

Bioavailability and Pharmacokinetics of Magnesium After Administration of Magnesium Salts to Humans

V.V. Ranade^{1*} and J.C. Somberg²

Therapeutically, magnesium salts represent an important class of compounds and exhibit various pharmacologic actions. Examples of magnesium salts are ionic magnesium and magnesium citrate in nephrolithiasis, magnesium salicylate in rheumatoid arthritis, magnesium hydroxide as an antacid as well as a cathartic, and magnesium mandelate as urinary antiseptic. Various anions attached to the cation magnesium, such as oxide, chloride, gluconate, and lactate, affect the delivery of the amounts of elemental magnesium to the target site and thereby produce different pharmacodynamic effects. This review examines the bioavailability and pharmacokinetics of various magnesium salts and correlates pharmacodynamic action with the structure-activity relationship.

Keywords: magnesium salts, oral repletion, hypomagnesemia, magnesium bioavailability, magnesium depletion, hypermagnesemia.

INTRODUCTION

Magnesium is known to play a central role in cellular function, and it strongly influences the excitability of the cardiovascular and neuromuscular system. Until recently, the main reason for the administration of magnesium has been for the administration in patients with suspected magnesium deficiency. However, now it is known that magnesium possesses positive pharmacodynamic effects, such as in controlling arrhythmias and possibly reducing sudden death in myocardial infarction patients. Beneficial effects are seen when plasma (extracellular) magnesium concentrations are increased from physiologic to much higher pharmacologic concentrations.

Cardiac dysfunction in patients with coronary artery diseases could be attributed to ischemia-induced deficient sequestration of calcium into the sarcoplasmic reticulum. It has been postulated that a substantial decline in intracellular calcium could prohibit

myocardial relaxation and improve diastolic dysfunction. One candidate to antagonize increased extracellular calcium concentrations is magnesium, which prevents intracellular calcium accumulation by occupying calcium-binding sites. In one recent study,¹ the hypothesis that improvement in left ventricular diastolic function can be brought about by intravenous administration of magnesium chloride was tested. Magnesium is a powerful vasodilator and decreases systemic vascular resistance in hyper- and normotensive patients with coronary artery disease. This effect is also present in the coronary arteries and explains the significant increase in coronary blood flow after magnesium administration. A reduction in left ventricular (LV) end-diastolic pressure is an important effect of magnesium and might explain in part the action of why intravenous magnesium administration in reducing mortality in coronary artery disease complicated by LV failure. These investigators¹ also conclude that, based on their studies, magnesium may be a clinically valuable drug for reducing the ischemic burden originally from increased LV end-diastolic pressure. Among other magnesium compounds, such as sulfate, oxide, gluconate, and chloride are effective in promoting continued uterine quiescence in patients recently treated for preterm labor, and magnesium has gained acceptance as a tocolytic drug averting uterine contractions.¹

¹Rush-Presbyterian-St. Luke's Medical Center, Chicago; ²American Institute of Therapeutics, Lake Bluff, IL.

*Address for correspondence: Rush-Presbyterian-St. Luke's Medical Center, Department of Clinical Pharmacology, 2242 W. Harrison Street, Tech 2000, Suite 260, Chicago, IL 60612-3515; e-mail: jsomberg@rush.edu

Magnesium is primarily an intracellular cation, and the effect of this drug is probably owing to its competition with intracellular calcium within the myometrial cell. Pharmacokinetically, the increase in the area under the curve (AUC) is dependent on the dose of oral or parenteral administration. There is not a linear relationship between dose and increase in AUC. Magnesium cation—the pharmacologically active moiety—in magnesium salts employed as drugs is reportedly released in the small intestine, the site of optimal magnesium absorption. There is also insignificant absorption in the colon. Radiolabeled studies with ^{28}Mg indicated that the maximum magnesium absorption occurs within the ileum and jejunum, and this process occurs at an equal rate throughout the small intestine.

The absorption of magnesium at physiologic doses can be described by a biphasic curve. A linear portion indicates passive diffusion of magnesium across a concentration gradient. Magnesium absorption is also minimally affected by dietary calcium intake, vitamin D, and parathyroid hormone. Some disease states associated with malabsorption, such as steatorrhea and intestinal bypass surgery, may also affect magnesium absorption. Although serum levels generally may not correlate well with clinical efficacy, serum measurements are still the most widely available method to assess magnesium status. Most clinicians, however, believe that if long-term tocolysis is achieved, the serum levels are only valid for avoidance of toxicity² and do not predict efficacy.

MAGNESIUM AND ISCHEMIC HEART DISEASE

Magnesium, a predominantly intracellular cation, is known to be the fourth most abundant cation in the human body and is second only to potassium in intracellular metabolism. Magnesium is vital in biochemical reactions and serves as a cofactor for several cellular enzymes, many of which involve energy metabolism and protein and nucleic acid synthesis. It is the ionized magnesium that is physiologically active, and, as recently as 1999, Wary et al³ determined the distribution of magnesium in the ionized form using ^{31}P -NMRs and ion-selective electrodes. Other techniques are the use of fluorescent indicators and ultracentrifugation equilibrium dialysis. Approximately half of the total magnesium in the body is present intracellularly in soft tissue and the other half is present in the bones. Less than 1% of the total magnesium content is present in the blood.

