

Magnesium Bioavailability from Magnesium Citrate and Magnesium Oxide

Jill S. Lindberg, MD, Margaret M. Zobitz, BS, John R. Poindexter, BS, and C. Y. C. Pak, MD, FACN

Center for Mineral Metabolism and Clinical Research, University of Texas, Southwestern Medical Center at Dallas

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This study compared magnesium oxide and magnesium citrate with respect to *in vitro* solubility and *in vivo* gastrointestinal absorbability. The solubility of 25 mmol magnesium citrate and magnesium oxide was examined *in vitro* in solutions containing varying amounts of hydrochloric acid (0–24.2 mEq) in 300 ml distilled water intended to mimic achlorhydric to peak acid secretory states. Magnesium oxide was virtually insoluble in water and only 43% soluble in simulated peak acid secretion (24.2 mEq hydrochloric acid/300 ml). Magnesium citrate had high solubility even in water (55%) and was substantially more soluble than magnesium oxide in all states of acid secretion. Reprecipitation of magnesium citrate and magnesium oxide did not occur when the filtrates from the solubility studies were titrated to pH 6 and 7 to stimulate pancreatic bicarbonate secretion. Approximately 65% of magnesium citrate was complexed as soluble magnesium citrate, whereas magnesium complexation was not present in the magnesium oxide system. Magnesium absorption from the two magnesium salts was measured *in vivo* in normal volunteers by assessing the rise in urinary magnesium following oral magnesium load. The increment in urinary magnesium following magnesium citrate load (25 mmol) was significantly higher than that obtained from magnesium oxide load (during 4 hours post-load, 0.22 vs 0.006 mg/mg creatinine, $p < 0.05$; during second 2 hours post-load, 0.035 vs 0.008 mg/mg creatinine, $p < 0.05$). Thus, magnesium citrate was more soluble and bioavailable than magnesium oxide.

INTRODUCTION

The occurrence of hypomagnesiuria in patients with nephrolithiasis appears to be higher than previously realized [1]. Our institution has found hypomagnesiuria (urinary magnesium less than 50 mg/day) to be present in 5.1% of 1116 patients who underwent ambulatory evaluation [1]. The cause of hypomagnesiuria appears to be dietary in origin [1], since intestinal magnesium has been shown to be normal in patients with nephrolithiasis [2].

There have been several reports [3–7] indicating that magnesium oxide or hydroxide may be useful in the management of recurrent calcium oxalate nephrolithiasis. It was believed that magnesium may act as an inhibitor of crystallization in the urine [8] and may bind oxalate in the gut [9].

However, previous studies have shown minimal rise in urinary magnesium [3–5] following oral administra-

tion of magnesium oxide or hydroxide, possibly due to its low solubility and absorbability from the intestinal tract. This finding may account for reports of marginal responsiveness and limited popularity of magnesium salts in the prevention of recurrent nephrolithiasis.

Recent experience with calcium citrate [10,11] suggests that magnesium supplementation as magnesium citrate might be more effective than magnesium oxide or hydroxide in increasing urinary magnesium because of the predicted higher solubility and bioavailability of the citrate salt. In this communication, we sought to test this hypothesis by directly determining solubility of magnesium salt in simulated gastric juice *in vitro*, and by measuring intestinal magnesium absorption from magnesium citrate and from magnesium oxide in human subjects.

It is shown that magnesium citrate has a greater aqueous solubility and provides more bioavailable magnesium than magnesium oxide.

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Dr. Lindberg is currently with the Department of Medicine, Letterman Army Medical Center, San Francisco, California.

Address reprint requests to Dr. C.Y.C. Pak, Center for Mineral Metabolism and Clinical Research, University of Texas, Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, Texas 75235.

MATERIAL AND METHODS

Magnesium Preparations

Magnesium preparations tested were magnesium citrate (Mission Pharmacal Co.) and magnesium oxide (USP). They were prepared into a tablet formulation of identical appearance and incipient (carboxymethyl cellulose) by the Mission Pharmacal Co., each tablet containing 121.6 mg of elemental magnesium.

