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Effect of Acute Magnesium Administration on the Frequency of Ventricular Arrhythmia in Patients With Heart Failure

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Background There is a high incidence of ventricular arrhythmia and sudden death in patients with heart failure. Unfortunately, currently available antiarrhythmic agents have only limited efficacy and may result in proarrhythmia and hemodynamic deterioration in these patients.

Methods and Results We studied the acute effect of intravenous magnesium chloride on the frequency and severity of ventricular arrhythmia in 30 patients with symptomatic heart failure using a double-blind, placebo-controlled crossover design. The left ventricular ejection fraction was 23.0±8.0% (mean±SD). No patient had a history of symptomatic ventricular arrhythmia or was receiving antiarrhythmic agents, calcium channel antagonists, or β-blockers. Patients were randomized to receive placebo (5% dextrose [D5W] in water alone) or magnesium chloride in D5W given as a bolus of 0.3 mEq/kg over 10 minutes followed by a maintenance infusion of 0.08 mEq/kg per hour for 24 hours. The magnesium concentrations 30 minutes and 24 hours after the bolus were 3.6±0.1 and 4.2±0.1 mg/dL, respectively. There was no significant change in serum potassium concentration during magnesium administration. Blinded analysis revealed that administration of intravenous magnesium chloride, compared with placebo, significantly decreased total ventricular ectopy per hour (mean±SEM, 70±26 versus 149±64, $P<.001$), couplets per day (23±11 versus 94±59, $P=.007$), and episodes of ventricular tachycardia per day (0.8±0.2 versus 2.6±1.0, $P=.051$).

Conclusions Intravenous magnesium chloride administration reduces the frequency of ventricular arrhythmia in patients with symptomatic heart failure. (***Circulation*. 1994;89:660-666.**)

Key Words • magnesium • arrhythmia • heart failure

Congestive heart failure is characterized by contractile dysfunction, frequent complex ventricular ectopy, and a high incidence of sudden death. Unfortunately, currently available antiarrhythmic agents have only limited efficacy in patients with congestive heart failure and may be associated with worsening ectopic activity and hemodynamic deterioration. Magnesium is a ubiquitous divalent cation that strongly influences cardiac cell membrane function and is an important catalyst of many enzymatic reactions in the myocyte. Alterations in extracellular or intracellular magnesium concentration could significantly influence the development and frequency of ventricular arrhythmia in patients with heart failure. These patients are predisposed to magnesium deficiency secondary to diuretic and digoxin administration, neurohormonal activation resulting in volume expansion, and poor oral intake and absorption.[1] Ventricular arrhythmia may arise in heart failure as a result of enhanced automaticity or triggered activity. Experimental studies suggest that magnesium administration may reduce or prevent the occurrence of ventricular arrhythmia induced by these mechanisms.[2,3] A beneficial effect of magnesium on complex ventricular ectopy in patients with heart failure could have important consequences because this arrhythmia may culminate in ventricular fibrillation and sudden death.

Despite the potential for therapeutic benefit, there are few studies of the antiarrhythmic effect of parenteral magnesium in heart failure,[4-8] and to the best of our knowledge, a randomized, placebo-controlled trial has not been performed. Therefore, we prospectively investigated the antiarrhythmic effect of acute magnesium infusion using a randomized, double-blind, placebo-controlled crossover design. Our hypothesis was that acute augmentation of serum magnesium concentration would reduce the frequency and severity of ventricular arrhythmia in patients with symptomatic congestive heart failure.

Methods

Eligibility and Exclusion

Study subjects were recruited prospectively by review of patients seen by the Heart Failure Program at the University of North Carolina at Chapel Hill. Inclusion criteria included age of 18 years or older, left ventricular ejection fraction ≤40% by radionuclide ventriculogram, presence of heart failure for at least 1 month, New York Heart Association (NYHA) class II to IV, and normal sinus rhythm. Exclusion criteria included a history of symptomatic ventricular ectopy, antiarrhythmic drug therapy (procainamide, quinidine, disopyramide, phenytoin, tocainide, mexiletine, ethmozine, flecainide, encainide, propafenone, amiodarone, sotalol), calcium channel antagonists, β-blockers, a PR interval >0.2 seconds, or a serum creatinine >2 mg/dL. Digitalis use was not an

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exclusion criterion. The protocol was approved by the Institutional Review Board of the University of North Carolina School of Medicine, and written consent was obtained from all patients before study entry.

