Clinical Practice Review

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Magnesium physiology and clinical therapy in veterinary critical care

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Abstract

Objective – To review magnesium physiology including absorption, excretion, and function within the body, causes of magnesium abnormalities, and the current applications of magnesium monitoring and therapy in people and animals.
Etiology – Magnesium plays a pivotal role in energy production and specific functions in every cell in the body. Disorders of magnesium can be correlated with severity of disease, length of hospital stay, and recovery of the septic patient. Hypermagnesemia is seen infrequently in people and animals with significant consequences reported. Hypomagnesemia is more common in critically ill people and animals, and can be associated with platelet, immune system, neurological, and cardiovascular dysfunction as well as alterations in insulin responsiveness and electrolyte imbalance.
Diagnosis – Measurement of serum ionized magnesium in critically or chronically ill veterinary patients is practical and provides information necessary for stabilization and treatment. Tissue magnesium concentrations may be assessed using nuclear magnetic resonance spectroscopy as well as through the application of fluorescent dye techniques.
Therapy – Magnesium infusions may play a therapeutic role in reperfusion injury, myocardial ischemia, cerebral infarcts, systemic inflammatory response syndromes, tetanus, digitalis toxicity, bronchospasms, hypercoagulable states, and as an adjunct to specific anesthetic or analgesic protocols. Further veterinary studies are needed to establish the frequency and importance of magnesium disorders in animals and the potential benefit of magnesium infusions as a therapeutic adjunct to specific diseases.
Prognosis – The prognosis for most patients with magnesium disorders is variable and largely dependent on the underlying cause of the disorder.

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Keywords: cat, cations, dog, electrolyte disturbances, metabolism

Abbreviations

DCT	distal convoluted tubule
NMDA	*N*-methyl-D-aspartate
NMR	nuclear magnetic resonance
PTH	parathyroid hormone
TAL	thick ascending limb
TdP	torsade de pointes
TRPM	transient receptor potential melastatin

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Introduction

Magnesium is a cation with an escalating role in critical care medicine. Over 50 years ago, Vitale[1] reported that magnesium deficiency resulted in uncoupling of oxidative phosphorylation in rat heart mitochondria. Since then, the knowledge base has expanded to recognize that magnesium plays a pivotal role in cellular energy production and cell-specific functions in every organ of the body. Excess or deficiency of this important cation can result in life-threatening complications.

Clinical studies in 1985 demonstrated that 20–65% of critically ill people have a magnesium disorder, primarily manifested as hypomagnesemia.[2,3] However, a study done 5 years later in hospitalized people identified with hypomagnesemia on routine screening reported that in only 10% of these cases had tests been specifically requested to evaluate magnesium.[4] The importance of assessing magnesium concentrations was exemplified

when a significantly higher mortality rate was documented in people who had hypomagnesemia at the time of hospital admission.[5]

The veterinary literature has documented the presence of magnesium disorders in both large and small animal patients, though reports have been rare. Some of the first veterinary reports of magnesium disorders were in large animals in the mid-1950s. Kemp and Hart[6] reported hypomagnesemia as a cause of tetany in lactating cows grazing on grass pastures following cold wet weather and rising temperatures.[6] Since that time, hypomagnesemia has been identified in confinement-housed dairy cows.[7] Hypomagnesemia has also been reported preoperatively in 54% of horses with colic.[8]

Magnesium disorders have also been documented in small animal patients. It was reported in a study evaluating magnesium concentrations upon admission in critically ill dogs that 54% had hypomagnesemia and 13% had hypermagnesemia.[9] A similar study in cats reported the presence of either hypomagnesemia or hypermagnesemia in 50% of hospitalized cats.[10] The cats with abnormal serum magnesium concentrations in this study were reported to have a longer hospitalization stay and a greater chance for natural death or euthanasia.[10]

The role of magnesium in critical care has evolved from simply recognizing and correcting abnormalities in magnesium concentration. Magnesium salt solutions are being administered as an infusion in human medicine as an adjunct to treatment of reperfusion injury, myocardial ischemia, cerebral infarcts, systemic inflammatory response syndrome, tetanus, digitalis toxicity, bronchospasm, and hypercoagulable states. Magnesium infusion is also being investigated as an addition to specific anesthetic or analgesic protocols.