Depleted amounts of magnesium are implicated in the development of several disease states such as con-

gestive heart failure, tachyarrhythmias, diabetes, and atherosclerosis. Magnesium deficiency can result in hypocalcemia, hypokalemia, dysphagia, anemia, central nervous system changes such as ataxia, vertigo, and neuromuscular irritability. The most common serum electrolyte abnormalities in chronic congestive heart failure have been hypomagnesemia, hypokalemia, and hyponatremia. Deficiencies especially in magnesium and potassium are known to occur commonly in heart failure as a consequence of reduced ion intake or as a result of an increased loss in magnesium owing to diuretic therapy. Magnesium therapy for deficiency replacement for the attainment of pharmacologic doses, has been effective in changing hemodialysis and in treating arrhythmias. Patients with heart failure who were treated with angiotensin-converting enzyme (ACE) inhibitors had significantly higher intracellular potassium and magnesium concentrations, which may contribute to the success of ACE therapy. In addition, treatment with digoxin and diuretic agents is influenced by or associated with significant alteration in magnesium balance. The intricate role of magnesium on a biochemical and cellular level in cardiac cells is crucial in maintaining stable cardiovascular hemodynamics and electrophysiology function. Electrocardiographically, magnesium deficiency causes an increase in heart rate, mildly prolongs the PR and QRS intervals, significantly prolongs the QT interval, flattens ST-T segments, and contributes to the development of U waves. As a result of these findings, magnesium supplementation mostly by either oral or parenteral routes is gaining importance in maintaining health in patients.⁴

Magnesium absorption primarily takes place in the distal small intestine with some absorption in the colon. The effectiveness of oral magnesium supplementation is determined by its rate of uptake from the intestine into blood. If blood magnesium levels exceed a critical renal threshold, the excess will be rapidly excreted, thereby limiting its availability to tissues. Magnesium disappears quickly from plasma after intravenous administration. Transfer of magnesium from blood to extravascular space is a fast and efficient process, and the intracellular concentration of magnesium is high compared with that in blood. Approximately one third of serum magnesium is bound to albumin. Of the filtered magnesium, approximately 25% to 30% is reabsorbed proximally, 50% to 60% is reabsorbed into the ascending limb of Henle's loop, and 2% to 5% is reabsorbed distally. Biochemically, magnesium activates ATPase enzymes involved in establishing and maintaining intracellular electrolyte balance.

The activation of these enzymes results in the hydrolysis of adenosine triphosphate (ATP) and the resultant transmembrane transport of a variety of ions. One recognized Mg^{2+} -ATPase is ouabain-sensitive Mg^{2+} (Na^+ - K^+)-ATPase, which is associated with the transcellular sodium pump. Additionally, the cellular proton and calcium pumps are believed to be regulated by Mg^{2+} -ATPases. The sodium pump regulates cellular sodium and potassium concentrations. The proton pump is involved with mitochondrial ATP generation, and the calcium pump preserves intracellular calcium concentrations. These Mg^{2+} ATPases are thought to be found in all compartments and they possess other yet unknown functions.

Based on the observations of several investigations, currently serum magnesium analysis appears to be clinically the most practical, accessible, and expeditious method of identifying changes in magnesium homeostases. Whang et al⁵ determined serum magnesium concentrations in patients with incidence of hypomagnesemia. Commonly found signs and symptoms associated with clinical magnesium deficiency and hypomagnesemia include several nervous system manifestations such as hyperactive deep tendon reflexes that can progress to ataxia, twitching, mental obtundation, convulsions, and coma.

Endocrine causes of magnesium deficiency include hyperthyroidism and hyperaldosteronism, and excess renal losses of magnesium are associated with glycosuria and appear to be responsible for the high frequency of hypomagnesemia found in diabetics. Clinically, increased renal excretion has been reported in metabolic acidosis associated with starvation, ketoacidosis, and alcoholism. The mechanism of this hypomagnesemia associated with metabolic acidosis may be related to loss of magnesium from bone and muscle. Thus, metabolic acidosis, whether from starvation, ketoacidosis, alcoholic ketoacidosis, or diabetic ketoacidosis, can each contribute to magnesium deficiency and hypomagnesemia through excessive renal magnesium loss. Miscellaneous causes of hypomagnesemia may include excessive lactation, exchange transfusions, and acute intermittent porphyria. Clinical epidemiologic studies suggest that there may be a cause-effect relationship between magnesium deficiency and vascular lesions.⁵ In hard-water regions with high magnesium content, the incidence of atheromatous vascular lesions appears to be decreased. In population studies, high plasma magnesium concentrations have been found in association with lower serum lipid concentrations and decreased cardiovascular mortality. Experimental magnesium depletion is associated with hypertriglyceridemia, hypercholesterolemia, and decreased high-density lipoprotein concentrations. In

addition, experimental magnesium depletion has been reported to accelerate atherogenesis in rabbits fed a high cholesterol diet. However, it should be emphasized that at the present time more clinical studies are required to elucidate the clinical relationship between Mg depletion and vascular disease. Magnesium deficiency and hypomagnesemia are thought to approximate or contribute to a number of clinical conditions, including toxicity, congestive heart failure, hypertension, and cardiac rhythm disturbances. Studies by Gottlieb et al⁶ support the view that recognition and treatment of the disorders are important in the management of congestive heart failure, and they found that acute elevation of serum magnesium concentration decreases the frequency of ventricular arrhythmias. Teo et al⁷ reported that intravenous magnesium administration in patients with acute infarction significantly decreased mortality. The American Heart Association recommends the use of intravenous magnesium among the drugs used in the management of ventricular tachyarrhythmias in patients with acute myocardial infarction (AMI). This recommendation is based on the relationship of hypomagnesemia to refractory ventricular fibrillation and to refractory potassium repletion. In the later phase of AMI, Ceremuzynski and Van Hao⁸ concluded that treatment with magnesium can be used effectively to restore normal rhythm in patients with arrhythmias.