Study Design

This study was a randomized, double-blind, placebo-controlled crossover trial requiring 4 days of hospitalization in the General Clinical Research Center. The sequence was baseline-magnesium-washout-placebo or baseline-placebo-day 3-magnesium. Day 1 (baseline) included a cardiac history, physical examination, blood chemistry determination, serum digoxin concentration, and a 12-lead ECG. All patients were monitored by telemetry and Holter throughout the study. On day 2, a peripheral heparin lock was placed for blood drawing, and a second peripheral intravenous line was placed for the administration of the randomized treatment. After determination of blood chemistries, the subject was given a bolus dose of magnesium chloride (0.3 mEq/kg) in 5% dextrose (D5W) in water or placebo (D5W alone) over 10 minutes followed by a continuous infusion of magnesium chloride (0.08 mEq/kg per hour) or placebo for 24 hours. Eight subjects were dosed on the basis of lean body weight because of obesity. Lean body weight in kilograms was calculated as 45.5 (women) or 50 (men) plus (2.3 multiplied by inches above 5 feet).[9] Blood pressure and heart rate were recorded at baseline and at 2, 4, 6, 8, 10, 15, 20, and 30 minutes and at 1, 1.5, 2, 3, 5, 7, 12, and 24 hours. Serum magnesium concentrations were determined at baseline, at the end of the bolus (10 minutes), and at the following intervals: 15, 20, and 30 minutes and 1, 1.5, 2, 3, 5, 7, 12, and 24 hours. In a subset of 14 patients, serial potassium concentrations were also obtained. On day 3 (washout day for the subjects who received magnesium on day 2), a blood sample for electrolytes was taken, and Holter monitoring was continued. On day 4, the protocol was the same as on day 2 except that the alternate therapy was given to complete the crossover design. On day 5, the subject had a final blood sample taken and was discharged.

Magnesium Analysis

One milliliter of whole blood was centrifuged at 1200*g* for 5 minutes. The supernatant was removed, and the concentration of magnesium in the serum was determined by atomic absorption spectrophotometry.[10]

Ambulatory ECG Recording

Ambulatory ECG monitoring was performed with an Oxford MR20 two-channel (leads V_1 and V_5) AM recording device. The Holter tape recordings were analyzed on a full disclosure unit (Oxford) that printed out each individual QRS complex for subsequent visual examination. Complete determination of premature ventricular contraction (PVC) frequency with description and quantification of complex forms (multiform PVCs, couplets, and ventricular tachycardia) was undertaken for each hour of the monitoring period by manual analysis of the full disclosure data. Time representing artifact was subtracted from each hour of the recording so that the means per hour reflected only time for which interpretation was possible. A minimum of 18 hours per day of usable data was required, on both the treatment and placebo days, to include a tape in the data analysis. Full-scale real-time tracings of calibration signals, a period of baseline rhythm, and each episode of ventricular tachycardia were printed. A physician investigator (C.A.S.) verified all episodes of ventricular tachycardia on days 2 and 4. Counts of PVCs per hour and couplets per day in a 10% sample of the study data were also verified by the same investigator. Intraclass correlations between the two observers were high between counts for total ventricular ectopic beats (r=.99), couplets (r=.99), and the number of episodes of ventricular tachycardia (r=.99). The technician and physician were blinded as to the identity of the recording under analysis.

For the purpose of this study, total ventricular ectopy was defined as the mean number of PVCs per hour, including the premature beats in couplets and episodes of ventricular tachycardia. Ventricular tachycardia was defined as ≥3 consecutive premature ectopic beats at a rate of >100 beats per minute. Ventricular tachycardia was judged to be sustained if the duration was >30 seconds or if it resulted in hemodynamic compromise requiring intervention with either medication or cardioversion. The rate and duration (number of beats) of each episode of ventricular tachycardia were determined.

Statistical Analysis

The present study was designed to take into account the spontaneous variability of ventricular arrhythmia. The study sample size of 30 was estimated to have at least an 80% power to detect a target difference of 50% in arrhythmia frequency between the magnesium and placebo days. The results are expressed as mean±SEM unless otherwise indicated. The Wilcoxon signed-rank test was used for statistical comparisons of the frequency of ventricular arrhythmia and of the fastest rate and longest duration of episodes of ventricular tachycardia between monitoring periods. The presence of a period effect (exposure × day) or a carryover effect was determined by the Wilcoxon rank-sum test.[11] The possibility of a carryover effect was analyzed in two ways. The differences between the average ventricular ectopy over two treatment periods (magnesium and placebo) and baseline (day 1) for both sequences were compared. Additionally, the differences between ventricular ectopy on washout and baseline days were compared for each sequence.

