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Oral Magnesium in Coronary Artery Disease: Fresh Insight on Thrombus Inhibition

MICHAEL SHECHTER, MD, MA

Despite enormous strides in the understanding, prevention, and treatment of coronary artery disease (CAD) and acute myocardial infarction (MI) over the past 20 years, CAD remains the leading cause of death for both men and women in the United States. The management of acute MI now routinely involves a complex array of effective interventions including reperfusion therapy and cardioprotective and antithrombogenic agents. Yet both morbidity and mortality remain unacceptably high, particularly in the elderly.

Promise of Magnesium

Magnesium continues to undergo study as a cardioprotective agent. In acute MI, it is relatively safe, inexpensive, and easy to use either as an adjunct or an alternative to thrombolytics and other agents.

Magnesium, nature's physiologic calcium channel blocker, is the second most common intracellular cation in the human body after potassium) and a crucial cofactor for many physiologic processes. Although clinical trials of intravenous (IV) magnesium in acute MI have yielded conflicting results, magnesium has demonstrated antiarrhythmic, antithrombogenic, and vasodilating effects that have limited infarct size and protected against reinfarction.

Recent evidence points to a beneficial role for oral magnesium as a regulator of platelet dependent thromboses (PDT). In a study of CAD patients published in the July 15, 1999, issue of the *American Journal of Cardiology* described below, my colleagues and I discovered PDT was reduced by 35% in patients who received oral magnesium supplementation.

Magnesium, CAD and MI

There is impressive evidence that magnesium deficiency participates in the pathogenesis of CAD. Magnesium supplements have reduced development of atherosclerosis in animal studies. Magnesium deficiency has been associated with several important CAD risk factors including hypertension, diabetes mellitus, dyslipidemia, arrhythmia, coronary vasospasm, and thrombosis.

The first epidemiological links between magnesium status and CAD were the observations that mortality from ischemic heart disease was lower in populations living in areas with "hard" water than in "soft" water regions. Hardness of water is

caused by high concentrations of both calcium and magnesium, but evidence has shown that protection against cardiovascular damage is afforded primarily by magnesium, not calcium. Autopsies of patients in soft water areas have shown more coronary atheromata and evidence of old and recent MI, and lower levels of magnesium in cardiac tissue.

Low serum magnesium concentrations at admission have been reported in many patients with acute MI, but not in all. Acute depression of serum magnesium levels is accompanied by an increase in free fatty acid levels triggered by release of catecholamines that also lower tissue magnesium levels. Acute and chronic reduction in extracellular magnesium levels is associated with lowered myocardial magnesium, which increases the risk of damage from myocardial ischemia.

Magnesium deficiency, demonstrated better by mononuclear blood cell magnesium that serum level [Elin RJ. Magnesium metabolism in health and disease. *Dis. Mon.*;**34**:1-218.], predisposes to excessive morbidity or mortality of acute MI patients. These patients have been shown to have low mononuclear blood cell magnesium, which is predictive of in-hospital mortality: the lower the magnesium level, the higher the mortality. Dietary magnesium intake was found to be lower in patients who had ventricular arrhythmia during acute MI. Some laboratory and clinical trials suggest that magnesium can reduce total and low-density lipoprotein cholesterol (LDL-C) and increase high-density lipoprotein cholesterol (HDL-C).

The Thrombogenesis Connection

The benefits of IV magnesium infusion treatment of acute MI patients remain controversial, having been demonstrated in some randomized, controlled clinical trials but not others. My colleagues and I demonstrated that IV magnesium therapy reduces mortality in the thrombolysis-ineligible patients with acute MI, including the elderly. However, a multicenter megatrial showed no benefit and even a nonsignificant trend toward harm.

Why have trials of magnesium therapy in MI produced inconsistent results? A plausible explanation is that trials administer magnesium at different times after infarction. Best results are obtained with the least delay in infusing magnesium after the ischemic event. Table 1 lists the known physiologic activities of magnesium that provide clues to its protective effects. The cascade and its suppression of platelet activation have immediate and longer-term benefits in CAD patients.