Previous reports have suggested that there is a strong correlation between clinical hypokalemia and hypomagnesemia. Whang et al⁹ reported that 42% of hypokalemic patients were also hypomagnesemic on routine testing of serum magnesium concentrations. In the same study, hypomagnesemia was found in 29% of hyponatremic patients and 23% of hypophosphatemic patients. Therefore, this study suggests that in the absence of routine serum magnesium analysis, the detection of hypokalemia, hyponatremia, hypophosphatemia, or hypocalcemia should alert the clinician to order a serum magnesium analysis because of the high probability of coexisting hypomagnesemia. This is especially true if hypokalemia is observed.

There is a close linkage between magnesium and potassium concentration not only clinically, as evidenced by the 42% of hyponatremic patients who are hypomagnesemic, but also experimentally. Magnesium-depleted rats have reduced skeletal muscle (cell) potassium concentrations despite provision of potassium. This loss is accompanied by kaliuresis as well as phosphaturia. In another study, potassium depletion was accelerated when magnesium deficiency was superimposed. Restoration of muscle potassium was impeded when coexisting magnesium depletion was not concurrently repleted with potassium. In vitro studies

using red blood cell membranes have shown that magnesium depletion increases membrane permeability, resulting in loss of cellular potassium and intracellular accumulation of sodium. In squid axone and ascites tumor cells, decreased ATPase activity has been reported with magnesium depletion. Exposure to a low magnesium concentration causes cultured cardiac cells to decrease potassium transport. This effect of low magnesium concentration occurred primarily on ouabain-sensitive $\text{Na}^+\text{-K}^+\text{-ATPase}$. Normally, magnesium enhances inward rectification of potassium concentration by blocking cell potassium efflux through potassium channels. With magnesium depletion, potassium channels become unblocked because of the relative lack of magnesium, resulting in increased efflux of cellular potassium. There is also evidence that potassium and Na-Cl cotransport is decreased with magnesium depletion. Experimental observations indicate that the causes of cellular potassium loss resulting from magnesium depletion are multifactorial and include kaliuresis, altered cell membrane permeability, decreased $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity, decreased inward rectification, and decreased Na and K cotransport. Thus, it is important to recognize the pivotal role of magnesium in maintaining cellular potassium homeostasis.¹⁰

Data are accumulating that indicate that magnesium cation may be a promising agent for the protection of ischemic myocardium and modulation of reperfusion injury. Magnesium is a critical cofactor in more than 300 intracellular enzymatic processes, many of which are integrally involved in mitochondrial function of energy production, maintenance of transsarcolemmal ionic gradients, cell volume control, and resting membrane potential. The cardiovascular consequences of magnesium deficiency in animal and clinical studies have been summarized by Seelig¹¹ and include multifocal necrosis with calcium accumulation in mitochondria in a pattern reminiscent of myocardial ischemia and catecholamine-induced cardiomyopathy, atherogenesis, a heightened tendency to platelet aggregation, increased coronary and peripheral vascular resistances, sinus tachycardia and repolarization abnormalities, and ventricular tachyarrhythmia. A review of epidemiologic studies highlighted an inverse relationship between the magnesium content of drinking water and ischemic heart disease-related mortality in various populations.¹⁰ Intravenous infusions of magnesium in patients have been reported to reduce coronary and systemic vascular resistance, inhibit platelet aggregation, and terminate episodes of torsade de pointes type ventricular tachycardia.

Articles published by Christensen et al¹² and Herzog et al,¹³ when viewed in the context of six other

reports of in vivo animal models of coronary occlusion and reperfusion, are important contributions to the emerging database on the potential benefits of magnesium in ischemic heart disease. These reports span four different animal species, are complementary, and provide data on magnesium loading at various times along a continuum from a point well before coronary occlusion (equivalent to primary prevention in patients) to time points just before, during, and after coronary occlusion that ranged from 45 minutes to 72 hours. The treatment regimens are likely to have yielded blood or tissue concentrations of magnesium generally consistent with those observed in patients with AMI who received magnesium in clinical trials. Magnesium infusions can cause a multitude of cardiovascular and local cellular effects. Some investigators observed modest reductions in heart rate and arterial pressure that may have played a protective role but are unlikely to be the sole explanation for the ability of magnesium to reduce infarct size. Under the experimental conditions of Christensen et al^{12,14} and Herzog et al,^{13,15} no differences in hemodynamics or myocardial blood flow were seen in the magnesium-treated versus control animals, suggesting that any differences observed were likely to be due to a myocellular effect of magnesium.

Implications of the experimental data are that magnesium deficiency at the time of coronary occlusion is associated with a larger infarct, and short-term administration of supplemental magnesium just before coronary artery occlusion, during the time when the coronary artery is occluded, at the time of reperfusion, or within 15 to 45 minutes of reperfusion limits the size of the infarct. The benefits of supplemental magnesium are lost either when there is a delay of more than 15 to 45 minutes after the onset of reperfusion or when reperfusion is sufficiently late such that only negligible amounts of myocardial tissue are available for salvage. If the coronary artery is subtotally occluded and distal perfusion is maintained, no incremental benefit of magnesium is observed. Confirmation of these observations is found in the reports of a greater infarct size in magnesium-deficient animals and of reduced infarct size in animals pretreated with magnesium in which AMI is produced by another method, ie, isoproterenol infusion.

