Magnesium plays a vital role in the daily functions of many organ systems. Magnesium is a cofactor for ATP production and thus fundamental to all biologic processes within the body. Recently, attention has been given to abnormalities of serum magnesium in companion animals. In human and veterinary intensive care units, disturbances in serum magnesium concentrations not only are common but also may play a role in mortality and survival. The following discussion reviews the normal physiology of magnesium; metabolism; and the causes, diagnosis, and treatment of hypomagnesemia and hypermagnesemia. A review of current veterinary literature pertaining to magnesium disturbances is also presented.

FUNCTIONS OF MAGNESIUM

Magnesium is important for many of the body’s metabolic functions. It is vital in the production of ATP and is a cofactor for more than 300 cellular enzyme reactions. In addition to being used as a coenzyme for the sodium–potassium–ATPase pump that functions to maintain ion gradients across cell membranes, magnesium is a coenzyme for the calcium–ATPase and proton pumps. Alternations in ATPase pump function affect membrane potentials and gradients, explaining the role of magnesium in proper skeletal and cardiac muscle function. Magnesium is also vital for nucleic acid synthesis and protein synthesis.

Magnesium helps regulate intracellular calcium levels by blocking calcium channels. One established mechanism for this effect is that magnesium noncompetitively binds calcium channels directly. Magnesium also inhibits the transmembrane–receptor binding sites for inositol 1,4,5-triphosphate–gated calcium channels, preventing opening of the ion channels. Other sites for the calcium channel–blocking effects of magnesium are still under investigation. Due to its effects on different ion pumps, magnesium plays a role in the regulation of smooth muscle vascular tone and, subsequently, blood pressure regulation. Hypotension is one of the predominant cardiovascular abnormalities of hypermagnesemia in both human and veterinary patients, although the exact pathogenesis is unknown.

ABSTRACT: Magnesium alterations can have a noticeable effect on the neuromuscular, cardiovascular, and metabolic systems. With recent advances in point-of-care testing, it is now easier to monitor for changes in the serum magnesium concentration and implement therapies in the critical care setting. This article reviews the normal homeostatic mechanisms, clinical abnormalities, and therapeutic strategies for magnesium disturbances in critically ill patients.
MAGNESIUM DISTRIBUTION
Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation. Most of the body’s magnesium (50% to 60%) is located within bone; the remainder is distributed throughout the body, including skeletal muscle, the heart, and the liver. The majority of magnesium that is not located in bone is found in intracellular stores, with less than 2% in the extracellular fluid. One-third of the magnesium in bone is exchangeable with serum; the rest of the intracellular magnesium moves between the intracellular and extracellular space in a fashion similar to potassium.

Within the serum, magnesium is found in three forms. The first form is the ionized active form, constituting 55% of the magnesium in serum; the second form, making up 15%, is the magnesium fraction that is complexed to anions, such as phosphate, bicarbonate, and citrate; the third form is the protein-bound fraction, comprising the final 30% (the majority of this fraction is bound to albumin).

REGULATION WITHIN THE BODY
Magnesium homeostasis occurs largely through regulation of intestinal absorption and renal excretion. Although many hormones are involved in the regulation of magnesium, such as adrenal, thyroid, and parathyroid hormones, no single substance has been found to play a primary role. Within the intestinal tract, magnesium is absorbed primarily through the jejunum and ileum, with the colon and rectum absorbing smaller amounts. Bioavailability does play a role in intestinal absorption. Diets that contain large amounts of free fatty acids, oxalate, phosphates, and fiber decrease whole body levels by binding the magnesium and preventing its absorption. In addition, high-calcium diets may interfere with magnesium absorption.

Low dietary magnesium levels increase the fractional absorption of magnesium in the gastrointestinal tract. Various studies in humans have conflicting findings on vitamin D regulation of intestinal absorption of magnesium, with results showing both vitamin D–dependent and vitamin D–independent methods of magnesium absorption. Parathyroid hormone (PTH) has also been investigated. Although it may act to decrease urinary magnesium excretion in the kidneys at high doses experimentally, evidence of PTH regulation of magnesium in the body has not been established.

Like many other substances in the body, primary excretion of magnesium is through renal mechanisms. Plasma magnesium concentration is regulated within a tight range by the kidneys. Under normal circumstances, increased magnesium intake stimulates increased excretion by the kidneys, preventing accumulation within the body. As the glomerular filtration rate decreases, so does the excretion of magnesium. As a consequence, renal impairment is a common cause of hypermagnesemia.