Table 1. Possible Cardioprotective Mechanisms of Magnesium
Antiarrhythmic effects
Calcium channel blocking effects
Improvement of LDL-C/HDL-C ratio
Improvement of nitric oxide release from coronary endothelium
Improved response to potassium repletion
Inhibition of platelet-dependent thrombosis
Protection against free radical-induced injury
Protection against reperfusion damage
Reduction in lipid levels
Reduction of potassium loss
Vasodilating effects (improved myocardial collaterals and reduced afterload)

Current Study Results. To test our hypothesis that magnesium treatment plays a regulating role in thrombogenesis, we recently conducted a randomized, prospective, double-blind, crossover trial of the effects of oral magnesium supplementation on PDT in 42 patients (37 men, 5 women, mean age 68±9 years) with documented CAD, all of whom were taking aspirin. Excluded from the study were patients with unstable angina, severe congestive heaart failure (CHF), chronic diarrhea, renal failure, MI, within the preceding 3 months, abnormal thyroid function, peripheral vascular disease, chronic liver disease, or type 1 (insulin-dependent) diabetes mellitus. In the study population, 55% of the patients had prior MI, 75% had a history of hypercholesterolemia, 58% had systemic hypertension, and 6% had type 2 (non-insulin-dependent) diabetes mellitus.

Patients received either magnesium oxide tablets (800 to 1200 mg/d [483 to 724 mg elemental magnesium]) or placebo for 3 months, followed by a 4-week washout period, and then crossover treatment for 3 months. Subjects continued taking their regular medications, which included aspirin and various combinations of beta blockers, lipid-lowering agents, ACE inhibitors, calcium antagonists, and diuretics. Before and after each phase, PDT was assessed using an ex vivo perfusion model (porcine aortic media held in a Badimon chamber). Other measured parameters included platelet aggregation, platelet P-selectin flow-cytometry, monocyte tissue factor procoagulant activity (TF-PCA), adhesion molecule density, and serum lipids and electrolytes.

Compliance with the study medication was 89%, and no serious adverse effects were reported. Among the 36 subjects included in the final analysis, no significant differences were found in baseline values before each treatment period. Before treatment began, baseline analysis revealed significant positive correlations between PDT and fasting blood sugar (r = 0.44), resting systolic blood pressure (r = 0.37), apolipoprotein B (r = 0.29%), and total cholesterol level (r = (0.42). No significant correlation was observed between PDT and TF-PCA, either at baseline or following treatment.

After 3 months of oral magnesium supplementation, the median PDT was reduced by 35% (P<.05) (Table 2), and 75% of the patients demonstrated a decrease in PDT with magnesium oxide treatment (P<.05) (Figure) No association was observed between the presence of risk factors (hypertension, smoking, diabetes mellitus) and the degree of change in PDT after treatment. Magnesium treatment produced no significant effect on platelet aggregation. P-selection expression, monocyte-derived TF-PCA, serum lipids, fibrinogen, or apolipoprotein adhesion molecules, MAC-1 was significantly reduced (P<.03) during treatment.

Table 2. Effects of Oral Magnesium on Platelet Function, Monocyte Function, and Lipids

	Baseline	Magnesium	*P*
Platelet Function			
PDT (ppm2/mm)	91	59	< .05
PLT aggregation (max ohms)	9±6	8±4	.40
P-selectin (% gated)*	33±20	35±23	.69
Monocyte Function			
MAC-1	95±44	76±29	.03
VLA-4	55±22	49±17	.27
PECAM-3	198±114	164±68	.14
Sialyl L	71±46	55±29	.18
TF-PCA(ug/10 cells)	124±127	239±248	.09
Lipids			
Total cholesterol (mg/dL)	173±28	180±12	.10
Triglycerides (mg/dL)	148±93	148±100	.99
HDL-C (mg/dL)	40±10	41±9	.26
LDL-C (mg/dL)	104±26	110±27	.22
Fibrinogen (mg/dL)	307±66	309±51	.83

