Metabolic and Clinical Effects of Oral Magnesium Supplementation in Furosemide-Treated Patients with Severe Congestive Heart Failure

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Summary

Background: Magnesium depletion and hypomagnesemia are common among furosemide-treated patients with chronic congestive heart failure.

Hypothesis: This investigation evaluated clinical and metabolic effects of oral magnesium supplementation.

Methods: Ten patients with severe congestive heart failure maintained on high dose furosemide (≥ 80 mg/day) received a supplement of oral magnesium citrate 300 mg/daily for 30 days. Clinical parameters were followed, and peripheral blood mononuclear cell magnesium and zinc content, serum and urine magnesium, potassium, zinc, calcium, phosphorus, and creatinine were assessed.

Results: Peripheral blood mononuclear cell magnesium content and serum potassium rose significantly at the end of the study (2.09 ± 1.89 to 3.99 ± 2.26 $\mu\text{g}/\text{mg}$ cell protein, $p < 0.05$, and 4.17 ± 0.38 to 4.39 ± 0.27 mEq/l, $p < 0.05$, respectively), while the other parameters remained unchanged.

Conclusion: In some of these patients, oral magnesium supplementation is effective in achieving substantial increments in intracellular magnesium and serum potassium which, in turn, may have cardioprotective effects.

Key words: peripheral blood mononuclear cell magnesium; peripheral blood mononuclear cell zinc; serum magnesium, zinc, calcium, potassium; magnesium citrate; congestive heart failure

Introduction

Magnesium (Mg) is essential for many enzymatic reactions, for energy requiring metabolic processes, protein syn-

thesis, and for anaerobic phosphorylation.^{1,2} Since Mg is predominantly intracellular, normal serum concentrations may coexist with intracellular Mg depletion.¹⁻⁴ Magnesium deficiency is rare in healthy populations;² however, a few medical conditions may be associated with Mg depletion and hypomagnesemia, and chronic congestive heart failure (CHF) is one of them.^{1-3,5,6} The mechanisms involved may include reduced dietary content and intestinal absorption, increased urinary Mg excretion secondary to renal hypoperfusion, activation of the renin-angiotensin-aldosterone system, increased catecholamine secretion, and digitalis, when administered.^{1-3,6} Loop diuretics, especially furosemide, frequently given to such patients, may aggravate Mg depletion directly by promoting magnesuria and kaliuria and indirectly causing intravascular volume depletion and, therefore, additional activation of the renin-angiotensin-aldosterone axis and catecholamine secretion.^{1-3,6-10}

Since Mg depletion is frequent in furosemide-treated patients with CHF and serum Mg concentrations are not revealed in most of them, we undertook this study to evaluate the effects of oral Mg supplementation on relevant clinical data and on parameters of homeostasis of magnesium, zinc, calcium, phosphorus, sodium, potassium, and creatinine.

Severe CHF was the sole relevant pathophysiologic condition in these patients who have been constantly treated with high doses of furosemide.

Patients and Methods

Ten patients, 7 men and 3 women, age 40 to 76 years, with moderate to severe steady state CHF, New York Heart Association (NYHA) class III–IV, were enrolled. The clinical characteristics of the study group are presented in Table I. The patients received chronic furosemide treatment, 80–160 mg/day, for at least 3 months. Exclusion criteria were renal failure (serum creatinine > 1.5 mg/dl), low serum concentrations of magnesium, hypokalemia, diabetes mellitus, hypertension, chronic gastrointestinal disorders, liver cirrhosis, anemia (hematocrit $< 35\%$), acute intercurrent illnesses, or thyroid or parathyroid disorders.