The expanding role of magnesium in critical care medicine necessitates that clinicians have an understanding of the function of magnesium within the cell, problems leading to magnesium disorders, and the limitations of current laboratory testing. This clinical practice review will describe the multifaceted intracellular role of magnesium, its distribution, absorption and excretion, advances in laboratory testing, and current recommendations for treating magnesium abnormalities in animals. In addition, the application of magnesium infusion as an adjunct to therapy in humans and animals will be highlighted. The potential benefits of magnesium measurement and infusion in small animal patients is then demonstrated with 2 case examples.

Magnesium Distribution

The majority (99%) of magnesium is contained within cells, with less than 1% found in the extracellular fluid. Serum magnesium is either protein-bound (30–40%), complexed (4–6%) to anions such as citrate, phosphate, bicarbonate, lactate, or sulfate, or ionized (55–65%). Of the protein-bound serum magnesium, 60–70% is bound to albumin with the remainder bound to globulins. Ionized magnesium is the form that is physiologically active in the serum.[12–14]

Although all cells contain magnesium, the largest tissue fraction is in bone (67%).[15] Most bone magnesium lies within the mineral lattice with a lesser amount part of the surface-limited exchangeable pool.[16,17] Skeletal muscle contains 20% and other soft tissues contain 19% of the total body magnesium. Magnesium in soft tissues and surface-limited exchangeable bone can be mobilized to maintain homeostasis between the ionized extracellular and cytosolic magnesium concentrations.[18,19]

Cytosolic magnesium is maintained at a constant concentration of 0.5–1 mmol/L despite significant fluctuations in extracellular magnesium concentrations (Figure 1).[20] Intracellular buffering occurs by transporting magnesium through cell and organelle membranes and by intracellular protein binding. Influx and efflux of magnesium across the cell membrane is driven by the concentration gradient of magnesium and calcium passing through the transient receptor potential melastatin (TRPM) channels.[21]

Cytosolic magnesium concentration is also controlled by redistribution of magnesium in and out of the mitochondria, endoplasmic reticulum, and sarcoplasmic reticulum. The movement of mitochondrial magnesium is mediated in part by neurotransmitters such as norepinephrine and second messenger molecules such as cyclic adenosine monophosphate (cAMP) and adenosine diphosphate (ADP).[20,21] Higher concentrations of these mediators promote efflux of magnesium from the mitochondria. The movement of magnesium into cellular organelles against a concentration gradient can occur with an electroneutral exchange of magnesium transporter proteins. Some transporters are calcium-dependent, a factor that highlights the close relationship of intracellular calcium and magnesium.[22]

Normal Cellular Functions of Magnesium

Magnesium plays a pivotal role in the electrophysiology and ion flux across cell and mitochondrial membranes, controlling oxidative phosphorylation. Sodium–potassium adenosine triphosphatase (ATPase) and calcium ATPase require magnesium as a cofactor.[23] Without the magnesium ion, ATP cannot be efficiently transported into the mitochondria or effectively hydrolyzed to release energy. In addition, magnesium plays a key role in the activation of T cells,[24] depolarization of myocardial cells and neurons,[25] and contractility of the vascular endothelium.[26–28]