Although the latest experiments of Christensen et al^{12,16} and Herzog et al^{13,17} lend support to the intriguing notion that early treatment with magnesium limits infarct size by as much as 50%, they do not conclusively establish the mechanism by which magnesium exerts its benefit. The available data suggest that a combination of mechanisms may act additively or even synergistically to protect myocytes: (1) reduce

vulnerability to oxygen-deprived free radicals, (2) decrease cytosolic calcium levels by inhibition of inward flux of calcium ions through sarcolemmal calcium channels and possible intracellular sites as well, (3) reduce myocardial oxygen demand via sinus slowing and lowering of arterial pressure, (4) coronary vasodilation and enhancement of collateral development, and (5) inhibition of platelet aggregation and prevention of coronary thrombosis.

The reduction of infarct size with magnesium has profound research and clinical implications. The Langendorff model of du Toit and Opie¹⁸ suggests that to achieve cardioprotective effects with magnesium, the blood level must be elevated before or within a short interval after reperfusion of a totally occluded coronary artery by thrombolysis or percutaneous transluminal coronary angioplasty or after spontaneous reperfusion. Because thrombolysis and spontaneous reperfusion are both characterized by stuttering cycles of reperfusion and reocclusion until sustained reperfusion is achieved, magnesium regimens that include a loading bolus and infusion are probably necessary. In addition to limitation of myocardial necrosis, such a regimen might also offer protection against stunning and more necrosis should late reocclusion of the infarct-related artery occur. Finally, during the critical early hours of AMI, it is imperative to maintain an adequate coronary perfusion pressure: magnesium-loaded boluses that are too large, delivered too rapidly, or given in conjunction with other vasodilating agents, such as nitrates, may cause a decrease in arterial pressure leading to a reduction in subendocardial perfusion.

Based on the experimental data on magnesium in AMI, it is possible to formulate hypotheses to help understand that very early administration of magnesium in an animal infarct model can reduce infarct size if reperfusion of the artery occurs early. Moreover, two additional animal studies underscore the fact that magnesium sulfate decreases myocardial infarct size when administered before but not after coronary reperfusion. It should be noted that the beneficial effects of magnesium in the latter two studies were likely the result of a direct myocellular effect as evidenced by the absence of any difference in myocardial blood flow or hemodynamics between the magnesium-treated and control animals. Furthermore, by inhibiting catecholamine release, magnesium may prevent infarct extension.¹⁹

ASSESSMENT OF MAGNESIUM STATUS

Assessing magnesium status is problematic because there is no simple, rapid, and accurate laboratory test

to indicate total body magnesium stores. For the past several decades, the clinical chemistry laboratory has offered two tests to assess magnesium status: the total serum magnesium concentration and magnesium excretion in urine. These two tests address the output of magnesium but do not provide meaningful information about intracellular magnesium. There are several other tests that may be of value in assessing magnesium status and can be organized into three groups: tissue magnesium, physiologic assessment of magnesium, and ionized magnesium.

Tissue magnesium

Determinations of total magnesium in tissue, primarily serum determination, have yielded most of the data on magnesium. Red blood cells (RBCs) and muscle have also been used to assess magnesium status. These tissues predominate in magnesium determinations of tissue content because of the ease of blood and muscle specimen collection. Assays for total tissue magnesium have two difficulties: the physiologically active component of magnesium (ionized magnesium) cannot be specifically determined and information about the total magnesium concentration in one tissue may not provide information about other body pools of magnesium.

Serum

The optimal specimen for determining magnesium is serum, rather than plasma, because an additive such as an anticoagulant could be contaminated with magnesium or affect the assay procedure. Because the magnesium concentration in RBCs is approximately three times greater than that in serum, it is important to prevent hemolysis and to harvest the serum promptly. The serum magnesium concentration is increased by 0.05 mmol/L with the lysis of RBCs to effect a serum hemoglobin concentration of 41.1 mmol/L.

A reference system for magnesium has been established by the National Reference System for Clinical Laboratories of the National Committee for Clinical Laboratory Standards (NCCLS). The definitive method for magnesium is isotope dilution/mass spectrometry and the reference method is flame atomic absorption spectrometry (FAAS). Standard reference material (SRM) 929 is a preparation of magnesium gluconate dihydrate available from the National Institute for Standards and Technology (Gaithersburg, MD). Furthermore, SRM 909 is a human serum with certified values for many analytes, including magnesium.

The determination of the total serum magnesium includes three states: approximately 60% is ionized, nearly 33% is bound to protein, and the remaining 7%

is complexed to phosphate, citrate, and other anions. Approximately 75% of the protein bound fraction is bound to albumin and the remaining 25 % to globulins. The total serum magnesium concentrations (determined by FAAS) in the US population were normally distributed, with the central 95 percentile for adults (aged 18–74) between 0.75 and 0.96 mmol/L. Most clinical laboratories rely on a colorimetric method, using primarily calmagite or methyl thymol blue as the chromophore. The colorimetric procedures are more susceptible to interference by endogenous and exogenous compounds compared with FAAS.