Study Design

On the morning of the first day, patients were admitted for clinical evaluation and complete physical examination includ-

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Received: April 22, 1999

Accepted with revision: August 26, 1999

TABLE I Clinical characteristics of the study group

Patient No.	Age/gender	Cause of CHF	NYHA class / LVEF %	Furosemide daily dosage (mg)	Other drugs
1	58 M	Dilated cardiomyopathy	III/30	80	Captopril, amiodarone
2	70 F	Ischemic heart disease	IV/20	120	Propafenone, aspirin
3	74 M	Ischemic heart disease	III/35	80	Enalapril, amiodarone, amlodipine
4	46 M	Dilated cardiomyopathy	III/30	80	Captopril, digoxin
5	44 M	Ischemic heart disease	III/30	80	Captopril, aspirin
6	42 F	Mitral stenosis	III/40	80	Amiodarone, aspirin
7	55 M	Ischemic heart disease	III/38	80	Enalapril, amiodarone, aspirin
8	73 M	Ischemic heart disease	IV/30	120	Enalapril, amiodarone
9	76 F	Ischemic heart disease	IV/20	120	Benazepril, digoxin
10	58 M	Ischemic heart disease	IV/30	160	Captopril, digoxin, aspirin

Abbreviations: CHF = congestive heart failure, NYHA = New-York Heart Association LVEF = left ventricular ejection fraction.

ing determination of supine and standing blood pressure, heart rate, and electrocardiogram (ECG) tracing. Their dietary Mg and zinc (Zn) intakes were estimated and blood was drawn for evaluation of peripheral blood mononuclear cell (PBMC) content of Mg and Zn, and for serum concentrations of Mg, Zn, sodium, potassium, calcium, phosphorus, urea, and creatinine. Thereafter, 24-h urine was collected for determinations of Mg, Zn, sodium, potassium, calcium, phosphorus, and creatinine. On the following day, oral granules of Mg citrate (Diasporal, Protina GmbH, Ismaning, Germany) containing 300 mg Mg (12 mmol) was initiated and continued for 30 days. On Day 31, reevaluation of all the above mentioned parameters was performed. Patients were maintained on their usual diets, fluid intake, and drug regimens, including daily furosemide dosage, and thus served as their own controls.

Peripheral Blood Mononuclear Cell Magnesium and Zinc Determination

Peripheral blood mononuclear cells were isolated from 20 ml heparinized blood samples by gradient centrifugation on Ficoll Hypaque according to Boyum.¹¹ The isolated cells were washed, resuspended in 1 ml phosphate-buffered saline (PBS), counted, and stored at -70°C . Twenty-four hours before Mg and Zn determinations, the cell samples were digested in 1 ml concentrated NaOH. The Mg and Zn determinations were performed on atomic absorption spectrophotometer SpectrAA 800 (Varian-Tecktron, Australia). Total protein was determined by Bradford assay.¹² The results were calculated as μg of Mg or Zn per mg cell protein.

Serum Mg and Zn were also determined by atomic absorption spectrophotometry, serum and urine sodium and potassium by flame photometry, and phosphorus and creatinine by standard photocolometric procedures.

The study was approved by the local ethics committee and written informed consent was obtained from each patient.

Statistics

Statistical analysis was performed using paired, two-tailed Student's *t*-test.

Results

The mean daily dietary intake of Mg was 385 mg [recommended daily allowance (RDA) = 300 mg/day] and of Zn 17 mg (RDA = 15 mg). At the end of the study period, blood pressure, pulse rate, ECG, and CHF functional class remained unchanged. In preliminary studies from this laboratory, we had established the range of PBMC Mg in healthy controls. The values obtained were 2.0–3.8 $\mu\text{g}/\text{mg}$ protein. Figure 1 depicts PBMC Mg in our group of patients before and after Mg supplementation. Values rose from 2.09 ± 1.89 to 3.99 ± 2.26 [mean $\pm$ standard deviation (SD)] $\mu\text{g}/\text{mg}$ cell protein ($p < 0.05$). As can be seen, some of the patients initially had values of PBMC Mg below the lower limit of normal while the others were within normal range. Figure 2 illustrates data of serum potassium before and after Mg supplementation. Values rose from 4.17 ± 0.38 to 4.39 ± 0.27 (mean $\pm$ SD) mEq/l ($p < 0.05$). The PBMC Zn values did not change significantly during the study period [1.76 ± 0.82 to 1.25 ± 0.96 (mean $\pm$ SD) $\mu\text{g}/\text{mg}$ cell protein ($p = \text{NS}$)]. Table II depicts serum levels of Mg, Zn, calcium, phosphorus, sodium, urea, and creatinine. All values remained statistically unchanged. Urinary excretion rates of Mg, Zn, calcium, phosphorus, sodium, and potassium remained unchanged at the end of the study period.

