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Intravenous Magnesium Sulfate With and Without EDTA as a Magnesium Load Test—Is Magnesium Deficiency Widespread?

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Abstract Serum/plasma measurements do not reflect magnesium deficits in clinical situations, and magnesium load tests are used as a more accurate method to identify magnesium deficiency in a variety of disease states as well as in subclinical conditions. The objective of this study was to determine if people are indeed magnesium deficient or if the apparent magnesium deficiency is due to the composition of the infusate used in the load test. Magnesium load tests were performed on seven patients using three different Mg solution infusions—a Mg–EDTA (ethylene diamine tetraacetic acid)-nutrient cocktail used in EDTA chelation therapy containing several components including vitamins and minerals, and the same cocktail without EDTA and an infusion of an identical amount of magnesium in normal saline solution. There was no significant difference in the amount of magnesium retained in the 24 h after infusion among the three infusates. All infusates resulted in very high magnesium retention compared to previous published magnesium load studies. Magnesium deficiency may be widespread, and the relationship of Mg deficiency to related diseases requires further study.

Keywords Magnesium deficiency · EDTA · Metabolic syndrome · Magnesium status · Chelation therapy · Magnesium load test

Introduction

Mg is the fourth most abundant cation in the body and its intracellular concentration is exceeded only by potassium [1]. Mg activates more than 300 enzymes in the human body [2]. Deficiency of Mg has been linked to a variety of clinical disease states including

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hypertension, myocardial infarction, cardiac dysrhythmias, coronary spasm, and premature artherosclerosis [3]. In addition, patients with diabetes have been found to be at particular risk for Mg deficiency [4]. Conditions related to the deficiency of Mg may be linked to its functions as a cofactor for enzymes related to cell respiration, glycolysis, and ion transport (e.g., Na–K–ATPase). In fact, the central position of Mg in its role in energy storage, transfer, and utilization is mediated through its function in the formation of Mg–ATP, the ultimate form of stored energy in biological systems. In addition, Mg has functions related to protein synthesis through its action on nucleic acid polymerization, binding of ribosomes to RNA, and the synthesis and degradation of DNA [5]. Mg is also an integral player in calcium biology via its ability to maintain low resting concentrations of intracellular calcium ions. It competes with calcium for membrane-binding sites and, as such, has been described as a "calcium channel blocker" [6].

In degenerative diseases, Mg deficiency has been shown to be related to the generation of free radicals [7]. Mg deficiency has also been shown to negatively influence the generation of nitric oxide, and therefore, the impact of such deficiency may be responsible in part for the pathogenesis of endothelial dysfunction and its relationship to vascular disease, diabetes, and other diseases associated with aging [8].

In a previous study, we showed that, after the infusion of 686 mg of elemental Mg as Mg sulfate in an EDTA chelation "cocktail", 83% of the infused Mg was retained in the initial 24 h after infusion [9]. This degree of retention of Mg has generally been recognized to represent evidence of severe Mg deficiency. However, in that study, it was not clear if the apparent Mg retention was due to a true Mg deficiency or if the components of the chelation cocktail affected Mg retention. Guldager et al. [10] infused 3 g of EDTA in saline, without any Mg, into a group of peripheral vascular disease patients and collected 24 h urines of the patients and the controls. There was a highly significant decrease in the Mg in the 24-h urines of the EDTA patients vs. the controls, indicating that the EDTA increased Mg retention. The serum Mg in these patients did not increase, so it is probable that the EDTA caused Mg to enter intracellular compartments. This present study was designed to determine the effects of components of the Mg infusates on Mg retention.

Patients and Methods

The study was approved by the Clinic Human Studies Review Board, Wisconsin Dells, WI, USA. The study was explained to the subjects, and patients signed an informed consent before the study. Data are available to the participants upon request. Participants did not incur any medical fees as a result of their participation and were not paid for their participation.