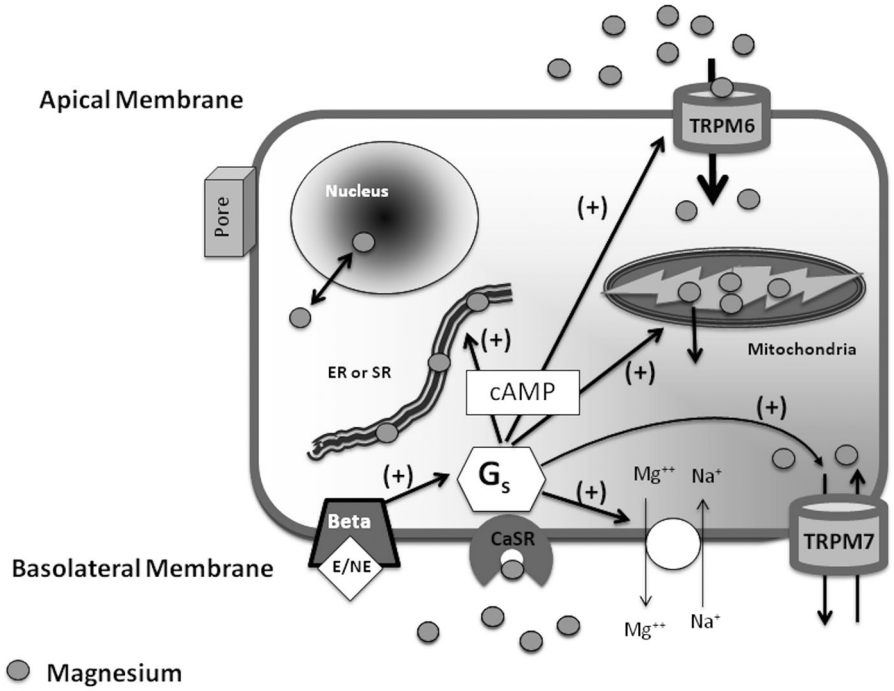

Figure 1: Mechanisms regulating intracellular magnesium. Cytosolic magnesium is maintained at 0.5–1 mmol/L via three mechanisms: (1) intracellular protein binding, (2) influx and efflux of magnesium across the plasma membrane of the cell, and (3) sequestration within and transport out of organelles. CaSRs sense low extracellular Mg^{2+} levels, stimulating a Gs protein, which increases intracellular cAMP levels. High intracellular cAMP levels cause Mg^{2+} to be released from the cellular organelles, increasing cytoplasmic Mg^{2+}. Mg^{2+} is then rapidly lost through the plasma membrane via Na^+/Mg^{2+} exchanger and potentially via intracellular to extracellular Mg^{2+} movement through the basolateral TRPM7 channel. Thus, cytosolic Mg^{2+} levels remain constant. Beta receptor stimulation will also stimulate Gs proteins, increasing cAMP and having the same overall effect of total cell Mg^{2+} loss. Stimulation of CaSRs via low interstitial (extracellular) Mg^{2+} levels will also increase expression of TRPM6 channels on the apical membrane of some cells (ie, intestinal and renal epithelial cells), allowing Mg^{2+} to enter the cell from the lumen, with subsequent transfer of Mg^{2+} from the intracellular compartment into the interstitial space as needed. The cell nucleus appears to be relatively permeable to Mg^{2+} and does not appear to play a significant role in cellular Mg^{2+} regulation.
TRPM, transient receptor potential melastatin; CaSR, calcium/magnesium sensing receptor; ER, endoplasmic reticulum; SR, sarcoplasmic reticulum; Gs, stimulatory G protein; cAMP, cyclic adenosine monophosphate; Mg^{2+}, magnesium ion; Na^+, sodium ion; TRPM6 is expressed primarily in intestinal and renal epithelial apical membranes; TRPM7 is ubiquitously expressed on the basolateral membranes of cells.

Magnesium affects cellular functions through its relationship with cytosolic calcium. As a divalent cation, magnesium competes with calcium for many of the divalent cation channels and receptor sites. Magnesium will compete with calcium for passage through the transient receptor potential cation (TRPM) channels.[21] Magnesium also influences the electrochemical gradient that drives the exchange of calcium and other cations.[29] In addition, magnesium can bind to the internal portion of many of the calcium channels, inhibiting the passage of calcium through those channels.