FIG. 1 Peripheral blood mononuclear cell magnesium (PBMC Mg) values before and after Mg repletion in each patient. (A) Values before Mg supplementation, (B) values after Mg supplementation.

FIG. 2 Serum potassium concentrations before and after magnesium administration. (A) and (B) values as in Figure 1.

Discussion

Patients with CHF on diuretics are at risk of hypomagnesemia and, more frequently, of Mg depletion. Since Mg is mostly an intracellular cation, it may be substantially depleted from this compartment before hypomagnesemia is evident. According to various reports, prevalence of hypomagnesemia in patients with CHF was 7–37%, while that of Mg depletion was 43–55%.^{1,3,5–8,10,13–16} In the study of Dorup *et al.*,⁸ 42 of 76 patients (55%) receiving diuretic treatment were Mg depleted, but in only 5 was serum Mg below normal limits.

A number of physiologic mechanisms may be adversely affected by Mg depletion, especially within the context of severe CHF. These may include sinus node dysfunction, shortening of the relative refractory period, and extension of the absolute refractory period.¹ Resulting cardiac arrhythmias may include ventricular tachycardia or fibrillation, torsade de pointes, digitalis-induced arrhythmias, multifocal atrial tachycardia, paroxysmal atrial tachycardia, and atrial flutter or fibrillation.^{1,2,6} Mg deficiency may also produce hypokalemia via a number of mechanisms.^{1,3,6} The incidence of cardiac arrhythmias in patients with CHF is increased in the presence of hypokalemia and is substantially reduced by pushing serum potassium toward the upper limits of normal, via Mg administration.^{3,6} Furthermore, the combination of hypokalemia and digitalis therapy is especially dangerous, and the respective adverse effects may be eliminated by Mg repletion.^{1,3,6} Mg

depletion may also bring about impairment in myocardial metabolism and so further reduce contractility.⁶ This situation may be aggravated by other consequences of Mg deficiency, including increased catecholamine levels, coronary and systemic artery constriction, and enhanced platelet aggregation,^{1,5,6} which, in patients with severe CHF, may tip the delicate functional balance unfavorably and sometimes fatally.

Controversy exists as to the accessible tissue most representative of myocardial cells. In this respect, assessment of Mg in PBMC is one of the methods in use.^{17,18}

Theoretically, oral supplementation of Mg to patients with severe CHF maintained on high dose loop diuretics is sound and useful. In fact, in a recent thorough review on management of electrolyte abnormalities in CHF, it has been recommended that oral Mg be administered to such patients on an empiric basis.³ Only a handful of reports have been published attempting to evaluate the effect of prolonged oral Mg supplementation in such patients with respect to various relevant pathophysiologic manifestations and/or to intracellular Mg content.^{5,8,19–21} Dorup *et al.*⁸ selected a group of 36 patients with hypertension and/or CHF maintained on chronic diuretic therapy in whom intracellular muscle Mg and/or potassium content was reduced. Serum concentrations of these electrolytes were within normal limits. Twenty patients of this group were given oral Mg hydroxide 12.6 mmol daily for 2–12 weeks, while the remaining 16 received the same therapy for 26 weeks. In the first group, muscle Mg and potassium rose, but not to normal values, while in the second group of 16 patients these parameters became normal by the end of 26 weeks. Serum concentrations of Mg and potassium did not rise throughout the study period. In a recent report,¹⁹ the effect of oral Mg lactate, 10.4 mmol daily, supplemented for 3 months was evaluated in 12 patients with CHF in class II–III NYHA and in 12 age- and gender-matched healthy controls. Magnesium concentrations in serum, plasma, or red blood cells as well as urinary excretion rates of Mg did not change during the study period; however, some increase in urinary excretion of Mg was noted by the end of 3 months.