Solubility of Magnesium Salts in Simulated Gastric Juice

The following assumptions were made in this experimental design [12]. (a) The amount of hydrochloric acid secreted into the gastric lumen is 2.4 mEq/hr during basal state and 24.2 mEq/hr during peak stimulation (with pentagastrin), figures derived in normal women at the Dallas Veterans Administration Hospital. (b) The dissolution of magnesium preparations in the gastric lumen following ingestion without food largely takes place in one hour. (c) Magnesium salt is taken orally with water without food (as was done in the oral magnesium loads described below). (d) The volume of gastric fluid is 300 ml including secreted juice and water ingested with the magnesium preparation. It was further assumed that gastric acid secretion is not further stimulated by the ingestion of a magnesium salt. This assumption is physiologically inaccurate, but a reasonable premise to take in an experiment designed to assess solubility of magnesium salt at several fixed levels of acid content.

Based on the above premises, simulated gastric fluids were represented by 300 ml distilled water without acid simulating *achlorhydria*, 0.72 mEq hydrochloric acid per 300 ml water for *low basal acid secretion*, 2.4 mEq hydrochloric acid per 300 ml water for *mean basal acid secretion*, 7.26 mEq hydrochloric acid per 300 ml water for *low peak acid secretion*, and 24.2 mEq hydrochloric acid per 300 ml water for *peak acid secretion*.

Dissolution was initiated by adding 25 mmol of either magnesium citrate or magnesium oxide (each containing 608 mg elemental magnesium) to the above solutions at 37°C. While the suspension was kept under constant stirring with a Teflon-coated magnetic bar, a 1-ml aliquot was removed at 5, 15, 30, and 60 minutes. The aliquot was filtered through a 0.22- μ m Millipore filter (Millipore Corp., Bedford MA). The filtrates were analyzed for magnesium, citrate, and pH. The total magnesium content in the filtrate at 60 minutes represented magnesium recovery or solubility expressed as percentage of total magnesium (25 mmol or 608 mg) in the magnesium salt that appears in solution.

Ionic Composition in Simulated Jejunal Fluid

It was assumed that the environment of the stomach, duodenum, and upper small bowel is "open" (aerobic) [12]. In this open system which allows an escape of carbon dioxide, neutralization of acid gastric effluent by sodium bicarbonate would be analogous ultimately to the neutralization by sodium hydroxide. It was further assumed that 100 ml duodenal and pancreatic secretions would be added to the gastric effluent, that 30 minutes would be required for the passage of fluid from the stomach to jejunum and that pancreatic enzymes and other electrolytes do not alter the physicochemical properties of magnesium salts.

To 300 ml of filtrate from each of the previous experiments (1-hr incubation with a magnesium preparation as described above) a solution of sodium hydroxide (0.05–1 N) or hydrochloric acid (0.05–1 N) was added to bring the pH of the solution to 6 or 7. The total volume was then brought to 400 ml by addition of 100 ml of distilled H₂O after 30 minutes of incubation at 37°C under constant stirring while pH was kept within 0.1 unit of designated pH by titration with sodium hydroxide or hydrochloric acid. Filtrate was obtained as before and analyzed for sodium, magnesium, citrate, and pH. This filtrate environment represents the simulated proximal jejunal fluid.

The reduction of total magnesium content in the filtrate following titration and 30 minutes of incubation reflected reprecipitation of magnesium salt. The anionic complexation of magnesium in the simulated jejunal fluid at pH 6 and 7 following reprecipitation was calculated by a computer program of Finlayson [13]. From the calculated values of pH, concentration of sodium, magnesium chloride, and citrate, and the known stability constants, this computer program calculated ionic strength and the amount of ionic magnesium and of soluble magnesium complexes.