Blood pressure, heart rate, and electrolyte levels during magnesium and placebo infusion were compared by paired Student's t test. The trapezoidal rule was used to determine the area under the curve for magnesium and potassium serum concentrations on placebo and magnesium days. This method averages two adjacent values and multiplies them by the distance between the two values. These individual areas are summed to produce an overall area under the curve. Subjects were included if they had at least 50% of the serum electrolyte concentration data points. Interpolation was used to supply missing values. Spearman rank correlation coefficients were used to test the strength of the relation between the difference in ventricular arrhythmia frequency on magnesium and placebo days and various study variables.

Results

Study Patients

The protocol was successfully completed by 30 of the 35 patients who were enrolled. Incomplete Holter monitoring excluded 2 patients, and heart failure exacerbation before randomization excluded 2 other patients. One diabetic patient developed symptomatic hypoglycemia on the placebo day and was excluded from analysis. There were 21 men and 9 women aged 49±9.6 years (mean±SD). The etiology of heart failure was predominantly nonischemic. Heart failure was secondary to hypertension and/or alcohol abuse in 19 subjects (1 subject also had sarcoidosis) and to coronary artery disease in 4 and was idiopathic in 7 subjects. All subjects had clinical evidence of heart failure, with 70% being NYHA class II and 30% being class III. Left ventricular ejection fraction was significantly depressed at 23±8.0% (mean±SD), with a range of 9% to 38%. At the time of the study, all of the subjects were receiving an angiotensin-converting enzyme inhibitor and digoxin, and 97% (29 of 30) were receiving diuretic agents. Potassium supplementation was being given in 48% of the patients (14 of 29) who were receiving

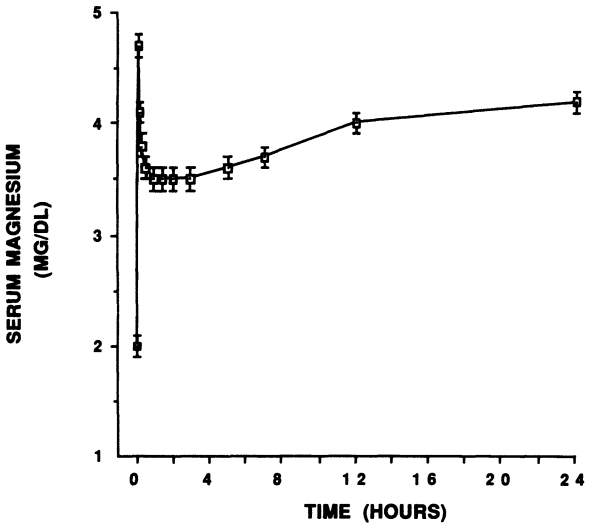

FIG 1. Graph shows serum magnesium concentration (mean±SEM) before (time=0) and after magnesium infusion (n=24 to 29).

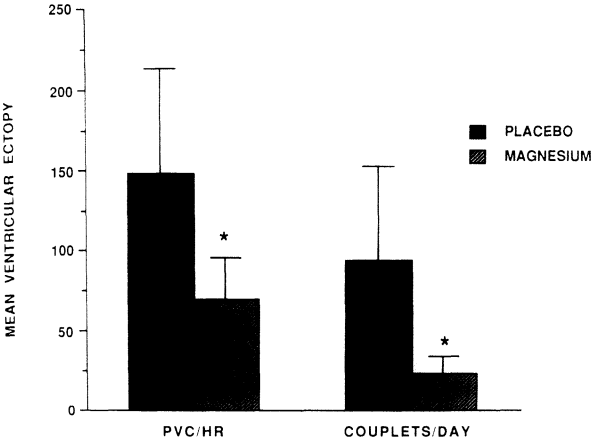

FIG 2. Bar graph shows the frequency (mean±SEM) of total premature ventricular contractions per hour (PVC/HR) and couplets per day on placebo (solid bar) and magnesium (hatched bar) days in 30 subjects with heart failure. An asterisk indicates a statistically significant difference ($P<.01$) between placebo and magnesium days.

