td>47.8 ± 5.3</td>
<td>ns</td>
</tr>
<tr>
<td>LV wall thickness (mm)</td>
<td>11.3 ± 1.8</td>
<td>11.0 ± 1.7</td>
<td>11.5 ± 2.1</td>
<td>ns</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>47 ± 8.1</td>
<td>48 ± 7.0</td>
<td>46 ± 8.6</td>
<td>ns</td>
</tr>
<tr>
<td>S-creatinine (mmol . l⁻¹)</td>
<td>93 ± 14</td>
<td>92.5 ± 12.1</td>
<td>91.4 ± 15.1</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or number (% of patients).

†Defined as the absence of any of the above mentioned diseases.
‡Comparing placebo and magnesium groups.
§AF=atrial fibrillation; HCMP=hypertrophic cardiomyopathy; COPD=chronic obstructive pulmonary disease; LVEDd=left ventricular end-diastolic diameter; LV=left ventricular.

100 ± 22 beats . min⁻¹ vs 92 ± 26 beats . min⁻¹ for the placebo group (P=0.09) on the first 12-lead electrocardiogram after recurrence of atrial fibrillation.

Sotalol and magnesium study

One hundred and thirty-one patients were included in this study. Forty-two of these patients had reached the end-point in the magnesium study. Sixty-four patients were randomized to treatment with placebo and 67 to treatment with magnesium. Clinical characteristics for all patients are presented in Table 3. In three patients, study treatment was withdrawn before the planned direct current cardioversion: in one patient because of stroke (magnesium group) and in one patient from each group due to development of congestive heart failure.

Clinical characteristics for patients with sinus rhythm after pharmacological or direct current cardioversion are presented in Table 3. Both groups were comparable for all variables except for a higher proportion of patients with lone atrial fibrillation in the placebo group.

Pharmacological conversion

Pharmacological conversion to sinus rhythm, after initiating sotalol and study drug treatment, was achieved in 15 of 64 (23%) in the placebo group and in 19 of 67 (28%) in magnesium group, (P=ns), Table 2. The pharmacological conversion rate was not dependent on the mean duration of atrial fibrillation, 5–2 vs 4–7 months (P=ns) for patients with and without conversion. The presence of the known or unknown duration of atrial fibrillation did not significantly influence the pharmacological conversion rate, 29% vs 19% (P=ns).

Success rate at cardioversion

Sinus rhythm was restored in 114 of 131 (87%) patients, with pharmacological or direct current conversion, and maintained for >1 h. The rate of conversion to sinus rhythm did not differ significantly between the placebo and magnesium groups, Table 2.

Recurrence of atrial fibrillation

There was no significant difference in maintaining sinus rhythm between the magnesium and placebo groups, Table 2. After 6 months there was a tendency for a higher proportion of patients to be in sinus rhythm in the magnesium group (29 of 57, 51%) compared to the placebo group (24 of 72, 42%), (P=ns). However, the cumulative proportion of patients in sinus rhythm did not differ between the two groups (Log rank test:
In the magnesium study there were no significant differences in serum magnesium, at the end of study, between patients who maintained sinus rhythm ($0.86 \pm 0.07 \text{mmol} \cdot \text{l}^{-1}$) and patients with relapse of atrial fibrillation ($0.85 \pm 0.08 \text{mmol} \cdot \text{l}^{-1}$). In the sotalol and magnesium study there was a small significant difference, with higher serum magnesium in patients with relapse of atrial fibrillation ($0.85 \pm 0.08$ vs $0.80 \pm 0.09 \text{mmol} \cdot \text{l}^{-1}$, $P<0.001$).

**Side effects**

Flatulence and mild diarrhoea were noted in four of 67 (6%) and in 21 of 64 (33%) in the placebo and magnesium groups, respectively ($P<0.001$) in the magnesium study. Corresponding figures in the sotalol and magnesium study was in seven of 64 (11%) and in 16 of 67 (24%) in the placebo and magnesium groups, respectively ($P=0.05$). However, in most patients, side effects were transient and well tolerated. In two patients, randomized to magnesium, gastrointestinal side effects disappeared after dose reduction.

