Oral Magnesium Supplementation in Patients with Essential Hypertension

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To elucidate the effects of magnesium on high blood pressure, a 4-week study of oral magnesium supplementation (MgO 1 g/day) was conducted in 21 outpatients with uncomplicated essential hypertension. During the study, blood pressure and intraerythrocyte sodium concentration decreased significantly, and the erythrocyte ouabain-sensitive ^{22}Na efflux rate constant (K_{oa}) and intraerythrocyte magnesium concentration both increased. Serum triglyceride and free fatty acid concentrations were reduced. Furthermore, the elevation in K_{oa} significantly and positively correlated with both the increase in intraerythrocyte magnesium concentration and the decrease in mean blood pressure. There was a significant inverse correlation between the prestudy K_{oa} and the decrease in mean blood pressure. In addition, when patients were divided according to their overall decrease in mean blood pressure, the prestudy intraerythrocyte sodium concentration was significantly higher in patients with a mean blood pressure decrease of more than 7 mm Hg than that of patients whose mean blood pressure decrease was less than 7 mm Hg. These results suggest that oral magnesium supplementation may lower blood pressure through the activation of a cell membrane sodium pump and may reduce serum lipid concentration. It also suggests that the lower the prestudy K_{oa} or the higher the prestudy intraerythrocyte sodium concentration, the more effective the oral magnesium treatment is in lowering blood pressure. Therefore, we concluded that appropriate oral magnesium intake might be effective as a nonpharmacological treatment for essential hypertension. (*Hypertension* 1989;13:227–232)

Epidemiological surveys, clinical investigations, and experimental studies have currently reported[1-36] that magnesium may play an important role in the pathogenesis of hypertension and atherogenesis. A recently proposed hypothesis[37] suggests that an impairment of the cell membrane sodium transport system is responsible for the increased total peripheral resistance found in essential hypertension. Magnesium controls cell membrane sodium pump activity, which in turn plays a major role in sodium-potassium transport across cell membranes, thereby affecting vascular tone and reactivity and blood pressure by influencing a Na^+-Ca^{2+} exchange mechanism.[1-8] Furthermore, the atherogenic plasma lipid profile has been improved by magnesium supplementation.[9,10]

Thus, this study was designed to evaluate the effects of oral magnesium supplementation on blood pressure and on serum lipid profiles in patients with essential hypertension and to elucidate the role of magnesium in controlling the cell membrane sodium pump.

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Patients and Methods

Twenty-one male outpatients with uncomplicated mild to moderate essential hypertension and normal renal function, ages 30–56 years (44±7 years, mean±SD), were enrolled in this study. Patients were given oral magnesium supplementation in the form of magnesium oxide (MgO) 1 g/day (600 mg Mg daily) for 4 weeks and received no other medication for at least 1 month.

The following measurements were performed for each patient before entry into the study and at the end of the study. A 24-hour urine sample was collected and analyzed for urinary volume and sodium, potassium, calcium, magnesium, and phosphorus excretion. Supine blood pressure and heart rate were measured after the patient had been resting supine for at least 30 minutes. Venous samples were obtained from the patients at 9 AM after an overnight fast to measure serum sodium, potassium, calcium, magnesium, phosphorus, total cholesterol, triglyceride, and free fatty acid concentrations; plasma renin activity; plasma aldosterone concentration; intraerythrocyte sodium (RBC Na), potassium (RBC K), and magnesium (RBC Mg)

TABLE 1. Twenty-four-Hour Urinary Volume and Electrolyte Excretion Before and After Oral Magnesium Treatment

Study	UV (ml/day)	U-Mg (meq/day)	U-Na (meq/day)	U-K (meq/day)	U-Ca (meq/day)	U-P (mg/day)
Pre	1418±359	7.411±3.587*	203.4±77.7	39.5±19.6	10.07±4.89	783.6±315.5
Post	1432±502	10.65±5.045	207.6±94.6	44.7±21.1	9.89±5.91	706.7±256.3

Values are mean±SD. UV, urinary volume; U-Mg, urinary magnesium; U-Na, urinary sodium; U-K, urinary potassium; U-Ca, urinary calcium; U-P, urinary phosphorus.
*$p<0.01$ for prestudy vs. poststudy values.