Clinical Data

All subjects participated in the study after an informed written consent was obtained. Magnesium absorption was determined in 17 healthy normal volunteers (11 women and six men aged 22–40 years). None of the normal volunteers had renal stones, renal disease, bone disease, peptic ulcer, intestinal resection, inflammatory disease, or chronic diarrhea. Their endogenous creatinine clearance exceeded 70 ml/min. None of the subjects took any medication for 7 days preceding the study, or any drug other than the prescribed magnesium preparation during the study.

Study Protocol

All patients underwent three oral load tests, chosen in random order: magnesium citrate (25 mmol), magnesium oxide (25 mmol), or control load (distilled water only). Before each load, they adhered to a restricted diet with an approximate daily composition of 200 mg magnesium, 400 mg calcium, 800 mg phosphorus, and 100 mEq sodium for 3 days. The magnesium loads and control loads were patterned after the methods described before [14,15]. All subjects fasted from 6:00 p.m. before the oral magnesium administration except for 300 ml of distilled water at 8:00 p.m. and again at midnight. On the test day 600 ml of distilled water was drunk at 6:00 a.m. At 8:00 a.m. an oral load of magnesium with 300 ml of distilled water or 300 ml of distilled water alone was given. Urine was collected in 2-hr pools from 6:00 to 8:00 a.m., 8:00 to 10:00 a.m., and 10:00 a.m. to noon. All blood and urine samples were analyzed for magnesium and creatinine.

Calculation of Magnesium Load Response

In a previous study, magnesium absorption was indirectly estimated from the increment in urinary magnesium following the oral magnesium load from the urinary magnesium value during the 2 hours preceding the magnesium load [16]. This calculation is based on the assumption that the fasting magnesium excretion should be maintained at the same level throughout the period of observation following magnesium load. However, some subjects showed a continued decline in fasting magnesium excretion. Thus, this test of magnesium absorption was slightly modified from that described previously [16]. Accordingly, the difference in urinary magnesium following each magnesium load (in mg/mg creatinine) from that obtained during the corresponding time period of the control load was determined. Thus, magnesium absorption was represented by: (a) increment in urinary magnesium during 4 hours post-load, or the difference in urinary magnesium following magnesium load (8:00 a.m.–noon) from urinary magnesium following the control load (8:00 a.m.–noon); (b) increment in urinary magnesium during the first 2 hours post-load, or the difference in urinary magnesium following magnesium load (8:00–10:00 a.m.) from urinary magnesium post-control load (8:00–10:00 a.m.); and (c) increment in urinary magnesium during the second 2 hours post-load, or the difference in urinary magnesium following magnesium load (10:00 a.m.–noon) from that post-control load (10:00 a.m.–noon).

In a previous publication [5] it was shown that urinary magnesium reaches a peak either during the first or second 2 hours after an oral magnesium load, and

declines thereafter. Thus, in 13 normal subjects given an oral load of 25 mmol of magnesium, the urinary magnesium rose significantly from the fasting value of 5.2 ± 2.5 SD mg/2 hr, to 9.4 ± 3.7 mg ($p < 0.025$) during the first 2 hours and to 11.6 ± 5.0 mg ($p < 0.0005$) during the second 2 hours, but it declined to 6.1 ± 2.4 mg during the fifth and sixth hours after the magnesium load (not significantly different from the fasting value). For this reason, we have omitted urine collection during the third 2 hours following oral magnesium load.

Analytical and Statistical Methods

Magnesium was determined by atomic absorption spectrophotometry, citrate by an enzymatic method using a kit from Boehringer–Mannheim Biochemicals (Indianapolis, IN), sodium by flame photometry, and pH was measured using a Radiometer (Copenhagen, Denmark) pH meter. All in vitro solubility experiments were performed in triplicate. Results of replicate experiments agreed to within 5% of each other. The Kruskal–Wallis test was used to compare solubility results (ionic, complexes, and total magnesium) from magnesium citrate from those of magnesium oxide. Statistical analysis for oral magnesium loads was accomplished by paired sample t test.