At the onset of the study, patients were instructed in the accurate collection of 24-h urine specimens to avoid metal contamination. Twenty-four-hour urine samples were collected in 4-l sample containers (Fisher Scientific Co., Pittsburgh, PA, USA) 2 days before chelation therapy (days 1 and 2), the day of chelation therapy (day 3), and the following day (day 4). Control urine samples were collected on Monday and Tuesday and the post-infusion urine samples on Wednesday and Thursday. In phase 1 of the study, on Wednesday morning of the study week, an intravenous infusion of 2.25 g of EDTA mixed in sterile water with 5 g of sodium ascorbate, 2,500 IU of heparin, 3 ml of 2% procaine, 100 mg pyridoxine HCl, 4 meq KCl, 1 ml of 8.4% sodium bicarbonate, 1,000 μg hydroxycobalamin, 1 ml vitamin B complex, and 7 ml magnesium sulfate equivalent to 686 mg of elemental magnesium was

given in an arm vein over a 2.5-h period. During phase 2, patients received an identical infusion without any EDTA, and during phase 3, subjects received 686 mg elemental Mg in saline [9, 11]. Order of the phases was random. The procedures were 2 to 4 weeks apart. Magnesium contents of the urine samples were measured, and the Mg retention calculated using the following formula modified from Jeppesen [12]:

$$\%\text{Mg retention} = [\text{infused Mg} - (\text{urine Mg on day 3} - \text{average urine Mg on days 1 and 2})/\text{infused Mg}] \times 100.$$

Day 3 was the following day after the infusion; days 1 and 2 were baseline days immediately preceding the infusion. In addition, Mg content was also measured on day 4.

Since the time of our original chelation study, published and anecdotal data have revealed that the clinical efficacy of EDTA chelation therapy could be achieved with a smaller dose of EDTA with fewer potential side effects. Therefore, we reduced the dose of EDTA to 2.25 g.

Magnesium concentrations in the urine were determined using flame atomic absorption using a Perkin-Elmer 5000 flame atomic absorption spectrometer using standard techniques (Perkin-Elmer, Norwalk, CT, USA) and reference materials as described [13].

Statistics

Statistical analyses of the data were performed using two-way analysis of variance (SAS Institute, Cary, NC, USA, version 9.1). The main effects were the variable components of the infusions in the three phases. Values are mean ± SEM.

Results

Means for magnesium losses among the three phases were not statistically different (Table 1). Approximately 70% of the infused Mg was retained during the 24-h period after the infusion (day 3) in phase 1. Retention of Mg in phases 2 and 3 were similar. By day 4, the 24-h Mg excretion was not significantly different from the averages of days 1 and 2 in all three phases of the study.

Table 1 EDTA and Cocktail Effects on Magnesium Losses and Retention on the Day of the Infusions (Day 3) Minus Average of Days 1 and 2

Subject no.	Cocktail	Cocktail minus EDTA	Saline
1	263	285	345
2	245	156	50
3	203	116	116
4	193	144	198
5	182	210	276
6	133	80	96
7	205	289	268
Mean ± SEM	203±16	182±31	193±41
% Retention of infused magnesium	70.3±2.3	73.3±4.5	71.9±6.0

Values are mean ± SEM. All infusates contained 686 mg of Mg. Values for cocktail, cocktail minus EDTA and saline are urinary magnesium losses (mg) on day 3 minus the average for days 1 and 2. There were no significant differences among the three different infusates tested

Discussion

In this study, Mg retention was greater than 70% for all infusates. High Mg retention is probably not due to components of the infusate because infusion of Mg added to saline also led to significant Mg retention. The presence of EDTA in the cocktail did not increase the retention of Mg, and retention was still approximately 72% when Mg sulfate was added to saline alone and infused. Suboptimal Mg status appears to be present in essentially all of the subjects.

From analyzing the data on Mg load tests published over the last 30 years, it appears that there is great variation in the percentage of Mg that can be expected to be retained by normal patients vs. patients with various medical conditions. It is clear that serum/plasma Mg measurements do not necessarily reflect Mg deficits in clinical situations [14]. Thus, alternative measurements of Mg status were attempted, and ultimately, the Mg retention test was suggested as a more accurate method to identify Mg deficiency in a variety of disease states as well as in subclinical conditions. Other methods including bone Mg, muscle Mg, NMR spectroscopy, single ion channel analysis, leukocyte Mg, intraerythrocyte Mg, and Mg balance studies are more expensive and/or invasive but may not be more informative than the Mg load test. Even the intracellular Mg measurements have shown inconsistent correlation with serum levels and other tissue levels, as well as Mg load test data [15].