The majority of the magnesium presented to the glomerulus is freely filtered. Most (70%) is reabsorbed in the thick ascending limb of the loop of Henle, where it is actively transported, whereas approximately 30% of filtered magnesium is reabsorbed passively in the proximal tubules. Movement of the magnesium back into the peritubular fluid occurs via electrical gradients formed by the active transport of sodium chloride. Magnesium is also excreted in milk and is lost in lactating animals.

DIAGNOSIS AND MEASUREMENT
Although low total serum magnesium levels reflect total body depletion, normal serum magnesium levels may exist in the presence of total body depletion. Despite this, measuring serum levels remains the easiest and most available option for assessing magnesium status. Methods such as measuring ultrafilterable magnesium via centrifugation were used prior to the availability of magnesium with ion-selective electrodes. Ultrafilterable magnesium is the non–protein-bound fraction in the serum and includes both ionized magnesium and magnesium complexed with anions.

Veterinary studies have evaluated ionized, total serum, and total body magnesium levels. Bechuk and colleagues evaluated in situ ionized magnesium levels from abdominal muscle tissue samples of animals undergoing surgery for gastric dilatation–volvulus and compared these with serum magnesium levels. The
study, which was aimed at comparing magnesium levels in dogs with and without cardiac arrhythmias, found no correlation between serum magnesium levels and tissue ionized magnesium levels.

Established normal values exist for serum levels of total and ionized magnesium; however, these numbers vary, depending on the laboratory, population base, and machine being used. Current literature focuses on ionized magnesium now that the use of analyzers with ion-selective electrodes is more widespread. Recent studies evaluating both total and ionized serum magnesium have found a higher prevalence of magnesium abnormalities than in earlier literature,15,18,20–22; however, this may be a factor of better diagnostics and awareness of this ion in medicine today. It is unclear at this time whether ionized magnesium levels would correlate better with clinical signs than total magnesium levels in veterinary patients.

The diagnosis is often made from evaluation of biochemical profiles in sick animals. Most patients with mild hypomagnesemia remain asymptomatic, and the condition may resolve with treatment of the underlying cause.23 Normal ranges for total magnesium levels are provided in Table 1.

### HYPMAGNESEMIA

In humans, studies have long shown hypomagnesemia to be prevalent and important.21,22,24 Although study findings differ, an incidence greater than 50% has been found in some intensive care unit populations.20 Recent studies documented in the veterinary literature have also shown hypomagnesemia to be a common finding.15,18 Hypomagnesemia is most often caused by decreased intestinal absorption or increased renal loss.8 It can also be caused by redistribution between intracellular and extracellular stores (see box on this page). An example of this was shown in a study in which insulin injections given to rabbits caused increased magnesium uptake in a number of tissues, leading to increased levels of intracellular magnesium.10

Redistribution due to blood transfusion or disease states, such as pancreatitis, refeeding syndrome, and sepsis, is also possible. These diseases can cause chelation or sequestration of magnesium.1 Hyperadrenergic states such as sepsis can cause intracellular shifts as well as release of free fatty acids that chelate serum magnesium. Alternatively, treatment of certain disease states (e.g., insulin administration in diabetes) can cause intracellular shifts in magnesium.1,5,10

Animals in critical care settings are predisposed to hypomagnesemia for a variety of reasons. Peritoneal dialysis, diuretics, massive blood transfusions, or aggressive fluid therapy can initiate redistribution or increase renal losses.1,5 Clinicians should maintain a high index of suspicion for development of hypomagnesemia in patients that are at high risk, such as animals with diabetes mellitus or that are receiving diuretics.

### Clinical Signs

Hypomagnesemia manifests itself mainly through neuromuscular and cardiac abnormalities1,8 (see box on page 423). It can also affect other electrolytes within the body. Weakness, arrhythmias, and even esophageal motility disorders can occur.5 Experimental magnesium deficiency in dogs has been associated with neural and neuromuscular hyperexcitability. Signs include tetany, muscle spasms, fasciculations, and tremors. Ataxia, nys-
Magnesium Disturbances in Critically Ill Patients

In critically ill patients, magnesium disturbances can manifest in various forms, including neuromuscular, cardiac, and electrolyte abnormalities. These disturbances can lead to symptoms such as muscle tetany, tremors, seizure activity, ataxia, electrocardiographic changes, hypokalemia, hypocalcemia, and arrhythmias. The mechanisms behind these effects include the stimulation of acetylcholine release at the motor end plate and the intricate balance of magnesium and calcium. A decrease in the concentration of magnesium lowers the depolarization threshold of tissues, increasing neuronal excitability. Concurrent electrolyte abnormalities such as hypokalemia can potentiate the neuromuscular signs.