RESULTS

In Vitro Solubility of Magnesium Salts

In water (without added hydrochloric acid), magnesium citrate underwent partial dissolution with substantial magnesium recovery occurring in the first 5 minutes and plateau being reached by 30 minutes at 55% dissolution (Fig. 1). Magnesium oxide was virtually insoluble with 0.8% magnesium recovery.

The solubility of magnesium salts in different solutions at steady state (after 60 minutes of incubation) is summarized in Figure 2. The dissolution of magnesium oxide was proportional to the amount of hydrochloric acid in solution. In the presence of 24.2 mEq hydrochloric acid, the amount of magnesium oxide dissolved was 43% (261 mg magnesium), whereas it was 9% (or 55 mg magnesium) when 7.26 mEq hydrochloric acid was present.

The solubility of magnesium citrate was less pH dependent than magnesium oxide. The solubility of magnesium citrate essentially peaked at 0.72 mEq hydrochloric acid, with 87% of magnesium recovered (Fig. 2). The solubility of magnesium citrate was significantly greater than that of magnesium oxide in all solutions. Thus, at simulated peak acid secretion (24.2 mEq hydrochloric acid/300 ml), there was 86%

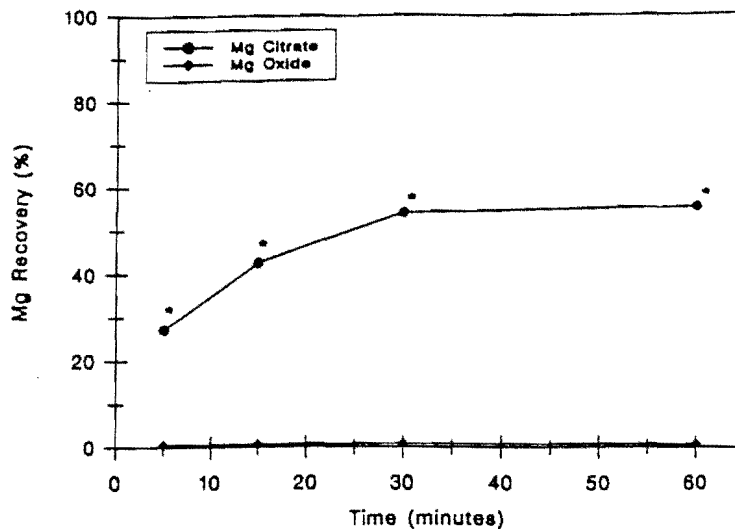


Fig. 1. Solubility of magnesium citrate and magnesium oxide in water (without hydrochloric acid) over 60 minutes. Magnesium recovery indicates percentage of magnesium salt dissolved in solution. An asterisk indicates a significant difference ($p < 0.05$) between the two magnesium salts during the same time period.

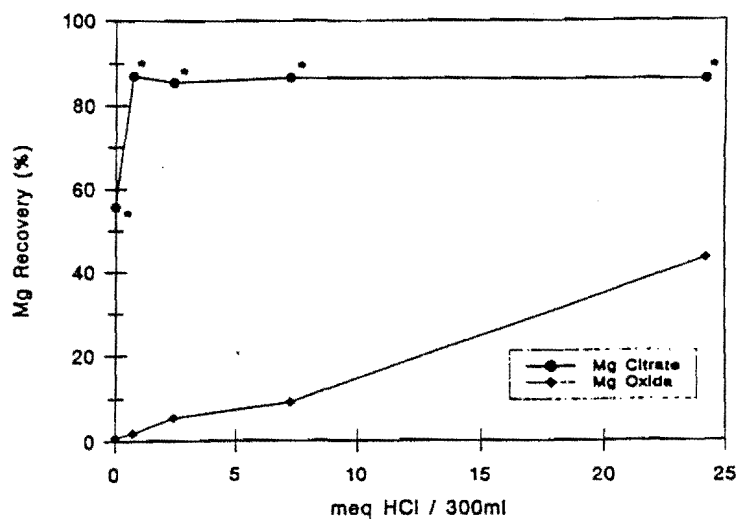


Fig. 2. Solubility of magnesium salts (after 60 minutes of incubation) in solutions containing varying amounts of hydrochloric acid. An asterisk indicates a significant difference ($p < 0.05$) between the two magnesium salts at the same hydrochloric acid concentration.

recoverability of magnesium from magnesium citrate as opposed to only 43% for magnesium oxide.