The total serum magnesium concentration, imperfect as it may be, is the entry level test to evaluate magnesium status in humans. The serum magnesium concentration is primarily controlled by the kidney and the dietary intake of magnesium. With the exception of bone, the total serum magnesium concentration has not been shown to correlate with other tissue pools of magnesium. In a study of 14 patients, Alfrey and Miller²⁰ found a correlation coefficient of 0.96 between bone and total serum magnesium concentrations. Other investigators have not confirmed these results. However, a portion of the bone magnesium pool is labile and available to partially support the serum magnesium concentration in states of chronic magnesium deficiency. The serum magnesium concentration may be of value for relatively acute changes in the intake or excretion of magnesium. For example, in a patient treated with furosemide, a loop diuretic, the concentration may decrease suddenly. However, the relationship between the total serum magnesium concentration and the total body magnesium status of a patient is difficult to interpret for several reasons (eg, state, distribution, equilibrium). For chronic changes in magnesium status, the serum magnesium concentration does not provide any significant information. Thus, the primary value of the total serum magnesium concentration is to determine acute changes in magnesium status or establish a baseline value.

Red blood cells

The total RBC magnesium concentration may be determined directly or indirectly using the total magnesium concentration of whole blood and the hematocrit. Deuster and colleagues²¹ evaluated three methods (two direct and one indirect) for determining total magnesium in RBCs and concluded that an indirect method using nitric acid to lyse the cells was reproducible, reliable, accurate, and easy to perform. Nuclear magnetic resonance spectroscopy has been used to determine ionized magnesium in RBCs. The total RBC magnesium concentration does not correlate with other tissue pools of magnesium. Three studies

found no significant concentrations in normal individuals. Six studies documented no correlation between total RBC and total mononuclear blood cell (MBC) magnesium concentrations in normal individuals. One study found no correlation between total muscle and total RBC magnesium. However, the ionized RBC magnesium was significantly greater in control subjects with a normal total serum magnesium concentration than in hypomagnesemic patients. Furthermore, when control individuals were given a low magnesium diet, there was a progressive fall in the total serum and ionized RBC magnesium concentrations. Thus, the ionized RBC magnesium concentration deserves further study.

Changes in total RBC magnesium have been linked to the following three diseases: hypertension, premenstrual syndrome (PMS), and chronic fatigue syndrome (CFS). There is conflicting information for total and ionized RBC magnesium in essential hypertension. An increase and no change have been reported for the total RBC magnesium concentration in patients with essential hypertension compared with normotensive controls. For ionized RBC magnesium in essential hypertension, one study found a significant decrease and another found no significant change compared with normotensive controls. Three groups found a decrease in total RBC magnesium in women with PMS. In a double-blind, randomized study, women with PMS who received an oral magnesium preparation (1080 mg of elemental magnesium daily) showed improved symptoms over those who received placebo.²¹ Last, patients with CFS had a significant decrease in total RBC magnesium and benefited from intramuscular magnesium. Another study assessed magnesium status in patients with CFS and in controls using the magnesium retention test and found no difference between RBC magnesium and the three diseases previously described.²² Clearly, more research is needed to understand the possible relationship between magnesium and hypertension, CFS, and PMS.

Mononuclear blood cells

The use of the total MBC test as a surrogate for the estimate of intracellular magnesium was proposed during the Second International Magnesium Symposium in 1976. Several studies with normal individuals have not shown a correlation between total MBC magnesium and that of serum or RBCs. Two studies found a correlation between total MBC magnesium and total muscle magnesium in humans. Dyckner and Wester²² initially found a correlation ($R = .74$) between total MBC magnesium and total muscle magnesium concentrations with nine individuals (three controls and six patients with hypertension), but the correlation be-

came nonsignificant ($R = .22$) when 16 patients with congestive heart failure were added to the study. Sjögren and colleagues²³ found a significant correlation between total MBC magnesium and total muscle magnesium in patients with type I diabetes mellitus. Studies with rats depleted by administration of furosemide did not find a correlation between total MBC and total cardiac or skeletal muscle magnesium concentration. Additional studies are needed to determine the relationship between total MBC magnesium and total muscle magnesium. Thus, the value of the total MBC magnesium test has yet to be determined.

Muscle

Muscle is an appropriate and important tissue for the assessment of magnesium status because it contains approximately 30% of the total body magnesium. However, relatively few studies have determined total muscle magnesium in humans because of the special skills and expense of the assay, which involves needle biopsy of the muscle, preparation of the tissue, and determination of magnesium by FAAS. Several studies have documented a lack of correlation between muscle and serum or RBC total magnesium concentrations. As indicated previously, the correlation between muscle and MBC total magnesium for humans is equivocal. More promising is the use of nuclear magnetic resonance spectroscopy to determine ionized magnesium noninvasively in muscle *in vivo*.

THERAPEUTIC IMPLICATIONS OF MAGNESIUM REPLACEMENT

The exact dose required in magnesium deficiency is poorly understood and dosing recommendations vary widely. It is important to establish the presence of adequate renal function before initiating treatment with magnesium. In severely ill hospitalized patients, administration of parenteral 50% MgSO_4 (magnesium sulfate) (2.1 mmol Mg/mL) is the preferred mode of therapy. Flink²⁴ recommends administering 48 mmol of intramuscular magnesium on hospital day 1 and injecting 17 to 25 mmol per day for the next 4 days. For the critically ill, convulsing hypomagnesemic patient, Flink recommends an intravenous loading dose of MgSO_4 4g (16 mmol Mg) followed by 48 mmol for the remainder of the day. On each of days 2 to 5, 25 mmol Mg is administered in divided doses, diluted in the day's intravenous fluids.