diuretic agents. Other cardiac medications included nitrates and clonidine in 3 subjects each. Magnesium supplementation was discontinued in 2 patients before study entry. In the 2 patients enrolled who had pacemakers, pacer spikes were detectable on the Holter record but did not interfere with the determination of ventricular ectopy. Baseline serum magnesium, potassium, creatinine, calcium, and digoxin concentrations were 2.0±0.1 mg/dL, 4.2±0.1 mmol/L, 1.2±0.04 mg/dL, 9.1±0.1 mg/dL, and 0.9±0.1 ng/mL, respectively. Two patients were hypomagnesemic (<1.5 mg/dL) before receiving the magnesium infusion, and 1 of these patients was also hypokalemic (3.2 mmol/L).

Baseline Ventricular Ectopy

There was wide variability in the degree of baseline (day 1) ventricular ectopy among the study subjects. The total number of PVCs per hour ranged from 0.04 to 680, with a mean of 110±30 and a median of 54. The average number of couplets per day was 80±31, with a range of 0 to 711 and a median of 18. Couplets were detected in 86% (25/29) of patients. Ventricular tachycardia was present in 62% (18/29) of patients. The average number of episodes of ventricular tachycardia per day was 2.3±0.9, with a range of 0 to 23 and a median of 1.0.

Magnesium Administration

For the group as a whole, the preinfusion serum concentration of magnesium was higher on the placebo day compared with the magnesium day, 2.2±0.1 mg/dL versus 2.0±0.1 mg/dL, respectively ($P=.037$). In the 16 subjects given magnesium on day 2, the preinfusion serum concentration of magnesium was significantly higher on the placebo day than the magnesium day (2.2±0.1 mg/dL versus 2.0±0.1 mg/dL, $P<.01$). By contrast, preinfusion serum magnesium concentration was similar on the magnesium and placebo days (2.1±0.1 mg/dL versus 2.0±0.1 mg/dL, P=NS) when magnesium was given on day 4. The total dose of magnesium chloride administered was 163±33 mEq (mean±SD), with a range of 117 to 258 mEq. Fig 1 shows the serum concentration of magnesium before (time 0) and during the magnesium infusion. The serum magnesium concentration was significantly increased over the entire 24-hour infusion period, calculated as area under the curve (n=14), compared with placebo ($P=.001$). Serum magnesium concentration was 3.6±0.1 mg/dL 30 minutes after the bolus (n=13) and 4.2±0.1 mg/dL after 24 hours (n=19) compared with placebo ($P<.001$).

The preinfusion serum concentration of potassium was 4.3±0.1 mmol/L (n=27) on the placebo and magnesium days. In a subset of patients, serum potassium concentrations were not significantly different at 30 minutes (n=8) or 24 hours (n=9) after magnesium infusion compared with placebo. There was also no significant difference between potassium concentration on the magnesium and placebo days calculated as area under the curve (n=8).

Magnesium and Ventricular Arrhythmia

The infusion of intravenous magnesium chloride significantly decreased the total number of PVCs per hour by 53% (70±26 versus 149±64, $P<.001$) compared with placebo (Fig 2). More complex forms of ventricular arrhythmia were also reduced during magnesium infusion, including couplets per day by 76% (23±11 versus 94±59, $P=.007$) and episodes of ventricular tachycardia per day by 69% (0.8±0.2 versus 2.6±1.0, $P=.051$) (Figs 2 and 3). In the 9 patients who had episodes of ventricular tachycardia on both the placebo and magnesium days, the rate of the fastest run was significantly reduced on the magnesium day compared with placebo (143±7 versus 179±8 beats per minute, $P=.008$). The longest episode of ventricular tachycardia also tended to decrease on the magnesium day (5±1 versus 9±2 beats per minute), but this did not attain statistical significance ($P=.211$).

Figs 3 and 4 show ventricular ectopy on each day of the protocol. There was no significant difference in ventricular ectopy on the placebo day compared with baseline or washout days. Because washout represented day 3 in the 16 patients who received magnesium infusion on day 2, no carryover effect was observed.