Treatment compliance, evaluated by tablet count, was good. In the magnesium study, study treatment was discontinued in four (6%) patients in the placebo group; one patient with diarrhoea, one patient lost to follow-up, one patient for unclear reasons and one patient in whom drug treatment was withdrawn because of transient atrioventricular block III. The corresponding withdrawal rate in the magnesium group was three (5%) patients; two patients because of diarrhoea and one patient discontinued study treatment after surgery for cerebral bleeding. In the sotalol and magnesium study, study treatment was discontinued in eight (6%) patients,
three (5%) in the placebo group and five (7%) in the magnesium group. Six of these patients were among the patients in whom sotalol was withdrawn. In addition, study treatment was discontinued in two patients in the magnesium group (diarrhoea, eczema).

**Side effects and safety of sotalol**

The daily mean dose of sotalol in all 131 patients was 189 mg. On relapse into atrial fibrillation, or at the end of the study, one (1%) patient was on 40 mg, three (2%) were on 60 mg, eight (6%) were on 80 or 120 mg, 66 (55%) were on 160 mg and 21 (17%) were on 240 mg or 320 mg. The initial daily dose of 160 mg was reduced in 20 (16%) patients, mostly because of bradycardia. However, the efficacy of lower doses of sotalol, in terms of maintaining sinus rhythm, was not different from that of higher doses. The percentages of patients in sinus rhythm after 6 months, for daily doses of \( \leq 120 \text{ mg} \), \( \leq 160 \text{ mg} \), and \( > 160 \text{ mg} \), were 70%, 40% and 44%, respectively. The daily mean doses of sotalol did not differ significantly between the placebo and magnesium groups (185 vs 190 mg).

Altogether 11 (8%) patients discontinued sotalol. As already mentioned three patients were withdrawn before direct current cardioversion. After cardioversion, sotalol was withdrawn in four patients in the placebo group (sinus arrest, bradycardia, atrioventricular block II and congestive heart failure) and in four patients in the magnesium group (depression, impotency and two because of dizziness).

One patient from each group, both after withdrawal of sotalol, was lost to follow-up after 1 month. One patient (magnesium group) relapsed into atrial fibrillation after coronary bypass surgery. One patient (magnesium group) died from a myocardial infarction.

In order to study a homogeneous patient population we excluded patients whose atrial fibrillation lasted less than 2 days, since patients whose atrial fibrillation is of short duration have a better outcome regarding maintenance of sinus rhythm[22]. Since patients whose atrial fibrillation is of \( > 2 \text{ days} \) require anticoagulation therapy with therapeutic international normalized ratio for at least 3 weeks, elective direct current cardioversion will be postponed for several weeks. For this reason, and in order to ensure magnesium treatment at least 1 week before direct current cardioversion, we only included patients whose atrial fibrillation was of \( > 1 \text{ month} \).

The cardioversion rate was not influenced by magnesium treatment, even though treatment with magnesium or placebo was initiated before direct current cardioversion. In earlier reports examining the efficacy of magnesium for conversion of supraventricular tachycardia, magnesium had been given intravenously[10,11,23]. Since these studies were not placebo-controlled and were performed in patients with atrioventricular re-entry tachycardia[23], or mixed supraventricular tachycardia[10,11], it is still undecided as to whether magnesium had an effect on conversion in atrial fibrillation.

**Discussion**

This randomized, double-blind, study is the first to evaluate the effect of oral magnesium, alone or in addition to treatment with sotalol, after direct current cardioversion in patients with persistent atrial fibrillation. Magnesium does not seem to have any effect on the recurrence rate of atrial fibrillation.