Hypomagnesemia is associated with a variety of cardiac arrhythmias in humans. Those mentioned in the literature include ventricular premature depolarization, ventricular tachycardia, atrial premature contractions, atrial fibrillation, supraventricular tachycardia, and torsades de pointes. Although these arrhythmias may occur in animals with hypomagnesemia as well, no definitive studies have documented them. The mechanism of arrhythmias revolves around magnesium limiting the loss of potassium from the myocardial cells and maintaining the plateau phase of the action potential. Magnesium depletion inhibits the sodium–potassium–ATPase pump and causes outward net movement of potassium from the cells. This drop in potassium decreases the resting membrane potential and leads to depolarization of the cell, which in turn causes an increase in excitability and subsequent arrhythmias. This mechanism is also the reason magnesium augments digoxin toxicity. There is not only a decrease in intracellular potassium but also an increase in intracellular calcium, which increases the toxic side effects of cardiac glycosides such as digitalis. The use of loop diuretics in cardiac patients may worsen the situation by causing magnesium wasting.

Metabolic disturbances have been well documented in the human literature in conjunction with hypomagnesemia. In dogs, hyponatremia has been associated with hypomagnesemia. The more common abnormalities include hypocalcemia and hypokalemia. One study documented that 22% of hypomagnesemic patients had concurrent hypokalemia. Calcium therapy was refractory unless magnesium was also supplemented. The mechanism by which this occurs is still unclear; however, low magnesium concentrations are known to impair the release of, and decrease organ response to, PTH.

Hypokalemia associated with hypomagnesemia is also well documented. In humans, concurrent hypokalemia has been reported in up to 42% of hypomagnesemic patients. One veterinary study reported hypokalemia in 31% of hypomagnesemic dogs. Low magnesium levels can cause kaliuresis due to impaired reabsorption at the proximal tubule as well as increased distal tubular potassium secretion. Similar to hypocalcemia, once magnesium supplementation is started, potassium levels begin to respond to appropriate therapy.

### Clinical Signs of Hypomagnesemia

<table>
<thead>
<tr>
<th>Neuromuscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Muscle tetany, tremors</td>
</tr>
<tr>
<td>• Seizure activity</td>
</tr>
<tr>
<td>• Ataxia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Electrocardiographic changes</td>
</tr>
<tr>
<td>— Peaked T waves</td>
</tr>
<tr>
<td>— Mild ST-segment depression</td>
</tr>
<tr>
<td>• Arrhythmias</td>
</tr>
<tr>
<td>— Ventricular tachycardia</td>
</tr>
<tr>
<td>— Torsades de pointes</td>
</tr>
<tr>
<td>— Supraventricular tachycardia</td>
</tr>
<tr>
<td>• Atrial fibrillation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrolyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypokalemia</td>
</tr>
<tr>
<td>• Hypocalcemia</td>
</tr>
</tbody>
</table>

**Hypomagnesemia is most often associated with decreased intake or increased loss of magnesium through renal or gastrointestinal routes.**
Magnesium Disturbances in Critically Ill Patients

424

excretion. Other contraindications for magnesium supple-
mentation include established hypermagnesemia and
myasthenia gravis. Because of its effects on muscle via
its calcium antagonistic effect, magnesium supple-
mentation in humans with myasthenia increases muscle
weakness and may lead patients to decompensate or to
have an acute crisis.

Long-term oral supplementation may be necessary in
some patients. An example of this would be a patient on
long-term diuretic and digoxin therapy. Oral supple-
mentation can be accom-
plicated with available for-
mulations (Table 2). Magnesium sulfate (Epsom salt) should
be avoided because of its cathartic effects. Recom-
manded canine doses are 1 to 2 mEq/kg/day; no specific
doses have been published for cats.

In patients with normal magnesium levels or mild
cases of hypomagnesemia, fluids that contain magnesium
can alter hemodynamics and should be given only in
emergency situations. Overdoses can be treated with
calcium gluconate (described in the following section).

During supplementation, it is important to monitor
serum electrolytes. We recommend checking magne-
sium, potassium, and calcium levels every 6 to 12 hours,
as no published data exist on the frequency of monitor-
ing. Renal function should be assessed before therapy is
started, and the dose should be reduced by 50% to 75%
when insufficiency and azotemia are present. Iatrogenic
oversupplementation or overly rapid administration can
produce toxicity, leading to signs of weakness, hypo-
tension, and respiratory depression.