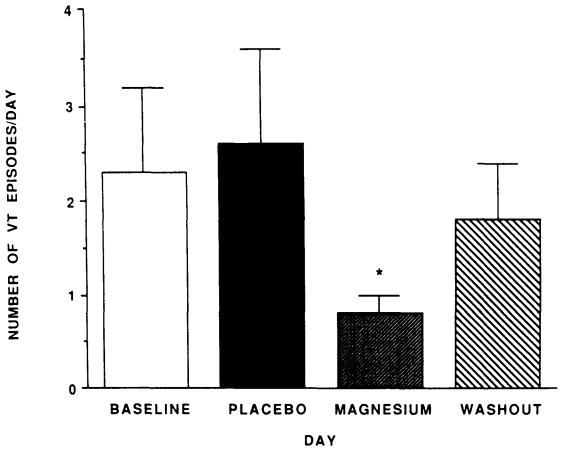

FIG 3. Bar graph shows the frequency (mean±SEM) of episodes of ventricular tachycardia (VT) on baseline (n=29), placebo (n=30), magnesium (n=30), and washout (n=16) days. An asterisk indicates a statistically significant difference ($P \leq .051$) between magnesium and placebo or baseline days.

Magnesium infusion resulted in a significant reduction in ventricular arrhythmia whether administered on day 2 or day 4. The Table shows the frequency of total PVCs and couplets per hour during successive time intervals on the washout day compared with the magnesium day. As serum magnesium concentration declined on the washout day, total ventricular ectopy and couplets per hour gradually increased compared with the magnesium day ($P<.05$).

When the 2 subjects who were hypomagnesemic and/or hypokalemic were excluded from the analysis, magnesium administration still resulted in a significant reduction in total ventricular ectopy per hour ($P=.001$) and couplets per day ($P=.014$) but not in episodes of ventricular tachycardia per day ($P=.108$). There was no significant relation between the change in total ventricular ectopy and the preinfusion serum magnesium (n=29; $r=-.11$, $P=.558$) or potassium concentration (n=30; $r=.24$, $P=.211$). The change in serum potassium concentration during the infusion of magnesium, calculated as area under the curve (n=8), also did not correlate with the degree of reduction of total PVCs per hour ($r=-.38$, $P=.352$), couplets per day ($r=-.36$, $P=.385$), or episodes of ventricular tachycardia per day ($r=-.37$, $P=.365$). Therefore, all subjects were included in the primary analysis.

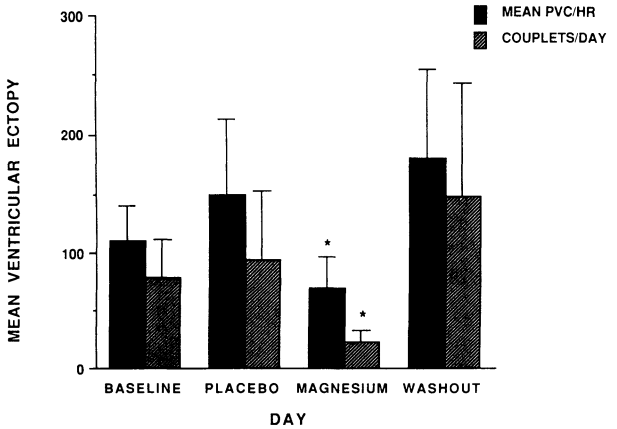

FIG 4. Bar graph shows the frequency (mean±SEM) of total premature ventricular contractions per hour (PVC/HR) (solid bar) and couplets per day (hatched bar) on baseline (n=29), placebo (n=30), magnesium (n=30), and washout (n=16) days. An asterisk indicates a statistically significant difference ($P<.01$) between magnesium and placebo, baseline, or washout days.

No subject developed hemodynamically significant ventricular tachycardia, ventricular fibrillation, or torsades de pointes during the magnesium infusion. One subject who did not demonstrate ventricular tachycardia on the placebo day had one episode of sustained but asymptomatic ventricular tachycardia (156 beats at a rate of 120 beats per minute) during magnesium infusion. This same subject also had three episodes of nonsustained ventricular tachycardia on the baseline day and one episode on the washout day. In 1 other subject, mean PVCs per hour increased by more than fourfold during magnesium administration compared with placebo, meeting the definition of proarrhythmia adopted by the CAPS investigators.[12] However, ventricular arrhythmia variability in this patient was high, and if ventricular ectopy on baseline and placebo days were averaged, no proarrhythmia was observed.

Effect on Blood Pressure and Heart Rate

Systolic and diastolic blood pressure and heart rate before magnesium infusion were 113±15 mm Hg, 70±10 mm Hg, and 78±12 beats per minute (mean±SD), respectively. Intravenous administration of magnesium chloride did not affect systolic or diastolic blood pressure. Heart rate transiently increased by 9% during the magnesium bolus compared with placebo (75±12 versus 82±10 beats per minute, $P<.02$). After completion of the bolus, there were no differences in heart rate between magnesium and placebo days over the following 24 hours.