Table 2 summarizes the data from a number of intravenous load tests. In most of the studies, the demarcation in Mg retention between patients and controls is roughly 20%. In our present study, all groups of patients had Mg retention of at least 70%. The presence of EDTA at a dose of 2.25 g in the infused Mg preparation did not explain the high retention because, when EDTA was omitted from the infusate, Mg retention remained high. However, we cannot with certainty conclude that EDTA results in no greater Mg retention because we

Table 2 Intravenous Magnesium Load Tests in Patients and Controls

Reference	Country	Patients, Mg retention, %	Disease/condition	Controls, Mg retention, %
Thoren [36]	Sweden	>20	G.I. fluid loss	NC
Caddell et al. [37]	USA	51.0	Post partum women	NC
Bohmer and Mathiesen [38]	Sweden	77.0	Alcoholics	22.6
Ryzen et al. [39]	USA	51.0	Alcoholics	15.0
Fort and Lifshitz [40]	USA	58.7	IDDM children	NC
Jeppesen [12]	Denmark	42.0	MI	22.0
Sjogren et al. [18]	Sweden	62	Crohn's disease	25
Rasmussen et al. [41]	Denmark	34.0	IHD	4.7
Martin [42]	UK	62.0	Elderly	NC
Gullestad et al. [19]	Norway	16–38	Various diagnoses	3–4
Gullestad et al. [29]	Norway	No patients	No patients	6.3–10.3
Gullestad et al. [30]	Norway	28.0	Elderly	6.0
Ozono et al. [43]	Japan	41.9	Hypertension	31.8
Toral Revuelta et al. [44]	Spain	28.0	Malnourished elderly	Not given
Hebert et al. [45]	Canada	70.0	Intensive care patients	NC
Papzachariou et al. [46]	UK	59.8	Pancreatitus	22.0
Waters et al. [9]	USA	83.0	CAD/DM	NC

Citations are in chronological order

NC no controls

only used 2.25 g of EDTA in the infusions vs. the prior study of 3.0 g that resulted in an even greater retention of 83% [9]. The results of Guldagner et al. also suggest a causal Mg retention by 3 g of EDTA without any Mg added to the infusate [10].

Components of the infusate in the present study also appear to have little influence on magnesium retention because the phase 2 Mg retention cocktail without EDTA, but otherwise the same vitamins and minerals, was not different from the cocktail containing only Mg and saline. Patients in our earlier study [9] all had evidence of degenerative diseases and retained even greater amounts of Mg than the patients in our present study, and the dose of EDTA in that study was 3 g. Earlier studies of the therapeutic effects of EDTA used 5 g of EDTA per treatment, 5 days per week, and showed dramatic positive clinical effects, as well as objective evidence of benefits such as improved EKGs, reduction in the calcification of heart valves, and dissolution of metastatic calcification in the kidneys [16, 17]. Only further studies on the dose-dependent effects of EDTA as well as careful choice of "normal" vs. "diseased" patients can help resolve the issue of whether EDTA can influence calcium and magnesium dynamics in vivo in correlation with clinical and biochemical findings.

A number of studies using the Mg retention test have shown that patients with coronary heart disease are Mg deficient compared to the controls. Jeppesen reasoned that Greenlanders have a lower rate of myocardial infarction as a result of their high-serum Mg, low-serum calcium, and prolonged bleeding time (known to be induced by Mg administration) [12]. After administering 30 mmol of intravenous Mg over 12 h in patients with acute myocardial infarction, the infarction patients retained 42% of the infused Mg over the next 24 h compared to only 22% in the control group. He also obtained quadricep muscle biopsies, which revealed an increased Mg content in the control group vs. the acute myocardial infarction groups, but differences were not statistically significant.

Sjogren et al. [18] showed that patients with Crohn's disease had lower tissue concentrations of Mg compared with controls, and after IV infusions of 60 mmol Mg, the Crohn's patients had significantly higher Mg retention than the controls. Gullestad et al. [19] showed that Mg retention in the 24-h urine was 3–4% in a group of individuals without known predisposition for Mg deficiency after an infusion of 30 mmol Mg sulfate. This was significantly lower than that for 661 hospitalized patients with known predisposition to Mg deficiency (cardiovascular disease, alcoholism, etc., whose percent retention varied from 16–38%). Interestingly, the serum Mg was similar in the patient groups and the controls except for the alcoholics, hypertensives, and young healthy controls who had significantly reduced levels.

This later finding, particularly in reference to "young healthy" controls, brings up the probability that dietary intake of Mg is suboptimal and Western diets may be contributing to an increasing problem of Mg deficiency that may be a component of the growing epidemic of the metabolic syndrome and related diseases.