concentrations; and erythrocyte sodium pump activity. Serum and urinary sodium, potassium, calcium, magnesium, and phosphorus concentrations were measured with an autoanalyzer. Intraerythrocyte electrolyte concentrations were determined by the method of Kaya et al[38] with slight modifications. RBC Na and RBC K were measured with a flame photometer, and RBC Mg was determined with an atomic absorption spectrophotometer. Erythrocyte sodium pump activity was calculated as the erythrocyte ouabain-sensitive ^{22}Na efflux rate constant (K_{os}) by the method of Walter et al[39] with slight modifications. We have described both of these techniques in a previous report.[40] Plasma renin activity and plasma aldosterone concentration were measured by radioimmunoassay with kits. Serum total cholesterol,[41] triglyceride,[42] and free fatty acid[43] concentrations were estimated by using an enzymatic method. Within 10 pairs of the sample obtained on different days, the coefficients of variation for measurements of serum magnesium concentration, RBC Mg, and RBC Na, which showed a small but significant change during the study, were 0.8%, 0.7%, and 1.0%, respectively. The coefficient of variation for K_{os} in six pairs of the same sample was 2.1%.

After the oral magnesium treatment, a placebo was given for an additional 4 weeks. Supine blood pressure and heart rate were measured at the end of the placebo treatment.

Differences between the data were tested by Student's paired t test. Correlation of the data was determined with a least-squares fit linear regression analysis. Values were expressed as mean±SD. A $p<0.05$ was considered statistically significant.

Results

During the 4 weeks of magnesium supplementation, mean blood pressure decreased from 111±6 to 102±6 mm Hg ($p<0.001$), and during the subsequent 4-week placebo treatment, it increased to 108±5 mm Hg ($p<0.001$). Heart rate was unchanged throughout the study. As presented in Table 1, the 24-hour urinary magnesium excretion was significantly increased during oral magnesium treatment, while no change occurred in the 24-hour urinary volume or sodium, potassium, calcium, or phosphorus excretion. Table 2 shows the data for serum electrolyte concentrations, plasma renin activity, and plasma aldosterone concentration. The changes in plasma renin activity or plasma aldosterone concentration during the study were not significant. There was a significant increase in serum magnesium concentration during the study. Serum sodium, potassium, calcium, and phosphorus concentrations were unchanged. Table 3 demonstrates the measurements of RBC Na, RBC K, RBC Mg, K_{os}, and serum lipid concentrations. Oral magnesium supplementation was associated with a decrease in RBC Na, an increase in RBC Mg, and an elevation in K_{os}. During oral magnesium treatment, serum triglyceride and free fatty acid concentrations were significantly reduced. Serum total cholesterol concentration also decreased, but not significantly. A change in body weight in patients was not found during the study.

Before the study, RBC Mg correlated positively with K_{os} ($r=0.53$, $p<0.02$) and inversely with RBC Na ($r=-0.48$, $p<0.05$). There were also correlations between RBC Na and blood pressure ($r=0.48$, $p<0.05$) and between RBC Na and K_{os} ($r=-0.57$, $p<0.01$). During the 4 weeks of oral magnesium treatment, as presented in Figures 1 and 2, the decrease in mean blood pressure correlated positively with the elevation in K_{os}, and the elevation in K_{os} correlated positively with the increase in RBC Mg. Figure 3 demonstrates an inverse correlation between the prestudy K_{os} and the decrease in mean blood pressure during the study. When patients were divided into two groups according to their decrease in mean blood pressure during oral magnesium supplementation, the prestudy RBC Na was

TABLE 2. Serum Electrolyte Concentrations, Plasma Renin Activity, and Plasma Aldosterone Concentration Before and After Oral Magnesium Treatment

Study	S-Mg (meq/l)	S-Na (meq/l)	S-K (meq/l)	S-Ca (meq/l)	S-P (mg/dl)	PRA (ng/ml/h)	PAC (pg/ml)
Pre	2.01±0.25*	140.9±2.09	4.05±0.33	4.53±0.21	3.29±0.39	1.42±0.89	86.0±35.6
Post	2.09±0.28	139.9±1.77	4.16±0.42	4.45±0.19	3.29±0.37	1.56±0.89	97.4±38.9

Values are mean±SD. S-Mg, serum magnesium; S-Na, serum sodium; S-K, serum potassium; S-Ca, serum calcium; S-P, serum phosphorus; PRA, plasma renin activity; PAC, plasma aldosterone concentration.
*$p<0.01$ for prestudy vs. poststudy values.