Magnesium is a cofactor required for the proper function of DNA and RNA polymerase, making it essential for protein synthesis.[30] The production of many essential substances, such as glutathione, glutamine, cAMP, and thiamine requires magnesium.[31–33] Magnesium must be present to prevent apoptosis, and its absence is associated with programmed cell death.[34–37]

Magnesium Absorption/Excretion

Total body magnesium content is dependent upon intestinal and renal magnesium absorption and excretion (Figure 2). Magnesium absorption occurs through the apical membrane of the cell and depends on the transmembrane electrochemical gradient. Absorption will be by either passive paracellular or active transmembrane route. Paracellular absorption occurs by diffusion through intercellular pores. Transmembrane movement depends upon the presence and activity of channels (eg, TRPM 6,7), ion pumps, and membrane pores.[38–40]

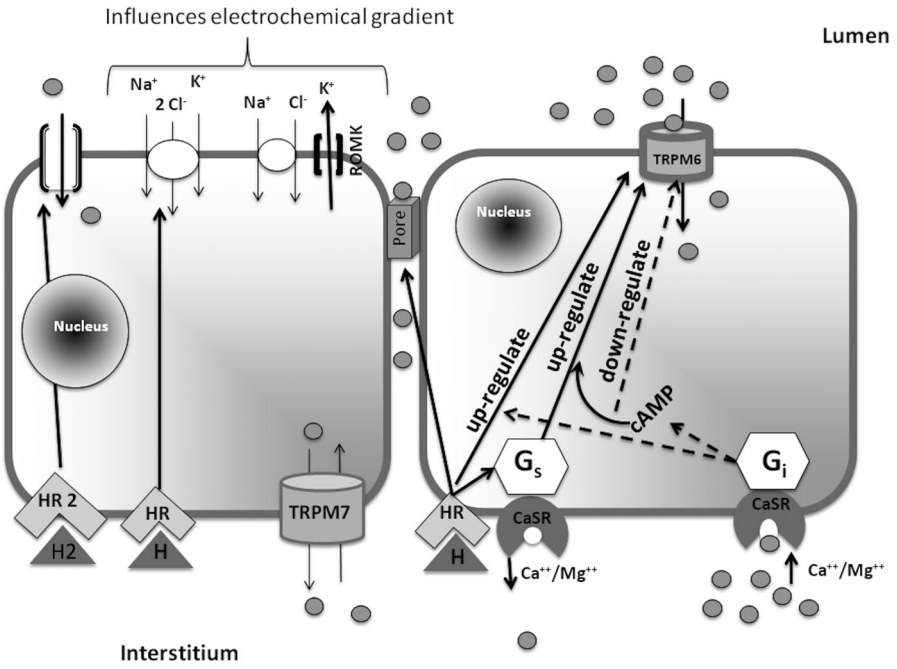

Figure 2: Composite model of renal tubular and intestinal cell maintenance of total body magnesium. Mg^{2+} absorption can occur through paracellular and transcellular pathways. The transcellular route occurs under TRPM6 and TRPM7. Paracellular absorption occurs through a pore located in the tight junctions between cells (Claudin-16 or paracellin-1). Paracellular Mg^{2+} absorption increases with an increasing transepithelial electrochemical voltage gradient and is the primary mechanism for Mg^{2+} absorption in the cortical TAL of the loop of Henle. The transepithelial electrochemical voltage gradient is created primarily by the $Na^+/K^+/2Cl^-$ transporter and the ROMK channel on the luminal membrane of the cTAL cells. Low interstitial Mg^{2+} stimulates the CaSR on the basolateral membrane of renal cTAL cells, which then stimulates the $Na^+/K^+/2Cl^-$ transporter and ROMK creating a favorable transepithelial voltage gradient and leading to paracellular movement of Mg^{2+} from the lumen into the interstitium. The intestinal and renal DCT epithelium plays an integral role in total body Mg^{2+} regulation via transcellular absorption. A CaSR located on the intestinal epithelial basolateral membrane will also sense the interstitial Ca^{2+} and Mg^{2+} concentrations. The CaSR is coupled to either a Gs or Gi receptor. When Mg^{2+} levels are low, the CaSR stimulates a Gs, which leads to upregulation of the apically located TRPM6. TRPM6 facilitates absorption of Mg^{2+} from the lumen into the intracellular space. Mg^{2+} is transported out of the cell and into the interstitium via TRMP7 and via the Mg^{2+}–Ca^{2+} exchanger, both of which are located on the basolateral membrane of the cell. Hormones such as PTH and vitamin D can bind to their respective hormone receptors on the intestinal epithelium and upregulate expression of TRPM6. When interstitial Mg^{2+} levels are high, the CaSR stimulates a Gi protein that interrupts the pro-Mg^{2+} absorptive mechanisms that are typically stimulated by hormones such as PTH and vitamin D. The CaSR acts in a similar way in the basolateral membrane, sensing interstitial low or high Mg^{2+} and stimulating Gs or Gi, respectively. CaSR stimulation of Gs proteins causes upregulation of TRPM6, allowing Mg^{2+} to enter into the cell from the lumen. High interstitial Mg^{2+} levels are sensed by the CaSR and a Gi is stimulated. The Gi interferes with pro-Mg^{2+} absorptive hormones such as PTH, calcitonin, glucagon, ADH, vitamin D, aldosterone, and PGE_2. Hormones such as PTH, calcitonin, glucagon, and ADH (after binding to their respective receptors on the basolateral membrane of DCT epithelial cells) upregulate TRPM6. The hormones vitamin D, aldosterone, and PGE_2 stimulate Mg^{2+} absorption via an unknown mechanism.
H, hormone: parathyroid (PTH), antidiuretic hormone (ADH), calcitonin, glucagon; HR, hormone receptor H_2, hormone: vitamin D, aldosterone, prostaglandin E_2 (PGE_2); HR_2, hormone receptor; TRPM, transient receptor potential melastatin; ROMK, renal outer medullary potassium channel – inwardly rectifying potassium channel; Gs, stimulatory G protein; Gi, inhibitory G protein; Mg^{2+}, magnesium ion; cAMP, cyclic adenosine monophosphate; $Na^+/K^+/2Cl^-$, sodium–potassium–chloride; cTAL, thick ascending loop of Henle; DCT, distal convoluted tubule.