Bashir *et al.*⁵ studied various cardiovascular parameters in 21 patients with CHF in class II–IV NYHA secondary to coronary artery disease. Oral Mg chloride 15.8 mmol daily was supplemented for 6 weeks. Although initial serum Mg

TABLE II Serum magnesium, calcium, phosphorus, sodium, zinc, urea, and creatinine concentrations before and after Mg supplementation

Parameter	Baseline mean $\pm$ SD	After 30 days of Mg supplementation (mean $\pm$ SD)	p Value
Magnesium (mg/dl)	2.10 $\pm$ 0.28	2.02 $\pm$ 0.20	NS
Calcium (mg/dl)	9.51 $\pm$ 0.70	9.42 $\pm$ 0.80	NS
Phosphorus (mg/dl)	3.91 $\pm$ 0.70	3.93 $\pm$ 0.50	NS
Sodium (mEq/l)	137.73 $\pm$ 3.92	138.7 $\pm$ 2.79	NS
Zinc (mg/dl)	105.3 $\pm$ 17.6	109.9 $\pm$ 26.2	NS
Urea (mg/dl)	40.6 $\pm$ 10	37 $\pm$ 10	NS
Creatinine (mg/dl)	1.26 $\pm$ 0.2	1.28 $\pm$ 0.17	NS

Abbreviations: SD = standard deviation, NS = not significant.

and potassium levels were within normal limits, these parameters rose significantly following supplementation, but remained below the respective upper limits of normal. Urinary Mg excretion, however, rose significantly at the end of the study period. In another study²¹ comprising 40 patients with CHF, no effect of oral Mg administered for 8 weeks was observed on serum Mg concentrations or on the frequency of cardiac arrhythmias.

The principal target of the present investigation was to examine the effect of daily oral Mg citrate (12 mmol) administered for 30 days on intracellular Mg and Zn content in PBMC of furosemide-treated patients with severe CHF. In addition, we assessed the effect of Mg supplementation in these patients on serum concentrations and urinary excretion rates of Mg, potassium, sodium, calcium, phosphorus, Zn, and creatinine along with clinical follow-up. We deliberately excluded from the study patients with obvious Mg depletion manifested by hypomagnesemia and patients suffering from comorbid conditions that might have influenced Mg metabolism.

In studies from other countries it has been shown that a substantial percentage of such patients consumed diets with Mg content below RDA.¹⁹ By contrast, all our patients had dietary Mg content > 300 mg day, the recommended allowance.

Our results confirm previous observations indicating that serum concentration of Mg is an unreliable parameter of the state of its body stores. Some of our patients had low initial PBMC Mg (Fig. 1) while in others values were in the normal range. Also, while PBMC Mg rose minimally or did not change in some patients, others responded to Mg administration with a substantial rise in intracellular Mg. This variability may reflect differences in dietary habits and hence in Mg intake. It is also interesting that in some of our patients PBMC Mg rose following Mg administration to values considerably above upper limits of normal. It remains to be elucidated whether this finding represents an intermediate phase or a relatively steady state of PBMC Mg in response to a short-range Mg repletion.

It is reasonable to assume that oral magnesium citrate in the dosage we used produced, at least in some of the patients, repletion of Mg in myocardial cells as well as in other tissues.

As in previous reports, Mg supplementation in our patients resulted in a significant rise in serum potassium without its coadministration.^{1,6} This may be clinically significant, as it has been suggested that a rise in serum potassium in patients with CHF is associated with protection against cardiac arrhythmias.³

Magnesium and Zn coexist in a number of essential enzyme systems. Likewise, a physiologic interrelationship between calcium and Mg is known.^{1,6,9} It was therefore interesting to study the effect of Mg supplementation on homeostatic parameters of these two ions in a specific group of patients with long-term Mg depletion. Our results demonstrated no effect on serum concentrations or urinary excretion rates of these elements, nor on Zn PBMC content.

No clinical effect on cardiovascular parameters, such as the severity of CHF, blood pressure, or ECG findings was demonstrated following Mg repletion in our patients. It is possible that in order to assess such clinical effects, a larger group of patients and a longer period of Mg supplementation are required.

Acknowledgments

The authors thank Mrs. Ravit Bidlovski, Ofra Yehuda, and Einat Mokadi for their cooperation in preparation of the manuscript.

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