Adverse Effects

Transient flushing (n=12), burning at the intravenous site (n=3), and transient paresthesia (n=1) occurred during infusion of the magnesium bolus. No serious adverse effects occurred.

Discussion

Our study reports results of the first randomized, placebo-controlled trial to investigate the antiarrhythmic effect of acute parenteral magnesium administration on ventricular arrhythmia in patients with symptomatic heart failure. We found that magnesium infusion significantly reduced total ventricular ectopy, couplets, and episodes of ventricular tachycardia by 53%, 76%, and 69%, respectively. The rate of the fastest episode of ventricular tachycardia was also significantly decreased during magnesium administration. Serum magnesium concentration was substantially increased over the entire infusion period. The infusion was well tolerated. Magnesium administration produced no sustained effects on blood pressure or heart rate. A reduction in ventricular ectopy was observed even though the preinfusion magnesium concentration on the placebo day was higher than on the magnesium day, which could have diminished our ability to detect an antiarrhythmic effect of magnesium. Serum potassium concentration did not appear to change significantly during magnesium administration. Only rarely did ventricular arrhythmia frequency appear to increase during magnesium infusion.

Ventricular Ectopy During Magnesium Infusion Compared With Washout

	Premature Ventricular Contractions per Hour		Couplets per Hour	
Time in Hours	Magnesium	Washout	Magnesium	Washout
1-2	88±41	120±48	4±2	6±5
1-8	82±35	140±69	13±8	47±39
9-16	80±27	199±85*	12±7	54±33†
17-24	53±16	202±88†	7±4	48±26†

Results expressed as mean±SEM. n=16. *P* values based on comparison of magnesium and washout.
*$P<.05$, †$P\leq.01$.

Previous Work

There are limited data on the effect of magnesium on ventricular arrhythmia in patients with congestive heart failure. Dyckner and Wester[4] infused 30 mmol magnesium sulfate over 10 hours in 33 patients suspected of being magnesium deficient, including 20 patients with congestive heart failure. Ventricular ectopy was significantly reduced during 3 hours of monitoring conducted 12 hours after magnesium administration. The effect of magnesium in the subjects with heart failure alone was not reported. Camara et al[5] administered intramuscular magnesium to 3 patients hospitalized with heart failure caused by Chagas' disease. Episodes of nonsustained ventricular tachycardia were abolished, and ventricular ectopy was significantly reduced after magnesium administration. Frustaci et al[6] reported that parenteral magnesium administration abolished ventricular tachycardia and reduced ventricular extrasystoles by 80% in 3 patients with dilated cardiomyopathy and in 1 patient with right ventricular dysplasia, all of whom had low myocardial magnesium concentrations. There was no effect in 4 patients who had myocarditis and normal myocardial magnesium concentrations. Perticone et al[7] studied 10 patients with ischemic dilated cardiomyopathy and symptomatic ventricular tachycardia who had normal serum magnesium concentrations and were not taking diuretics. Intravenous administration of magnesium sulfate (6 g) daily for 1 week resulted in a significant reduction in the frequency of PVCs and couplets and abolished ventricular tachycardia by day 5. In contrast to the previous studies, Gottlieb et al[8] conducted a non–placebo-controlled trial in 30 patients with symptomatic heart failure. They found no reduction in ventricular arrhythmia during 6 hours of monitoring after magnesium sulfate infusion (0.2 mEq/kg over 1 hour) compared with a similar baseline period 1 week previously.

Our study differs from this previous work in several important respects. None of the prior investigations were placebo-controlled studies. By contrast, our investigation was randomized, double-blind, and placebo-controlled. All patients had well-documented chronic congestive heart failure secondary to systolic dysfunction and were receiving an angiotensin-converting enzyme inhibitor and digoxin. None of the patients were receiving other antiarrhythmic agents, calcium channel antagonists, or β-blockers that could have influenced the frequency of ventricular arrhythmia. The study was designed with a sufficient sample size and monitoring period to have the power to detect an antiarrhythmic effect of magnesium. Serum magnesium was also substantially increased, approximately twofold, over the entire infusion period.