In the critically ill magnesium-deficient patient with ventricular tachycardia and/or fibrillation, Iseri et al²⁵ recommend that 10 to 15 mL 20% MgSO_4 (8–12 mmol

Mg) be administered intravenously as a bolus over 1 minute. This is followed by 500 mL 2% MgSO_4 (40 mmol Mg) over the next 5 hours. If necessary, another 500 mL 2% MgSO_4 may be administered over the next 10 hours. As with potassium, magnesium therapy is interdicted with onset of renal failure. Parenteral magnesium therapy should be interrupted whenever hypotension (80 mm Hg systolic) or bradycardia (<60 beats/min) occur, serum magnesium concentrations exceed 2.5 mmol/L or when deep tendon reflexes disappear.

In the less critically ill, hypomagnesemic patient, oral magnesium replenishment is preferred. Oral repletion can be accomplished with magnesium oxide, magnesium lactate, and magnesium-containing antacids, such as Maalox or Mylanta. Gullestad et al²⁶ reported that in a group of 40 magnesium-depleted elderly patients (average age, 71) receiving oral magnesium (15 mmol daily) repletion was well tolerated. Only four patients (10%) reported mild diarrhea. Magnesium repletion was 7 days vs. 6 weeks. This affirms the importance of parenteral magnesium repletion in treating critically ill patients.

It is estimated that the total body store of magnesium is approximately 21 to 28 g or 1700 to 2300 mEq. Maintenance of necessary magnesium balance requires a daily dietary intake of at least 24 to 30 mEq, which is the official US recommended daily allowance (RDA) [1 g Mg = 83.3 mEq (41.1 mmol) or 1 mMole = 12 mg Mg or 1 mMole = 24.3 mg Mg]. The RDA for men is 350 to 400 mg, and for women, the value is 280 to 300 mg. For a complete listing of RDAs by gender, age, and specific condition, the reader should refer to RDA tables. Accurate measurement of total-body magnesium level is difficult because of the intracellular location of this element. Despite the limitations of the serum magnesium level, which corresponds to less than 1% of total body magnesium, this determination is by far the most available and represents the most expeditious method of evaluating possible disorders of magnesium metabolism. A magnesium level of less than 1.5 mEq/L is considered hypomagnesemic, and patients with magnesium levels greater than 2.1 Eq/L are considered hypermagnesemic.²⁷

Data regarding biopharmaceutics and pharmacokinetics of various magnesium salts appear to be limited. Conscientious effort was made to acquire as much data as possible from the literature (Table 1) and the conclusions presented here are based on the values that are reported in this table.

The use of magnesium sulfate (Epsom salt) as a cathartic in patients with impaired renal function can lead to severe toxicity owing to hypermagnesemia. Although toxicity is uncommon in healthy subjects, little

Table 1. Magnesium comparison chart.

Magnesium salts	Carbonate ⁴⁶	Chloride ^{38*}	Citrate ^{39,40†}	Fumarate ⁴³	Gluconate ^{38†}	Glycinate ⁴⁵
Elemental Mg++/ dose, mg (mEq)	232 (19.0)	64 (5.26)	—(25)	530 (44.16)	27 (2.2, tablets) 54 (4.4, liquid)	100 (8.33)
Solubility in water	Nearly insoluble	High	Very good	Good	Moderate	Good
Bioavailability	Extremely low	Good	Good	Good	Good; similar to chloride	Good
Oral absorption, % (mEq)		19.68 (1.04)	29.64 (ionic)		19.25 (0.82–0.43)	23.5
Delivery system	Tablets	Enteric coated tablets	Liquid, tablets	Tablets	Tablets, liquid	Ingestion
Dosage	70 mg elemental Mg (each tablet)	640 mg/d, 1–2 tabs TID	25 mEq Mg, 2–5 tablets	1 Tablet	648 mg/d, 2–4 tablets TID	100 mg
Side effects	GI distress, diarrhea	GI distress, diarrhea	Laxative, evacuant		GI distress, diarrhea	
Comments	Not very soluble at pH of GI tract; some GI side effects; laxative	Enteric coating could delay absorption; some GI side effects; cathartic	Therapy-limiting side effects; limited absorption; low citraturic response		Expensive formulation to achieve recommended daily allowance requirements	Good alternative in patients with intestinal resection

is known concerning the extent of absorption of magnesium after a cathartic dose of magnesium sulfate. The bioavailability of magnesium after a large oral dose of magnesium sulfate in normal volunteers was examined in the current investigation. Baseline 24-hour urinary excretion rates of magnesium and creatinine were determined over 3 consecutive days in six healthy men. The oral administration of 13.0 g (56.5 mmole) magnesium sulfate U.S.P., in four equal hourly increments, resulted in the urinary excretion (corrected for baseline excretion rate) of $4.0 \pm 2.9\%$ (mean \pm SD) of the dose of magnesium during the first 24 hours and $6.0 \pm 7.0\%$ of the dose during a 72-hour interval. Magnesium sulfate administration had no effect on the 24-hour urinary excretion rate of creatinine.