HYPERMAGNESEMIA

Hypermagnesemia has been documented much less
often than hypomagnesemia. In a study of animals that
were admitted to an intensive care unit with a variety of
illnesses, six of 48 dogs were hypermagnesemic com-
pared with 26 of 48 dogs that were hypomagnesemic.
The most common cause of elevated magnesium is renal
insufficiency or failure. In addition, iatrogenic overdose
has been documented and could result from parenteral
supplementation, oral antacids, or magnesium-contain-
ing cathartics.

A study reported two cases of iatrogenic hypermagne-
semia. The animals in both cases were treated for hypo-
magnesemia and were overdosed, with clinical signs
consistent with excess ionized magnesium. Both animals
were treated successfully without further complications.

Table 2. Available Formulations of Magnesium Supplementation

<table>
<thead>
<tr>
<th>Route</th>
<th>Available Formulations</th>
<th>Magnesium Concentration</th>
<th>Incompatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Magnesium gluconate</td>
<td>Variable</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Magnesium oxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Magnesium carbonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenteral</td>
<td>Magnesium sulfate</td>
<td>50% solution: 4 mEq/ml</td>
<td>Lipid emulsion 10%</td>
</tr>
<tr>
<td></td>
<td>(MgSO₄)</td>
<td>12.5% solution: 1 mEq/ml</td>
<td>Dobutamine hydrochloride</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sodium bicarbonate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Solutions containing calcium or lactate</td>
</tr>
<tr>
<td></td>
<td>Magnesium chloride (MgCl₂)</td>
<td>20% solution: 1.97 mEq/ml</td>
<td>Same as MgSO₄</td>
</tr>
<tr>
<td></td>
<td>Normosol-R</td>
<td>3 mEq/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma-Lyte 148</td>
<td>3 mEq/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma-Lyte 56</td>
<td>3 mEq/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma-Lyte M</td>
<td>3 mEq/L</td>
<td></td>
</tr>
</tbody>
</table>

7,8 We suggest
monitoring arterial blood pressure every 4 to 6 hours
during therapy.
Clinical Signs

Clinical signs of hypermagnesemia include depression, weakness, and hypotension; early signs include a loss of deep tendon reflexes. Hypotension related to a loss of vascular resistance can occur because of the effect of magnesium on calcium channels. If hypermagnesemia is severe enough, respiratory depression can develop due to the neuromuscular-blocking effects of magnesium. The mechanism for this effect is high serum magnesium concentrations blocking the calcium-dependent release of acetylcholine at the presynaptic neuromuscular junction.

Electrocardiographic changes, such as prolongation of the P–R interval and QRS duration, may also occur. These changes result from delayed conduction through the heart (atrioventricular and interventricular areas). As the magnesium concentration rises in the serum, cardiovascular signs progress. Initial findings may include an increase in heart rate with a drop in systemic vascular resistance and an increase in cardiac output. As magnesium levels climb, the heart rate returns to normal and QRS prolongation occurs. With highly elevated levels, there is a drop in mean arterial pressure and an increase in the P–Q interval. Eventually, with total magnesium levels higher than 4 mg/dl or a cumulative dose of more than 5.9 mEq/kg, ventricular fibrillation, asystole, and death can occur.

Treatment

The treatment of hypermagnesemia involves discontinuation of any supplementation. Monitoring arterial blood pressure, ionized magnesium levels, and electrocardiographic changes helps the clinician decide whether treatment is necessary. The next step in treatment should be geared toward increasing the renal excretion of magnesium by providing sodium-containing fluids to increase diuresis and promote urinary excretion. Loop diuretics can be administered to increase magnesium wasting.

Because a potential adverse effect of treatment is hypokalemia, electrolytes should be carefully monitored. In patients with moderate or severe renal dysfunction, dialysis (peritoneal or hemodialysis) may be necessary. Patients exhibiting severe neuromuscular signs may require intubation and mechanical ventilation until the magnesium can be cleared from the body. This severity of clinical signs has not been reported in veterinary medicine. In the only study that documents hypermagnesemia resulting from overdose, moderate to severe mental depression, hypotension, and bradycardia occurred, but all cases were diagnosed and treated before intubation became necessary. Because of the physiologic role of magnesium in the blockade of the autonomic nervous system, its effects could be antagonized by anti-cholinesterases, although intravenous calcium is the first-line treatment of choice.