TABLE 3. Intraerythrocyte Magnesium, Sodium, and Potassium Concentrations; Erythrocyte Ouabain-Sensitive ^{22}Na Efflux Rate Constant; Serum Triglyceride, Free Fatty Acid, and Total Cholesterol Concentrations Before and After Oral Magnesium Treatment

Study	RBC Mg (meq/l · cells)	RBC Na (meq/l · cells)	RBC K (meq/l · cells)	K_{os} (/h)	TG (mg/dl)	FFA (μeq/l)	Chol (mg/dl)
Pre	5.232±0.408*	13.35±1.13*	114.3±4.20	0.332±0.075†	102±40‡	0.66±0.13‡	195±36
Post	5.315±0.373	12.81±1.03	115.8±3.51	0.366±0.057	82±34	0.54±0.17	184±32

Values are mean±SD. RBC Mg, intraerythrocyte magnesium concentration; RBC Na, intraerythrocyte sodium concentration; RBC K, intraerythrocyte potassium concentration; K_{os}, erythrocyte ouabain-sensitive ^{22}Na efflux rate constant; TG, serum triglyceride concentration; FFA, free fatty acid concentration; Chol, total cholesterol concentration.
*$p<0.01$; †$p<0.001$, ‡$p<0.05$ for prestudy vs. poststudy values.

higher in patients with a mean blood pressure decrease of more than 7 mm Hg than in patients whose mean blood pressure decrease was less than 7 mm Hg, as shown in Figure 4.

Discussion

These results indicate that, in patients with essential hypertension, oral magnesium supplementation in the form of MgO 1 g/day (600 mg Mg daily) produced a significant reduction in blood pressure and a decrease in serum lipid concentrations. The form and dose appeared to be well tolerated as there were no complications of diarrhea or other side effects.

According to epidemiological data, an inverse relation between RBC Mg and blood pressure[11] and an inverse relation between urinary magnesium excretion and blood pressure[12] were found. Resnick et al[13] demonstrated that plasma renin activity showed a negative correlation with serum magnesium concentration in essential hypertension and that intraerythrocyte free Mg^{2+} was correlated negatively with blood pressure and positively with serum total magnesium concentration.[14]

In the present study, correlations such as those[11–13] mentioned above could not be found between serum magnesium concentration and plasma renin activity, or between blood pressure and either RBC Mg or urinary magnesium excretion. Because we had insufficient numbers of subjects within differing renin values, further investigation would be needed to clarify the relation between plasma renin activity and magnesium. Furthermore, although we also thought that intracellular free ionized magnesium was probably very important for control of vascular tone and blood pressure, we could not determine intraerythrocyte ionized magnesium concentration. However, as erythrocyte sodium pump activity increased linearly with not only intracellular ionized magnesium but also intracellular total magnesium concentration below and at physiological levels,[1] intracellular total magnesium concentration comprises, and may indirectly represent, intracellular ionized magnesium concentration.

The hypothesis[44] for explaining the role of a circulating sodium pump inhibitor in the pathogenesis of essential hypertension has been proposed. In our study, the efficacy of magnesium therapy in

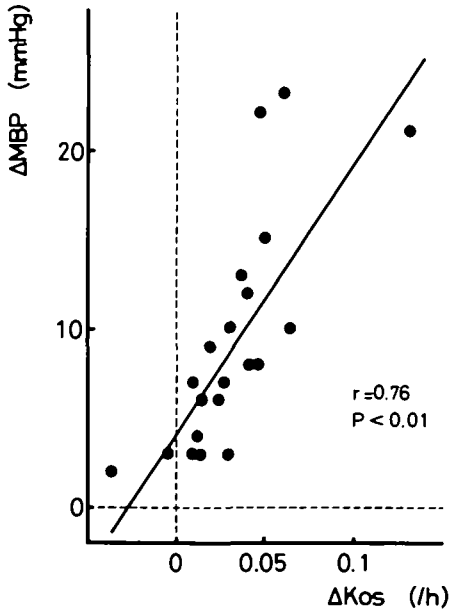

FIGURE 1. *Relation between decrease in mean blood pressure (ΔMBP) and elevation in erythrocyte ouabain-sensitive ^{22}Na efflux rate constant (ΔKos) during oral magnesium treatment.*

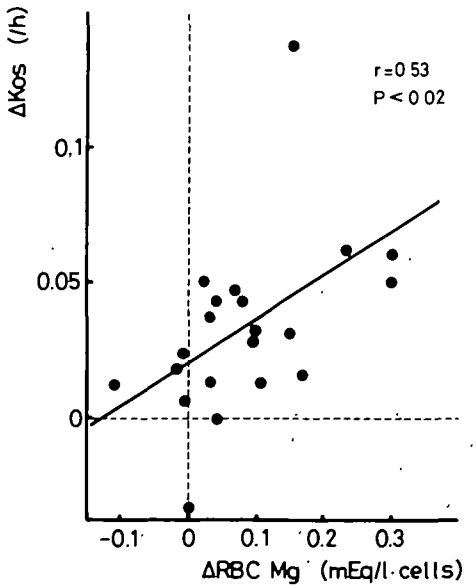

FIGURE 2. *Relation between elevation in erythrocyte ouabain-sensitive ^{22}Na efflux rate constant (ΔKos) and increase in intraerythrocyte magnesium concentration (ΔRBC Mg) during oral magnesium treatment.*