The basal membranes of these cells host receptors that regulate the passage of magnesium between the extracellular and intracellular compartments. Hormone receptors for vitamin D, antidiuretic hormone, glucagon, calcitonin, insulin, and, most importantly, parathyroid hormone (PTH) are important ligands that regulate magnesium uptake across the cell membrane and from cell organelles.[41–44] A calcium/magnesium cation sensing receptor (CaSR) is present on the basolateral membrane of intestinal and renal epithelium (loop of Henle, distal convoluted tubule [DCT], and possibly the collecting duct).[41–44] This G protein coupled receptor can up- or downregulate magnesium absorption in response to interstitial magnesium concentrations.[41,45,46]

Intestinal magnesium absorption

Intestinal magnesium absorption occurs in all segments of the small intestines and colon (5% duodenum, 10% jejunum, 15% proximal ileum, 10% distal ileum, 5% colon).[47] Intestinal magnesium absorption can be increased as much as 6-fold, depending on dietary magnesium and the needs of the body.[48]

Renal absorption and excretion

Magnesium is freely filtered through the glomerulus, with >95% of the filtered magnesium reabsorbed by the tubules. The thick ascending limb (TAL) of the loop of Henle absorbs the largest fraction (80%), followed by the proximal tubules (5–15%) and the DCTs (5–10%).[44,49] Magnesium absorption in the TAL is accomplished by a passive paracellular process driven by the lumen-positive electrochemical gradient within this segment.[49] Factors such as increased luminal flow, hypercalcemia, and hypocalcemia can decrease magnesium reabsorption in the TAL.

The quantity of magnesium reabsorbed from the DCT has a profound impact on total body and urine magnesium concentrations.[44,50,51] Reclamation of magnesium in the DCT is an active transcellular process and can be regulated by PTH, 1,25-dihydroxyvitamin D, prostaglandin E_2 (PGE_2), adenosine, antidiuretic hormone, calcitonin, aldosterone, glucagon, and insulin.[41,45,52]

Measuring magnesium

Accurate measurement of total body magnesium is a challenge due to its intracellular location and activity. The current clinical standard is to quantitate serum total or ionized magnesium concentrations by using ion-selective electrode methods.[53] Monitoring the biologically active serum ionized magnesium concentration is preferred over total magnesium concentration.[54,55] The serum should be tested close to collection time or frozen if testing is delayed to avoid variations in results.[56] Researchers have expressed concern that serum quantitation may not accurately reflect total body magnesium content.[51,57–59] However, Soliman et al[23] demonstrated that due to tightly regulated cellular mechanisms controlling magnesium homeostasis, a low ionized serum magnesium concentration will reflect a total body magnesium deficit.