The pH of the solution at steady state after incubation with a magnesium salt is demonstrated in Figure 3. In the presence of magnesium oxide, pH decreased from 4.6 to 3.5 as the hydrochloric acid content rose. When magnesium citrate was added, the pH was higher to

begin with, but it also declined (from 10.6 to 9.8) as more hydrochloric acid was present.

Reprecipitation Upon Alkali Titration

When filtrates following solubility experiments were titrated to pH 6 or 7, there was no decline in the concentration of soluble magnesium in the filtrate. Thus,

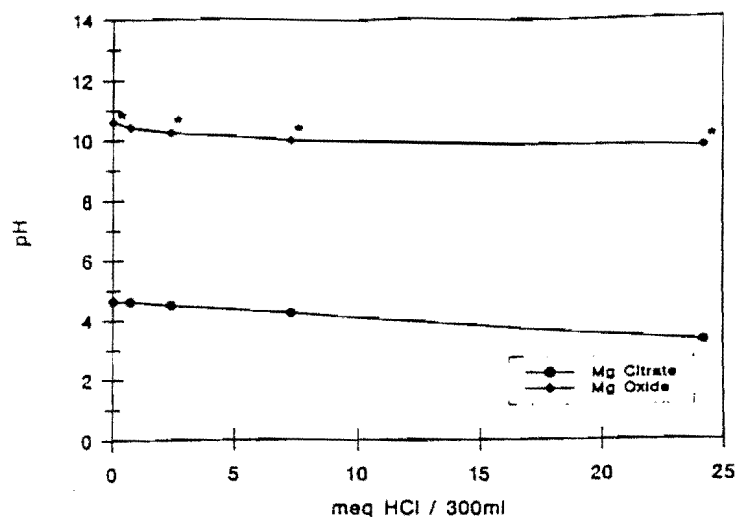


Fig. 3. "Composite" pH data obtained after 60 minutes of incubation. An asterisk means the same as in Fig. 2.

reprecipitation of neither magnesium oxide nor magnesium citrate occurred from each solution when pH was titrated to 6 or 7.

Anionic Complexation

In magnesium citrate experiments, a considerable amount of soluble magnesium citrate complexes formed (principally as MgCir). Thus, at both pH 6 and 7, approximately 36% of total magnesium in solution was present as ionic magnesium, the remaining 65% existing as soluble complexes (Table 1). The amount of ionic magnesium present rose from 4.84 mmol in distilled water to 7.43 mmol in the presence of 0.72 mEq hydrochloric acid (Table 1). Thereafter, it plateaued. A similar rise and plateau were observed for magnesium citrate complexes. For magnesium oxide, the formation of soluble magnesium complex did not occur. Thus, ionic magnesium content was equivalent to total magnesium content. Because of the limited solubility of magnesium oxide, the amount of ionic magnesium provided by magnesium oxide was significantly less than that obtained from magnesium citrate in solutions containing 0–7.26 mEq hydrochloric acid/300 ml. However, at simulated peak acid secretion (24.2 mEq hydrochloric acid/300 ml), magnesium oxide provided a slightly higher concentration of ionic magnesium than of magnesium citrate.

Magnesium Load Response

The results of magnesium load study are shown in Table 2. Increment in urinary magnesium from control load was significantly higher during 4 hours following

magnesium citrate load than following magnesium oxide load (0.220 ± 0.004 vs 0.006 ± 0.004 mg/mg creatinine, $p < 0.05$).

The differences in urinary magnesium for the time periods of 8:00–10:00 a.m. and 10:00 a.m.–noon from the corresponding time periods after control loads are shown in Table 1 and Figure 4. During the first 2 hours post-load (8:00–10:00 a.m.), the mean value for the increment in urinary magnesium for magnesium citrate was higher than that for magnesium oxide; however, the difference was not significant. However, during the second 2 hours post-load (10:00 a.m.–noon), the increment in urinary magnesium following magnesium citrate load was significantly greater than that obtained with magnesium oxide.