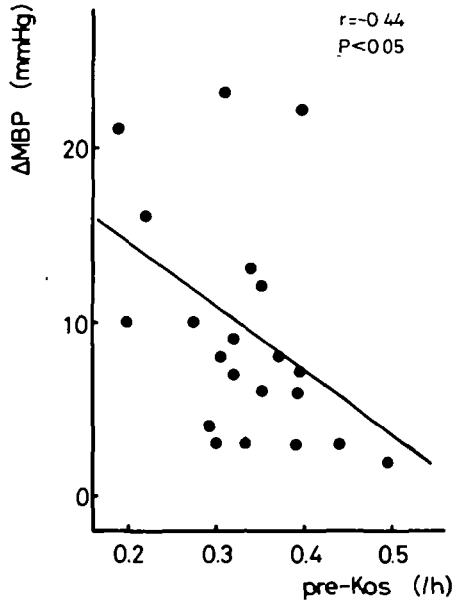

FIGURE 3. *Relation of prestudy erythrocyte ouabain-sensitive ^{22}Na efflux rate constant (pre-Kos) with the decrease in mean blood pressure (ΔMBP) during oral magnesium treatment.*

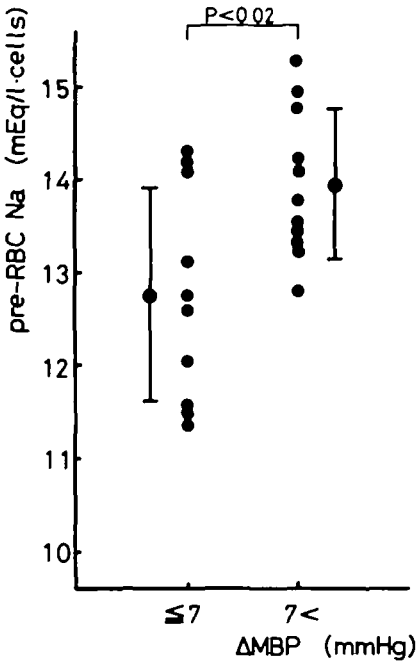

FIGURE 4. *Prestudy intraerythrocyte sodium concentration (pre-RBC Na) in patients with the decrease in mean blood pressure (ΔMBP) more than or less than 7 mm Hg during oral magnesium treatment.*

patients with essential hypertension was dependent on K_{os} and RBC Na. Therefore, we speculate that oral magnesium treatment is effective for lowering high blood pressure in patients with an increased level of a circulating sodium-potassium adenosine triphosphatase (Na^+,K^+-ATPase) inhibitor.

Essential hypertensive patients were given MgO in the present study, whereas Cappuccio et al[15] used magnesium aspartate in their study. Although the plasma magnesium concentration and urinary magnesium excretion significantly increased during magnesium supplementation, mean blood pressure did not change throughout the study. Their results[15] differ from ours, and that may be due to the difference in salt intake because urinary sodium excretion in our study was much more than in their study. The speculation that Japanese may have more sodium retention compared with Americans and Europeans because of a higher salt intake from diet coincides with the data in the present study that patients with the higher RBC Na showed the greater hypotensive effect during treatment with oral magnesium. On the other hand, a significant decrease in blood pressure in essential hypertensive patients resulted from oral magnesium treatment and thiazide administration.[16–18] One of us recently suggested[18] the possibility of intracellular magnesium deficiency in essential hypertensive patients receiving long-term thiazide therapy compared with untreated patients, and the hypotensive effect of oral MgO supplementation for hypertension in patients with thiazide treatment through the activation of cell membrane sodium pump. The hypotensive effect of oral magnesium may have overcome the vasoconstriction induced by magnesium deficiency that probably occurs with long-term thiazide therapy.[19]

In a study[20] with spontaneously hypertensive rats, the antihypertensive effects of oral magnesium supplementation was observed with the increase in urinary volume and excretion of sodium and calcium. There was no significant change in serum concentration, 24-hour urinary excretion of sodium, calcium, or phosphorus, or 24-hour urinary volume during the study.