Considering the high recurrence rate of atrial fibrillation, the drug-related side effects and the risk of proarrhythmias with antiarrhythmic treatment, the search for alternative treatments is imperative. Earlier observations have demonstrated the antiarrhythmic properties of magnesium. In patients with no clinical evidence of cardiac disease, magnesium given intravenously resulted in a prolongation of the atrial–His interval and the sinoatrial conduction time[21]. In patients with cardiac disease, magnesium resulted in an increase in the corrected sinus node recovery time[8]. In patients with conduction defects, magnesium increased the intraventricular, supraventricular and infraventricular conduction time[19]. Moreover, the observation that magnesium reduces the incidence of atrial fibrillation after heart surgery[15–17], and the effects of magnesium in trials of supraventricular tachycardia[10,11], indicates that magnesium may be useful in reducing the recurrence of atrial fibrillation after direct current cardioversion. Although most of these studies use intravenous magnesium, some small studies indicate antiarrhythmic effects after treatment with oral magnesium. Oral magnesium reduced ventricular ectopic activity in digitalized patients with chronic atrial fibrillation[19] and in patients with congestive heart failure[20]. Pre-operative treatment with oral magnesium reduced QTc, and postoperative arrhythmias in a small study of patients scheduled for mitral valve replacement[21].

The success rate of direct current cardioversion in our magnesium study (77%) is in accordance with previous studies in patients without antiarrhythmic treatment with class I or III drugs[3,4]. The higher success rate in the sotalol and magnesium study (87%) may suggest that sotalol reduces the defibrillation threshold.

In the sotalol and magnesium study, 34 of 131 (26%) patients converted to sinus rhythm after the initiation of oral sotalol and study treatment, despite the fact that no patient had a duration of atrial fibrillation <1 month. Moreover, the pharmacological conversion rate was not influenced by the duration of atrial fibrillation or the unknown duration of atrial fibrillation. Our finding, of a 26% conversion rate on oral sotalol, is in accordance with previous studies, in which five of 28 (18%) and five of 25 (20%) converted to sinus rhythm with oral sotalol[6,24]. It remains to be decided whether a more aggressive titration of sotalol dose before cardioversion would have resulted in a higher conversion rate.
Nevertheless, our finding that one patient out of four converted to sinus rhythm points to the necessity of adequate anticoagulation therapy before initiating sotalol therapy in patients with atrial fibrillation.

The relapse frequency of atrial fibrillation after cardioversion was high. In the magnesium study, only 17%, and thereby, only 13% of all patients scheduled for cardioversion, maintained sinus rhythm for >6 months. This is consistent with a study of Van Gelder et al., where corresponding figures for long-term maintenance of sinus rhythm were 17% and 10%, respectively, in patients without treatment by class I or III antiarrhythmics\textsuperscript{25}. In the sotalol and magnesium study, 46% remained in sinus rhythm after 6 months. These results are comparable with previous studies with sotalol\textsuperscript{5,6}. Our study followed patients for at least 6 and up to 42 months, revealing a further decrease over time, with only 33% of patients in sinus rhythm at the end of the study. However, it should be noted that in the study by Juul-Møller et al.\textsuperscript{9} only 15% of patients had a previous direct current cardioversion. In our study, 1–2 previous direct current cardioversions were performed in 86% of the patients. The remaining patients had a history of paroxysmal atrial fibrillation in which the occurrence rate for atrial fibrillation has been reported to be more frequent\textsuperscript{26}, although this was not observed in our study.

Relapse of atrial fibrillation was early among our patients. In the magnesium study, 73% patients relapsed into atrial fibrillation during the first month. Animal studies have shown that atrial fibrillation-induced electrical remodelling of the electrophysiological properties of the atria is reversible within the first weeks\textsuperscript{27}. In a recent study, treatment with verapamil, confined to this period after cardioversion, reduced early relapse frequency of atrial fibrillation\textsuperscript{28}. However, the timing of relapse was also early in the sotalol and magnesium study. Of those patients who relapsed into atrial fibrillation the recurrence rate was 45%, 70% and 88% within 1 week, 1 month and 6 months, respectively. This is in agreement with previous studies\textsuperscript{24}. Whether calcium antagonists in addition to sotalol may reduce early relapse of atrial fibrillation is unknown.