The baseline excretion rate of magnesium was significantly correlated with that of creatinine ($R = .875$) and inorganic sulfate ($R = .921$). All the subjects experienced mild or moderate diarrhea. Therefore, the authors concluded that magnesium is absorbed to a limited and variable extent in healthy adults after a cathartic dose of magnesium sulfate.²⁸

Magnesium sulfate is also the agent most commonly used for treatment of eclampsia and prophylaxis in patients with severe pre-eclampsia. It is usually given by either the intramuscular or intravenous route. The intramuscular regimen is most commonly a 4-g intravenous loading dose, immediately followed by 10 g intramuscularly and then by 5 g every 4 hours in alternating buttocks. The intravenous regimen is given

L-lactate ^{48,49§}	Oxide ^{37,40}	K Mg citrate ^{41**}	DL aspartate ⁴⁷	L aspartate ³⁷	Hydrox- ide ^{44¶}	Salicylate ³⁶	Sulfate ^{42#}	Aminoate ⁵⁰
84 (7)	241 (19–8)	—(24.5)	5	5	2 × 10.3 mmol	600	56.5 mmols	500 (41.6)
Excellent	Extremely low, 8.6 mg/IL	High solubility	Good	Good	Practically insoluble	Freely soluble	Moderately soluble	
Excellent	Extremely low	Good; similar to Mg citrate				86–100%		
42.3 (2.96)	22.8 (0.39) (2% ionic)		44.5	41.7			4 (oral dose), limited and variable extent	
Sustained- release caplets	Tablets, capsules	Tablet	Tablet	Tablet	Tablet (Maalox)	Tablet	IV solution	Tablet
1–2 caplets q 12 h	2–4 tabs TID	7 tablets, 3–5 mEq Mg ea	1 Tablet	1 Tablet	2 Tablets	600 mg, 1 tablet	Intravenous Mg 9.9–49.3 mg/ml	1 Tablet, 3 tablets (100 mg ea Mg)
Minor GI disturb- ances	Emesis, diarrhea	No GI side effects			Occasional regurgita- tion and mild diarrhea			
Sustained release increases absorption, reduces side effects; cathartic	Virtually insoluble at pH of GI tract; some GI side effects; antacid	Yielded a greater citratu- ric response in addition to primary absorbable K & Mg			Antacid; cathartic	Internal, antiinfective	Parenteral use may lead to magnesium toxicity	

*Cl serum level V_{dr} , 1.8 mg/dL.

†Urinary cumulative (excretion) increment, 16.5 mg/d; urinary peak excretion rate, 7.7 mg/h.

‡Cl serum level V_{dr} , 1.63 mg/dL.

§Cl serum level V_{dr} , whole blood 1.55 mmol/L; urinary cumulative (excretion) increment, 14.75 mmol/d.

¶ $t_{1/2}$, 52.3 min (Maalox, Rhone-Poulenc Rorer Pharmaceuticals, Collegeville, PA).

||AUC, 920 µgh/mL; $t_{1/2}$, 8.0 h; C_{max} , 117.0 µg/mL; t_{max} , 1.0 h.

#Cl plasma level V_{dr} , 0.82–1.2 mM, 2.42 mM/L; urinary cumulative (excretion) increment, ~7% dose; urinary peak excretion rate, 4.0% first 24 h then 6.9% at 72 h.

**Urinary cumulative increment 14.1 mg/d; urinary excretion rate 7.2 mg/h.

GI, gastrointestinal.

as a 4-g dose, followed by a maintenance infusion of 1 to 2 g/h by controlled infusion pump.

After administration, approximately 40% of plasma magnesium is protein bound. The unbound magnesium ion diffuses into the extravascular-extracellular space, into bone, across the placenta and fetal membranes, and into the fetus and amniotic fluid. In preg-

nant women, apparent volumes of distribution usually reach constant values between the third and fourth hours after administration and range from 0.250 to 0.442 L/kg. Magnesium is almost exclusively excreted in the urine, with 90% of the dose excreted during the first 24 hours after an intravenous infusion of magnesium sulfate. The pharmacokinetic profile of

magnesium sulfate after intravenous administration can be described by a two-compartment model with a rapid distribution (α) phase, followed by a relative slow β phase of elimination.

The clinical effect and toxicity of magnesium sulfate can be linked to its concentration in plasma. A concentration of 1.8 to 3.0 mmol/L has been suggested for treatment of eclamptic convulsions. The actual magnesium dose and concentration needed for prophylaxis has never been estimated. Maternal toxicity is rare when magnesium sulfate is carefully administered and monitored. The first warning of impending toxicity in the mother is loss of the patellar reflex at plasma concentrations between 3/5 and 5 mmol/L. Respiratory paralysis occurs at 5 to 6/5 mmol/L. Cardiac conduction is altered at greater than 7.5 mmol/L, and cardiac arrest can be expected when concentrations of magnesium exceed 12.5 mmol/L. Careful attention to the monitoring guidelines can prevent toxicity. Deep tendon reflexes, respiratory rate, urine output, and serum concentrations are the most commonly followed variables.²⁹

Several factors affect the concentration and distribution of magnesium in patients with chronic renal failure (CRF). Poor nutritional intake, impaired absorption from the intestine, vomiting, diarrhea, the use of diuretics, and acidosis may result in a negative balance. More commonly, accumulation of magnesium may be the consequence of reduced renal excretion. Magnesium concentrations are increased in serum and RBCs in CRF patients. Bone concentrations and total body magnesium also appear to be increased; muscle magnesium does not appear to be increased. Use of magnesium hydroxide-containing antacids as phosphate binders in patients with CRF was largely discontinued two decades ago after reports described increases in serum magnesium concentrations to toxic levels. More recently, the undesirable effects of aluminum-containing phosphate binders (encephalopathy, osteomalacia) have led several investigators to report favorable experiences using low concentrations of magnesium in dialysate and combination of magnesium and aluminum-containing antacids, as phosphate binders, while closely monitoring serum magnesium concentrations.