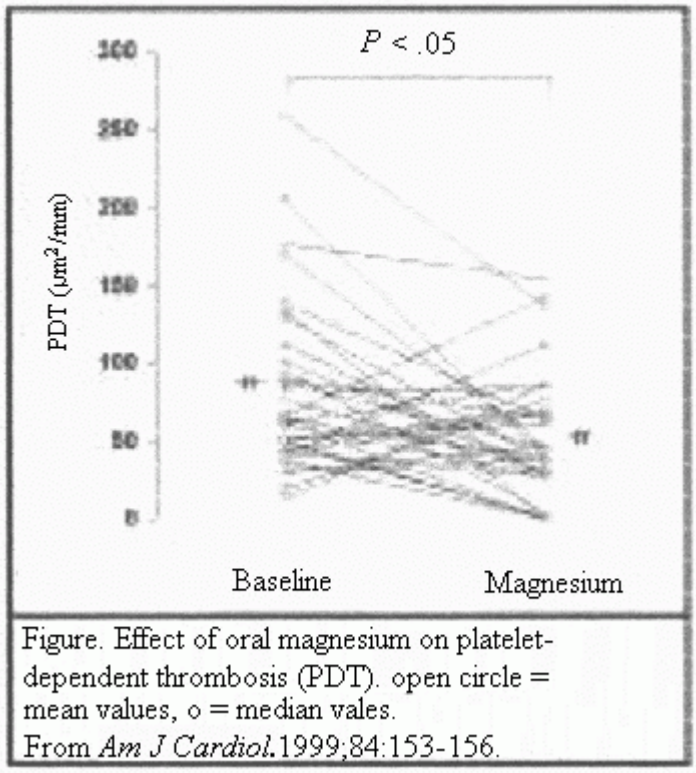

Figure. Effect of oral magnesium on platelet-dependent thrombosis (PDT). open circle = mean values, o = median vales.
From *Am J Cardiol.*1999;84:153-156.

Only 1 patient had a subnormal serum magnesium level at baseline (1.6 mg/dL). After 3 months of oral magnesium treatment, there was no significant change in serum magnesium levels in the study population (2.08±0.16 vs 2.11±0.14 mg/dL, *P*=.22).

Nor was there any correlation between baseline serum magnesium levels and PDT or between the change in serum magnesium levels and the change in PDT. However, the increase in magnesium level after treatment was significantly greater when baseline levels were low (r = 0.53, P=.0008).

Implications for Treatment

Our recent study demonstrated for the first time that an ex vivo measure of acute PDT was significantly reduced in stable CAD patients receiving oral magnesium therapy. This antithrombotic effect occurred despite 100% use of aspirin therapy. Magnesium therapy did not inhibit either platelet aggregation or P-selectin expression, a measure of platelet α-granule release reaction.

We observed no effect on collagen-induced platelet aggregation at an oral magnesium dose that caused significant inhibition of platelet adhesion and thrombus formation. Several factors may explain why. The entire study population was on aspirin therapy, which suppresses platelet aggregation but not platelet adhesion. The oral route of magnesium supplementation may not have produced magnesium concentrations high enough to inhibit platelet aggregation, as has been seen in IV magnesium infusion or bolus therapy. Thus, without apparent impact on in vitro platelet aggregation, oral magnesium may reduce PDT formation through its antiplatelet adhesion effects.

This study was limited by its modest size and the relatively low-risk status of the population, which may have attenuated the potential benefits of oral magnesium treatment. Our results suggest a need for further studies with larger numbers of patients and, possibly, higher doses of magnesium. The ex vivo experimental model of thrombus measurement is of undetermined clinical relevance, but it provided a simple and reproducible way to study how blood elements interact with thrombogenic surfaces.

This trial implies that the story of magnesium in acute MI, while marked by debate and paradoxical evidence, is far from over. Oral magnesium—an even easier and more economical treatment than IV magnesium—may hold the promise of added protection against reinfarction and arrhythmias, even in the current setting of nearly universal antithrombotic pharmacotherapy.

Using Oral Magnesium

According to the American College of Cardiology/American Heart Association Guidelines for the Management of Patients with Acute Myocardial Infarction, the weight of evicence favors the use of magnesium to correct documented deficits in magnesium and potassium, especially in patients who were receiving diurectics before the onset of infarction. In particular, patients exhibiting episodes of torsades de pointes-type ventricular tachycardia associated with a prolonged QT interval should receive 1 to 2 g magnesium administered as an IV bolus over 5 minutes. The relatively limited gastrointestinal absorption of magnesium makes oral prepartions inappropriate for acute indications.