When electrocardiographic or clinical signs are severe, the use of calcium gluconate is recommended. Calcium directly antagonizes magnesium at the neuromuscular junction. A dose of 50 to 150 mg/kg of calcium gluconate diluted by 50% in normal saline can be given as a slow intravenous bolus over 10 to 20 minutes. This dose can be repeated or followed with a continuous-rate infusion at 10 to 15 mg/kg/hr as needed. Continuous electrocardiographic monitoring is important during bolus therapy.

Hypomagnesemia can potentiate hypokalemia and hypocalcemia. Because magnesium blocks calcium channels on cell membranes, hypermagnesemia can cause hypotension, muscle weakness, and electrocardiographic abnormalities.

Magnesium Therapy in Patients with Normal Magnesium Levels

Magnesium has been used extensively as a therapeutic agent in patients with normal measured serum magnesium concentrations. In humans, an intravenous bolus of 1 to 6 g of magnesium over 20 to 30 minutes is given for therapeutic purposes. It has been used for treatment of cardiac arrhythmias, asthma, preeclampsia, eclampsia, and premature labor and as an adjunct during cardiopulmonary resuscitation.

Magnesium has been found to decrease bronchoconstriction and to relax uterine contractions. Both of these effects have been linked to inhibition of acetylcholine release at neuromuscular junctions and subsequent blockage of calcium influx by magnesium. In severe acute asthmatic attacks in humans, the effect of magnesium has been postulated to be multifactorial. First, it has been shown to relax smooth muscle via its inhibition of calcium channels, directly impairing bronchoconstric-
Magnesium Disturbances in Critically Ill Patients

The physiologic theory continues to revolve around the magnesium-antagonizing effect of calcium. One theory proposed that magnesium may block calcium channels in the brain. This action could prevent vasospasm, interfere with calcium-mediated reperfusion reactions, and decrease toxic mediators.

CONCLUSION

The use of magnesium in both human and veterinary medicine remains controversial. Appropriate testing and treatment recommendations are still a matter of debate. Despite this, evidence suggests that magnesium disturbances do occur in hospitalized companion animals. The most common clinical manifestations of hypomagnesemia include neuromuscular excitability, cardiac arrhythmias, and metabolic disturbances affecting other electrolytes. Manifestations of hypermagnesemia include hypotension and respiratory and cardiovascular depression. It is important to be able to characterize and treat magnesium disturbances as they occur and not ignore this important electrolyte.

Although the literature surrounding this topic is growing, further study is needed in the areas of diagnosis and treatment. Hopefully, as our knowledge base grows, we will be better able to understand the function and importance of magnesium in our patients.

REFERENCES


2. All of the following adverse effects can occur in patients with hypermagnesemia except
   a. hypotension. c. vomiting.
   b. ventricular fibrillation. d. respiratory depression.

3. The majority of magnesium in the body is found
   a. in the heart. c. intravascularly.
   b. in the liver. d. in bone.

4. The treatment of choice for patients exhibiting severe signs of hypermagnesemia, such as electrocardiographic changes, is
   a. calcium gluconate. c. Epsom salt.
   b. saline. d. lidocaine.

5. Hypomagnesemia causes all of the following neurologic signs except
   a. tetany.
   b. fasciculations.
   c. loss of deep tendon reflexes.
   d. nystagmus.

6. The effect of magnesium at the neuromuscular junction is due to its
   a. calcium channel–blocking effects.
   b. interference with the sodium–potassium–ATPase pump.
   c. ability to promote kaliuresis.
   d. inhibition of PTH release.

7. Which of the following is not a role of magnesium in the body?
   a. It is a coenzyme for sodium–potassium–ATPase pumps.
   b. It is used in the production of ATP.
   c. It helps regulate smooth muscle vascular tone and blood pressure.
   d. It maintains normal electrolyte gradients within the kidneys.

8. What is the most common cause of elevated magnesium?
   a. neurologic disease
   c. hypothyroidism
   b. renal insufficiency
   d. diabetes mellitus

9. Magnesium supplementation may be necessary when treating
   a. refractory hypokalemia.
   c. severe hypochloremia.
   b. hypercalcemia.
   d. hypernatremia.

10. Which of the following disorders is nonresponsive to magnesium therapy?
    a. tachyarrhythmia
    c. eclampsia
    b. severe asthma
    d. hypotension