Mason³⁰ studied salicylate plasma levels after administration of solid dose forms of aspirin, magnesium salicylate, and choline magnesium trisalicylate in healthy volunteers. Based on this study, there were no significant differences in the rate and extent of absorption of salicylate and it was not altered by these dose forms.

The extent of water solubility of magnesium salts appears to play an important role in the bioavailability

and oral absorption of these test compounds. Magnesium L-lactate and aspartate have the greatest water solubility, and, as a result, they exhibit greater bioavailability and oral absorption (and probably urinary excretion). The magnesium compound having good availability tends to possess greater serum (plasma) concentration. Magnesium salts of organic acids compared with those of inorganic acids have greater water solubility and therefore greater bioavailability and oral absorption. Among magnesium salts, magnesium sulfate has been extensively studied after intravenous administration and its palliative usefulness has been constantly demonstrated. Magnesium sulfate is known to be moderately soluble in aqueous preparations. Water solubility can be increased by administration of chelate salts of magnesium as in the case with magnesium salicylate. Most commonly used magnesium salts and their biopharmaceutics data are summarized in the Table 1. Other magnesium salts not as commonly used, for example, are salts of mandelic acid, phosphoric acid, silicic acid, hydrobromic acid, and boric acid, and these have been prepared and shown to possess some less significant biological activities as well.

CLINICAL TRIAL RESULTS OF MAGNESIUM THERAPY

In several articles, Antman et al³¹⁻³³ reviewed extensively the pros and cons of magnesium therapy. Magnesium is a coronary and hyperemic vasodilator calcium antagonist, antiarrhythmic agent, and antiplatelet drug that modulates autonomic function and limits reperfusion injury when given early in the setup of myocardial infarction. Magnesium blocks calcium entry into vascular smooth muscle cells via voltage- and receptor-operated channels and diminishes the reaction of vascular smooth muscle cells to various stimuli. Magnesium reduces the release of calcium form by actually dividing calcium into the sarcoplasmic reticulum, and it has important electrophysiologic effects that serve to maintain ionic balance across sarcolemmal membranes. However, magnesium also can induce complete heart block, cardiogenic shock, renal failure, symptomatic sinus bradycardia, and hypotension. Administration of magnesium is an inexpensive, easily administered therapy and its one of the advantages is that it can protect against reperfusion injury by inhibiting calcium influx into myocytes and thus reduce short-term mortality.

Recently, general clinical trials of magnesium in patients with AMI such as the Fourth International Study of Infarct Survival³⁴ and Second Leicester Intra-

venous Magnesium Intervention Trial³⁵ were conducted. The results of these trials have both supported and opposed a clinically important role of magnesium in MI therapy. Antman et al³⁶ after reviewing the subject concluded that the benefit of magnesium remains an open question despite the large number of patients enrolled in the trials. According to Antman et al, although hypothetical arguments against the use of magnesium have been raised (eg, suppression of release catecholamines from the adrenal gland and compromise of myocardial contractility), such arguments are outweighed by models demonstrating a reduced infarct size. Also clinical reports of reduction of the mortality rate when magnesium is administered during myocardial infarction in some studies is most important. However, careful selection of the patient and dose are critical for the appropriate use of magnesium. Boluses delivered too rapidly may provoke hypotension and coronary hypoperfusion, especially in patients receiving other vasodilators.³⁷

CONCLUSION

More knowledge about magnesium absorption, distribution, metabolism, and excretion is needed to use this agent effectively. Magnesium is known to play an important role in conditions such as AMI, atherosclerosis, hypertension, arrhythmias, diabetes mellitus, alcoholism, aldosteronism, hyperthyroidism, and renal tubular disorders.³⁸⁻⁴⁵ Magnesium therapy, for deficiency replacement and in higher pharmacologic doses, has been beneficial in improving hemodynamics.⁴⁶⁻⁵² The role of magnesium on biochemical and cellular levels, especially in cardiac cells, is crucial in maintaining stable cardiovascular hemodynamics and electrophysiologic function.⁵³ Among the common electrolytes, the difficulty in the accurate measurement of magnesium ion is well known. Furthermore, sophisticated, sensitive, and perhaps noninvasive (avoiding muscle biopsies) techniques for assaying this cation in serum (or plasma) and determining tissue levels will be available for routine use so that reliable, reproducible, and meaningful data can be accumulated. In the absence of routine serum magnesium estimation, detection of hypokalemia may trigger an order for serum magnesium determination in view of the high frequency of hypermagnesemia found in potassium-deficient patients. Prompt recognition and treatment of coexisting hypomagnesemia in hypokalemic patients can assist in avoiding the problem of patients who are refractory to potassium repletion.⁵⁴ Hyponatremia, hypophosphatemia, and hypocalcemia also are electrolyte abnormalities that war-

rant an investigation for an accurate serum magnesium determination. In the past, magnesium may have been forgotten because the knowledge of other elements has been greater and were directly related to syndromes in clinical medicine. As our knowledge about magnesium advances and technology permits us to undertake rapid determinations in a consistently reliable manner for the physiologically active ionized fraction or species of magnesium, the importance of magnesium in health and diseases will become more apparent and magnesium replacement therapy employed more frequently.

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