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

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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 sarcoplasmatic 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 investigators[1] 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]

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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 diphasic 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 toxicity[2] 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 al[3] 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 congestive 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 internal, 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 al[5] 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 al[6] 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 al[7] 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 Hao[8] 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 al[9] 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 Na^+-K^+-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 Na^+-K^+-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 Seelig[11] 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 al[12] 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 Opie[18] 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 animals 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%