Our data suggest that augmentation of serum magnesium concentration may result in an antiarrhythmic effect, independent of repletion of body stores. No carryover effect of magnesium infusion on the frequency of ventricular arrhythmia was evident when the placebo day followed the magnesium day. Furthermore, ventricular ectopy began to increase within several hours after completion of the magnesium infusion. This gradual increase in ventricular ectopy during the washout day as serum magnesium concentration was decreasing also suggests that the antiarrhythmic effect of magnesium may be dose related. A dose-response relation may help to reconcile the results of Gottlieb et al[8] with our study. Our dosing regimen maintained a 100% increase in serum magnesium during monitoring compared with a 33% augmentation at the end of a 6-hour monitoring period in their study.

Two studies of oral magnesium supplementation have been reported. Gottlieb et al[13] reported no effect of 8 weeks of oral magnesium chloride supplementation (128 mg TID as tolerated) compared with placebo on ventricular arrhythmia in 40 patients with congestive heart failure. Serum magnesium concentrations were not significantly changed at the end of treatment. In contrast, Bashir et al[14] found that a substantially higher dose of magnesium chloride (15.78 mmol/d or ≈1500 mg/d) significantly decreased ventricular ectopic activity, including nonsustained ventricular tachycardia in 18 patients with congestive heart failure on long-term loop diuretic therapy. Serum magnesium concentration was increased by only 6%, but this was statistically significant. Serum potassium was also significantly increased, by 10%. These oral studies also support the concept that the antiarrhythmic effect of magnesium may be dose related.

Antiarrhythmic Mechanisms

Ventricular arrhythmias may arise in heart failure by many mechanisms, including enhanced automaticity and triggered activity as well as reentry. Several basic and clinical studies suggest that magnesium may not affect ventricular arrhythmia arising from reentrant mechanisms.[15-18] By contrast, several laboratory studies indicate that magnesium may suppress ventricular arrhythmias secondary to enhanced automaticity or triggered activity.[2,3,19] Clinically, torsades de pointes[20] and digitalis-induced ventricular arrhythmias[21] have been

successfully treated with parenteral magnesium, regardless of the serum magnesium concentration.

The precise role of magnesium depletion in the generation of ventricular arrhythmia in patients with heart failure remains unresolved. Hypomagnesemia has been reported in 19% to 37% of patients with heart failure.[22-24] However, evaluation of magnesium status in patients with heart failure is problematic. A normal range has not been well defined, and only 1% of magnesium is in the serum. There have been conflicting reports about the relation between serum magnesium concentration and frequency of ventricular arrhythmia and prognosis in patients with heart failure.[23,24] Only a few investigators have studied the relation between ventricular arrhythmia and myocardial magnesium concentration. Ralston et al[25,26] found that myocardial magnesium concentration did not correlate with serum, lymphocyte, or skeletal muscle concentrations in 23 patients with NYHA class II through IV congestive heart failure. There was no significant difference in myocardial magnesium concentration between the 9 patients with a history of sustained ventricular tachycardia and the 14 patients without a history of ventricular arrhythmia. In contrast, Frustaci et al[6] found that magnesium infusion significantly reduced ventricular arrhythmia only in the 4 patients in the study with reduced myocardial magnesium concentration.

Magnesium has a number of other physiological effects that could contribute to its antiarrhythmic effect. Magnesium has important effects on potassium homeostasis,[27] coronary tone,[28] ventricular afterload,[29] and catecholamine release.[30] Further investigation will be necessary to determine the contribution, if any, of these effects to the antiarrhythmic action of magnesium we observed.

Study Limitations

Certain limitations of the present study should be considered as the results are interpreted. Our clinical trial examined the acute antiarrhythmic effect of parenteral administration of magnesium chloride. Whether similar beneficial effects on ventricular arrhythmia would occur during chronic oral administration of magnesium independent of an effect on serum potassium is unknown. Our study also was not designed to assess the impact of magnesium administration on symptomatic ventricular arrhythmia or on the frequency of sudden death in patients with congestive heart failure. Additional studies of larger numbers of patients will be required to resolve these important issues.

Conclusions

Our study demonstrated that acute parenteral administration of magnesium chloride, in a dose that augments the serum concentration twofold, results in a significant reduction in ventricular arrhythmia in patients with symptomatic heart failure. Our results suggest that further investigation of the dose-response relation and the effect of chronic oral magnesium administration on ventricular arrhythmia in a larger population of patients with congestive heart failure is warranted.

Acknowledgments

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