Following ingestion of magnesium citrate, the increment in serum magnesium between 8:00 a.m. and noon was significantly higher than with ingestion of magnesium oxide (0.126 ± 0.270 mEq/L vs 0.028 ± 0.014 mEq/L, $p < 0.05$).

DISCUSSION

This study utilized both an *in vitro* and an *in vivo* system to assess the bioavailability of magnesium citrate versus magnesium oxide.

The *in vitro* model system revealed that the solubility of magnesium oxide was pH dependent with greater solubility in solutions of higher hydrochloric acid content with negligible solubility in water. Magnesium citrate had a modest solubility even in water (55%) and achieved maximum solubility at simulated mean basal

Table 1. Anionic Complexation

	Mg citrate, n = 3		Mg oxide, n = 3	
	pH 6	pH 7	pH 6	pH 7
0 mEq HCl/300 ml				
Ionic Mg (mmol/300 ml)	4.84*	4.69*	0.21	0.21
Mg complex (mmol/300 ml)	9.16*	9.10*	0.00	0.00
Total Mg (mmol/300 ml)	14.00*	13.79*	0.21	0.21
0.72 mEq HCl/300 ml				
Ionic Mg (mmol/300 ml)	7.43*	7.41*	0.48	0.50
Mg complex (mmol/300 ml)	14.32*	13.92*	0.00	0.00
Total Mg (mmol/300 ml)	21.75*	21.33*	0.48	0.50
2.4 mEq HCl/300 ml				
Ionic Mg (mmol/300 ml)	7.08*	6.94*	1.18	1.23
Mg complex (mmol/300 ml)	13.48*	13.47*	0.00	0.00
Total Mg (mmol/300 ml)	20.55*	20.41*	1.18	1.23
7.26 mEq HCl/300 ml				
Ionic Mg (mmol/300 ml)	7.47*	7.24*	3.00	3.02
Mg complex (mmol/300 ml)	14.18*	14.10*	0.00	0.00
Total Mg (mmol/300 ml)	21.65*	21.34*	3.00	3.02
24.2 mEq HCl/300 ml				
Ionic Mg (mmol/300 ml)	7.40*	7.25*	11.06	10.97
Mg complex (mmol/300 ml)	13.88*	13.98*	0.00	0.00
Total Mg (mmol/300 ml)	21.28*	21.23*	11.06	10.97

The amount of magnesium (as ionic, complexed, or total) represents that remaining in solution after solubility and "reprecipitation" from dissolution of 25 mmol of each magnesium salt per 300 ml solution. Significant difference from the magnesium oxide system is represented by an asterisk ($p < 0.05$). Total Mg was directly analyzed, whereas ionic and Mg complex were calculated by a computer program [14].

acid secretion without further dissolution at higher acid concentration.

Magnesium citrate was at least nine times more soluble than magnesium oxide except in simulated achlorhydric to low peak acid secretory states (0–7.26 mEq hydrochloric acid/300 ml). At simulated peak acid secretion (24.2 mEq hydrochloric acid/300 ml) magnesium citrate was twice again as soluble. Magnesium recovery from magnesium oxide at peak acid secretion was 43%, which was still less than the 55% magnesium recovery achieved from magnesium citrate in water.

No reprecipitation of magnesium oxide or magnesium citrate occurred when the ambient fluid obtained following dissolution of magnesium citrate was titrated to pH 6 and 7 to mimic pancreatic bicarbonate solution. Following magnesium citrate dissolution, a substantial amount of magnesium was complexed to citrate, thereby reducing ionic magnesium content. No soluble complexes

formed following magnesium oxide dissolution.