Proposed mechanisms for the blood pressure–lowering effect of magnesium include an inhibition of sympathetic nervous activity[21–26] and peripheral vasodilation via control of sodium and calcium metabolism.[1–8,27–31]

Cytosolic calcium in the vascular smooth muscle cell, which is mediated by movements of calcium across the membrane, determines the degree of the tension.[8] Calcium influx to the vascular smooth muscle cell occurs through potential-operated channels, receptor-operated channels, and leak-operated channels.[45] Magnesium directly blocks the slow-calcium channel.[22,27,28] The release of intracellular stored calcium into the cytoplasm is also important for developed tension of vascular smooth muscle cells. Magnesium inhibits the release of calcium from sarcoplasmic reticulum by competition for a calcium receptor on a calcium-regulated efflux channel and drives calcium into the sarcoplasmic reticulum through stimulation of Ca^{2+}-ATPase.[29] Efflux of calcium from the arterial smooth muscle cell is accomplished by Ca^{2+}-ATPase activity and by the sodium-calcium exchange system.[3] Magnesium has been

known to activate not only Ca^{2+}-ATPase[4,5,29,30] but also Na^+,K^+-ATPase.[1,4-7] The erythrocyte sodium pump activity appeared to increase almost linearly with both intraerythrocyte total and ionized magnesium concentrations below and at physiological levels.[1] According to their study,[1] a greater change in RBC Mg than that found during our study was necessary to produce the change in sodium pump activity found during our study. However, the small change in RBC Mg may be important in the long-term coordination of sodium pump activity. An activated sodium pump produces a decrease in intracellular sodium concentration in the smooth muscle. The activity of the sodium-calcium exchange system is influenced by the intracellular sodium concentration, so that a decrease in intracellular sodium concentration in the smooth muscle may activate the sodium-calcium exchange, thus decreasing the intracellular calcium concentration and reducing the tension of the muscle.[44] Furthermore, although myocardial depressant actions of magnesium were also demonstrated,[32] we could not examine the hemodynamic effects of magnesium.

In our study, K_{os} correlated positively with RBC Mg and inversely with RBC Na in essential hypertensive patients. RBC Na also gave a positive correlation with mean blood pressure. During oral magnesium supplementation, there were significant increases in urinary magnesium excretion, serum magnesium concentration, RBC Mg, and K_{os}, and significant decreases in RBC Na and mean blood pressure. Furthermore, during magnesium treatment, positive correlations were found between the elevation in K_{os} and the increase in RBC Mg, and between the elevation in K_{os} and the reduction in mean blood pressure. These data support the possibility that oral supplemented magnesium is well absorbed and raises both the serum magnesium concentration and RBC Mg. In addition, the increased intracellular magnesium may activate sodium pump activity in the vascular smooth muscle cells, decrease the intracellular sodium concentration, and reduce the tension of the muscle cells through the activation of the sodium-calcium exchange system.[1-8] The lower the K_{os} or the higher the RBC Na in essential hypertensive patients, the more effective the oral magnesium treatment is in lowering blood pressure. In this study, we found no relation between the decrease in mean blood pressure and either serum magnesium concentration or RBC Mg. Therefore, the extent of blood pressure decrease during magnesium supplementation probably depended on the values of K_{os} and RBC Na. The hypotensive effect of magnesium may be determined by cell membrane sodium pump activity and intracellular sodium concentration.

Significant decreases in serum triglyceride and free fatty acid concentrations were found during magnesium supplementation; serum total cholesterol concentration was also reduced, but not significantly. It has been demonstrated that plasma free fatty acid, triglyceride, and total cholesterol levels are elevated in clinical and experimental magnesium deficiency,[33,34] and that those atherogenic plasma lipids are decreased by magnesium supplementation.[9,10] Although mechanisms[33-36] for the effects of magnesium on lipid metabolism have been proposed, we do not have a clear explanation for the hypolipidemic effect of magnesium in the present study. The improvement of disordered lipid metabolism by magnesium supplementation may prevent atherogenesis and reduce the risk of cardiovascular diseases including systemic hypertension and ischemic coronary artery disease.

In conclusion, oral magnesium treatment lowered blood pressure in patients with essential hypertension partly through the decreased intracellular sodium concentration caused by its activating effect on the cell membrane sodium pump. The values of K_{os} and RBC Na are valuable indicators for the degree of the hypotensive effect of magnesium. Furthermore, the reduction in serum lipid concentrations was also noted. These results suggest that an appropriate oral magnesium intake may be an effective nonpharmacological treatment for patients with essential hypertension, especially those with lower K_{os} and higher RBC Na.

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