This possibility is supported by manuscripts of Resnick and associates spanning from 1984 to 2000 [20, 21]. Using Mg-specific selective ion electrode apparatus and ^{31}P-NMR spectroscopy, there was a significant correlation between intracellular ionized Mg as well as intracellular free Mg and the presence of non-insulin-dependent diabetes mellitus (NIDDM) [22]. Other studies reported increased intracellular calcium, decreased intracellular Mg, and decreased cytosolic pH with the presence of essential hypertension [23]. A 1992 study revealed that oral glucose loading, even in normal subjects, elevates free calcium and suppresses free Mg [24]. These data suggest, in the author's words, "an ionic hypothesis of cardiovascular and metabolic disease in which a generalized defect in cell ion handling is present in all tissues." This trend leads to, in different tissues, the features of the metabolic

syndrome, hypertension, obesity, insulin resistance, and left ventricular hypertrophy, the latter related both to hypertension and, independently, vasoconstriction and increased contractility caused by high cytosolic calcium and lowered free Mg [24]. Arterial stiffness, as measured by high-frequency ultrasound analysis, is known to correlate with hypertension and coronary heart disease [25]. Resnick et al. [26] showed, using direct magnetic resonance determination of aortic distensibility, that in essential hypertension, there are statistically significant correlations between fasting glucose, abdominal visceral fat, and in situ intracellular Mg.

In a rat model, Barbagallo et al. [27] showed that glucose, at increasing mM concentrations, caused a significant increase in cytosolic-free calcium in vascular smooth muscle. The authors suggest that these cellular effects of hyperglycemia may underlie the predisposition of patients with diabetes and patients with insulin resistance to hypertension and vascular diseases. The same group of investigators showed that aging itself is associated with the onset of the elevation of intracellular calcium and reduction of intracellular Mg that is indistinguishable from effects seen in essential hypertension and diabetes mellitus independent of age [28]. These changes may predispose older persons to cardiovascular and metabolic diseases.

Wells et al. [28] identified a previously unknown genetic defect in Mg metabolism in salt-sensitive essential hypertension. This Mg-binding defect results in the inhibition of Mg entry into the cell, thereby reducing Mg-dependent enzymes from operating efficiently. The resulting lowering of Mg ATP results in the inability to extrude sodium ions, and hypertension develops as a consequence of smooth muscle dysfunction. The authors also found the Mg-binding defect was found in every one of 24 patients with type 2 diabetes, suggesting that this defect in Mg transport may be a contributor to NIDDM. These findings are of possible importance when considered in conjunction with the studies described above [18, 21–24, 26, 27].

Gullestad et al. evaluated 88 healthy Norwegians ages 18 to 66 years using a 30-mmol intravenous Mg load test over 8 h and measured the 24-h urinary Mg excretion [29]. They found no correlation between Mg retention and serum Mg or basal urinary Mg. The Mg retention in these healthy patients was 10.6% to −4%. The lowest and highest second standard deviation values were −19.5% and 27.5%, respectively. This result agrees well with the above historical consensus.

Another study by Gullestad et al. [30] on “healthy free-living elderly Norwegians,” mean age 73±6, using the same load test of 30 mmol of Mg revealed a retention of 28% compared to 6% in younger controls. This finding also roughly agrees with the literature and is very interesting when considered in the light of the findings of Barbagallo et al. [27] that elderly people show intracellular calcium and Mg ion concentrations similar to those found in hypertensives and people with diabetes.

A study of Mg deficiency using the “short-term” Mg loading test by Rob et al. [31] revealed that even low dose (0.1 mmol Mg per kilogram of body weight) infused over 1 h was still able to differentiate Mg-adequate patients from renal transplant patients with known Mg deficiency. After treatment with 5 mmol of Mg per kilogram body weight for 4 months, a cohort of the latter group reduced their Mg retention from 47% on average to 16%. The placebo transplant patients continued to retain the infused Mg at 58% of the dose. The utility of this short-term, low-dose Mg retention test can clearly help identify Mg deficiency and help ensure that patients are adequately repleted.

Finally, we could ask which tissue cells are the benefactors of the increased Mg retention in the patients studied. Bone may be a tissue compartment that may have taken up the infused magnesium since two thirds of the total body Mg content is contained in skeletal

tissue [32]. This is especially likely because it is known that the Mg content of bone falls with age [33] and in the osteoporotic state [34]. If the diet is Mg deficient and the small intestine and kidney cannot effectively increase Mg absorption, bone releases the element into the extracellular fluid to maintain the serum level [35].

Conclusion

These data demonstrate that Mg deficiency may be widespread. The composition of the infusate used in magnesium load tests appears to have minimal influence on magnesium retention and does not explain the reported magnesium deficiency. The importance of dietary factors, especially Mg, in the causation of the present epidemic of metabolic syndrome and its associated complications calls for additional efforts to identify and treat patients at risk of magnesium deficiency.

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