Overall, our results showed superior solubility of magnesium citrate versus magnesium oxide in various simulated states of gastric acid secretion. No solubilized magnesium was lost by reprecipitation of magnesium salt following simulated pancreatic bicarbonate secretion. However, substantial magnesium citrate complexation occurred following magnesium citrate dissolution. This complexation could theoretically attenuate the intestinal absorbability of magnesium from magnesium citrate. Our preliminary study suggests that ionic calcium is better absorbed than the calcium citrate complex.

Our *in vivo* study of magnesium bioavailability supported our *in vitro* findings. We found a substantially greater magnesium absorption from magnesium citrate as compared to magnesium oxide. The results suggest that the degree of gastric acid secretion in participating subjects was equivalent to or less than low peak acid

Table 2. Increment in Urinary Magnesium Following Oral Load of Magnesium Citrate or Magnesium Oxide

	Mg citrate, n = 17	Mg oxide, n = 17
Basal urinary magnesium excretion, 6:00–8:00 a.m.	0.0352 ± 0.0042	0.0326 ± 0.0036
Increment in urinary Mg (from control), mg/mg creatinine		
8:00 a.m.–12:00 noon	0.022 ± 0.004*	0.006 ± 0.004
8:00–10:00 a.m.	0.001 ± 0.003	0.005 ± 0.005
10:00 a.m.–12:00 noon	0.035 ± 0.005*	0.008 ± 0.004

Values are presented as mean ± standard error. Significant difference between the two magnesium phases is denoted by an asterisk ($p < 0.05$).

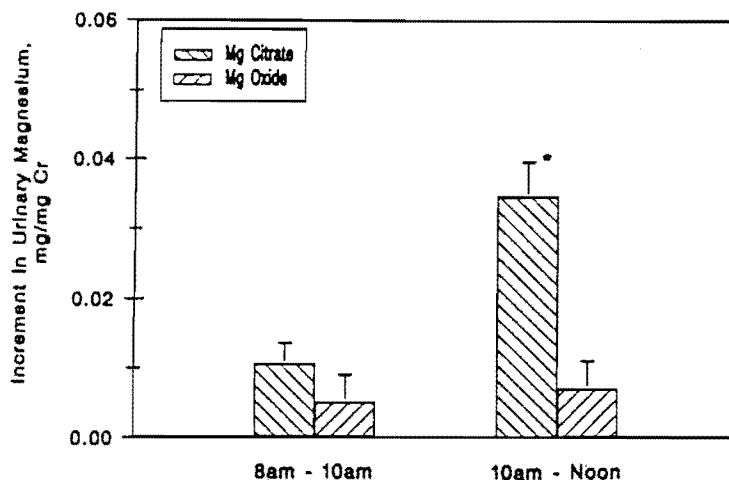


Fig. 4. Comparison of urinary magnesium at first (8:00–10:00 a.m.) and second half (10:00 a.m.–12:00 noon) post-magnesium load calculated as an increment from urinary magnesium obtained at the corresponding time period following control load. Significant difference between magnesium citrate vs magnesium oxide is shown by an asterisk ($p < 0.05$).

secretion, in which ionic magnesium content was shown to be greater for magnesium citrate than for magnesium oxide. Alternatively, some magnesium citrate complex could have undergone intestinal absorption.

Clinically, this study has important therapeutic implications in nephrolithiasis. The limited bioavailability of magnesium oxide could explain marginal magnesiuic action and efficacy of this drug in patients with calcium nephrolithiasis [2–5]. The greater bioavailability of magnesium citrate should make it more effective in raising urinary magnesium, as well as increasing urinary citrate, an important inhibitor of calcium oxalate crystallization. Thus, magnesium citrate may be an excellent choice of medical therapy in stone-forming patients with hypo-

magnesiuria and hypocitraturia.

Another population in which magnesium citrate may be utilized is the elderly population receiving diuretic therapy. In previous studies magnesium deficiency has been found in this population [17]. Low urinary citrate and low urinary pH have also been associated with diuretic therapy [18].

Long-term clinical trials are needed to evaluate the utility of magnesium citrate in these populations.

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