As for the use of oral magnesium in patients with CAD, acute MI, or cardiovascular risk factors, no firm guidelines have been developed. Clinical judgement must play a

central role in identifying at risk patients and implementing supplementation, including choice of formulation and dosage. Long-term magnesium supplementation may benefit various cardiovascular conditions, particularly hypertension. In particular, patients receiving short- or long-term therapy with thiazide or loop diuretics are candidates for magnesium replacement.

The potential of oral magnesium for ameliorating CAD will remain untapped until clinicians become aware that patients may be magnesium-deficient even when serum magnesium levels are normal. Checking serum magnesium levels for frank hypomagnesemia is especially important for patients hospitalized with CAD.

Some magnesium authorities advocate a more aggressive approach to correcting the widespread dietary shortfall in magnesium levels. The first step in a population-based approach is to encourage adequate dietary intake of magnesium-rich foods. Oral supplementation is reccommended for individuals with chronic deficiencies that are unlikely to be connected through dietary modification and for health patients with a high risk profile for CAD or a family history of premature CAD.

Oral supplementation of 500 mg/d elemental magnesium or less is considered safe for most individuals with normal renal runction. The most common adverse effect at doses higher than 600 to 700 mg/d is diarrhea. Before starting supplementation, it is advisable to assess renal runction; throughout supplementation, measurements of serum magnesium and potassium levels are recommended. The ideal duration of supplementation is unknown, but should last up to several months. Oral magnesium use may be tapered or discontinued once serum levels remain normal over the course of several weeks, or if diarrhea develops.

Suggested Reading

Seelig, MS, Elin RJ. Is there a place for magnesium in the treatment of acute myocardial infarction? *Am Heart J.* 1996;132:471-477.

Shechter M, Hod H, Chouraqui P, Kaplinsky E, Rabinowitz B. Magnesium therapy in acute myocardial infarction when patients are not candidates for thrombolytic therapy. *Am J Cardiol.* 1995;75:3321-323.

Shechter M, Kaplinsky E, Rabinowitz B. Review of clinical evidence—is there a role for supplemental magnesium in acute myocardial infarction in high-risk populations (patients ineligible for thrombolysis and the elderly)? *Coron Artery Dis*. 1996;7:352-358.

Shechter M, Kaplinsky E, Rabinowitz B. The rationale of magnesium supplementation in acute myocardial infarction. A review of the literature. *Arch Intern Med.* 1992;152:2189-2196.

Shechter M, Merz NB, Paul-Labrador M, et al. Oral magnesium supplementation inhibits platelet-dependent thrombosis in patients with coronary artery disease *Am J Cardiol.* 1999;84:152-156.

Q&A: Using Oral Mg in CAD

Q: *Do you use oral magnesium supplementation in your practice?*
DR. SHECHTER: Yes, oral supplementation of magnesium is prescribed in our clinic for selected patients.

Q: *How do you decide whether a patient with CAD or cardiovascular risk factors should receive oral magnesium?*
DR. SHECHTER: Most patients with CAD are magnesium deficient, especially elderly ones, those with CHF, and those taking digoxin. Unless they also have renal failure, these patients are candidates for oral magnesium.

Q: *Which patients are most likely to benefit from oral magnesium?*
DR. SHECHTER: Patients most likely to benefit include those taking diuretics, digitalis, or laxatives; those with diabetes mellitus; and, as I said, the elderly, who typically have a low dietary intake of magnesium. Several other factors also increase susceptibality to deficiency among elderly patients; reduced intestinal absorption and increased urinary output of magnesium, a high rate of disorders that impair absorption and renal function, and widespread use of magnesium-wasting medications.

Q: *Which formulations of magnesium supplementation are best absorbed*
DR. SHECHTER: Magnesium oxide, which was used in our clinical trial, is excellent. Other formulations with good overall absorption and bioavailabilty characteristics are magnesium gluconate and magnesium citrate.

Q: *Which formulation do you prefer?*
DR. SHECHTER: We use magnesium oxide in 400 mg tablets, each containing 241.3 g(10.86 mEq) of elemental magnesium, given 2 to 3 times daily.