Sotalol treatment was relatively well tolerated. The 8% withdrawal rate of sotalol in our study, is in accordance with the withdrawal rate of 11% observed in the study of Juul-Møller et al.\textsuperscript{9}. We also confirmed their observation, that the efficacy of lower doses of sotalol (≤ 160 mg daily), in terms of maintaining sinus rhythm, was not different from that of higher doses. No ventricular proarrhythmias were noted in our study. Proarrhythmias, predominantly torsades de pointes, are reported in 2-4% of patients treated with sotalol for supraventricular arrhythmias\textsuperscript{29}. Intravenous magnesium has shown efficacy in the treatment of torsades de pointes\textsuperscript{30}. As already mentioned, oral magnesium reduced the ventricular ectopic activity in patients with chronic atrial fibrillation and congestive heart failure\textsuperscript{19,20}. However, whether oral magnesium as an adjuvant to sotalol, reduces the risk of developing torsades de pointes, has to be evaluated in a larger trial than ours.

Treatment with oral magnesium had no slowing effect on heart rate. In fact, patients randomized to treatment with magnesium had a tendency to a higher mean heart rate at recurrence of atrial fibrillation. This finding is in contradiction to previous studies, in patients with new-onset atrial fibrillation\textsuperscript{31} and in electrophysiological studies in patients with sinus rhythm, in which a prolongation of the atrioventricular conduction time was observed after administration of intravenous magnesium\textsuperscript{31–33}. However, in a recently performed placebo-controlled study, in 30 patients with chronic atrial fibrillation, no effect on heart rate was observed after intravenous magnesium\textsuperscript{32}. These results indicate that magnesium does not have any clinically relevant effect on atrioventricular conduction in patients with atrial fibrillation.

In contrast to previous studies\textsuperscript{12,13}, magnesium deficiency was uncommon in our study, which could be explained by a less frequent use of diuretics and a more frequent use of drugs with electrolyte sparing capacity such as amiloride and angiotensin converting inhibitors. However, since only 1% of total body magnesium is located in the extracellular fluid, and, since serum magnesium does not correlate to the intracellular concentration of magnesium, and thus even less to the active free intracellular magnesium\textsuperscript{33}, the actual proportion of patients with true magnesium deficit in our studies is unknown.

**Limitations**

The lack of effect of magnesium in our study may be related to an inadequate dose of magnesium. There was only a modest increase in serum magnesium in patients randomized to treatment with magnesium. The daily recommended amount of magnesium is 4–5 mg·kg\textsuperscript{-1}·day\textsuperscript{-1}–body weight (14 mmol), with a current recommendation for supplementation of 5 to 10 mmol daily for individuals at risk for magnesium deficiency\textsuperscript{34}. The dose of 20·6 mmol·day\textsuperscript{-1} in our study was based on this recommendation, and the fact that most earlier studies with oral magnesium have been performed with a daily supplementation of 15 mmol\textsuperscript{20,21}.

Another problem is that absorption of oral magnesium supplementation varies, with approximately only 40% being absorbed. In studies evaluating the effects of magnesium in supraventricular tachycardia, magnesium has mostly been given intravenously, resulting in a higher serum level of magnesium than in our study\textsuperscript{7–9,10,11,16–18,23}. In patients with normal renal function it seems to be difficult to achieve corresponding serum levels of magnesium with oral administration. The absence of a clinically significant elevation of serum magnesium and the low proportion of magnesium deficiency, in our study, may indicate that the electrophysiological effects of intravenous magnesium in earlier studies are more likely to be ascribed to hypermagnesaemia rather than a correction of hypomagnesaemia.
Our study lacks estimation of magnesium deficiency, with 24 h urinary magnesium excretion or intracellular concentration of magnesium. Thereby, to what extent intracellular magnesium is increased by long-term therapy with magnesium was not evaluated. However, different methods to measure magnesium deficiency or intracellular magnesium seems to have little predictive value in assessing the status of myocardial magnesium.

In summary, oral treatment with magnesium alone, or as an adjuvant to sotalol, does not influence the recurrence rate of atrial fibrillation after elective cardioversion of patients with persistent atrial fibrillation.

We thank Ms Rigmor Härden, Ms Madelene Svensson, Ms Birgitta Nordlöf and South Hospital Pharmacy for skilled technical assistance.

References