Within the last decade, there have been significant advances in the research setting for reporting intracellular and tissue magnesium concentrations, allowing for more accurate assessment of total body magnesium concentrations. Two methods for determining intracellular magnesium used in research have potential for clinical application. Nuclear magnetic resonance (NMR) spectroscopy and spectroscopy of magnesium bound to fluorescent dyes are accurate and noninvasive methods used in research.[60,61] NMR spectroscopy measures the frequencies emitted from the magnesium molecules, quantifying the amount of intracellular magnesium.[61,62] NMR spectroscopy has been used in conjunction with brain MRI in patients with subarachnoid hemorrhage treated with magnesium to document increased intracellular magnesium concentrations.[62]

Fluorescent dyes have been used to determine intracellular magnesium concentrations of cell samples as well as extracellular magnesium concentrations of serum and whole blood.[63,64] The fluorescent dye binds to magnesium ions, and a lower wavelength is emitted than by the dye alone. The ratio of the two wavelengths detected by spectrometry is used to determine the magnesium concentration. This method is costly and requires tissue sampling for measuring intracellular magnesium, making it an impractical method in the clinical setting.

Magnesium Disorders

Total body magnesium concentration is affected by dietary intake, gastrointestinal function, hormonal balance, redistribution of the magnesium cation, and excretion into a third body space or urine. Magnesium disorders can manifest with a multitude of clinical signs, none of which are specific for the magnesium disorder. A summary of mechanisms, causes, clinical signs, and treatment recommendations for magnesium excess and deficiency is given in Tables 1 and 2.

Magnesium excess

The two most commonly reported causes of magnesium excess in both human and veterinary patients are renal failure and iatrogenic causes.[65–68] Hypermagnesemia can occur when magnesium-containing drugs such as antacids, laxatives, or enemas are administered to patients with underlying renal disease.[51,67]

Hypotension is one of the key clinical complications of magnesium excess. The vasodilating effect seen during magnesium excess likely results from magnesium blockade of calcium channels and a resultant inhibition of smooth muscle contraction.[69,70] Nakaigawa et al[71] found a significant decrease in arterial pressure, systemic vascular resistance, and coronary vascular resistance when varying doses (60–120 mg/kg) of magnesium sulfate were administered to anesthetized dogs.

Naturally occurring total hypermagnesemia has been reported to occur in up to 13% of critically ill dogs admitted to the ICU of one teaching hospital.[65] The same study found that dogs with hypermagnesemia were 2.6 times more likely to die of their underlying disease than

Table 1: Causes, clinical signs, and treatment of hypermagnesemia

Causes	Clinical signs	Treatment
Excessive intake or medications	**Cardiovascular**	**Both veterinary and human patients**
Magnesium carbonate containing phosphate binders (OsvaRen*, Renepho*, MagneBind**)	Hypotension	0.9% NaCl diuresis
Excessive dietary intake	Digoxin sensitivity	Calcium gluconate
Lithium therapy	**ECG**	Peritoneal or hemodialysis (especially if renal function is decreased)
Renal failure	Bradycardia	Loop diuretics
Endocrine	Prolonged P-R interval	**General**
Hyperparathyroidism	Cardiac arrest	If renal function is normal, hypermagnesemia generally corrects very quickly
Hypothyroidism	**Neuromuscular**	
Addison's disease	Decreased deep tendon reflexes	
	Severe mental depression	
	Flaccid paralysis	
	Gastrointestinal	
	Vomiting	
	Ileus	

*OsvaRen, Renepho, Fresenius Medical Care North America, Waltham, MA.
**MagneBind, Nephro-Tech Inc, Shawnee, KS.

dogs with normal serum magnesium.[65] Dogs with renal disease had the highest median values for serum magnesium. The concept that naturally occurring hypermagnesemia may have prognostic value warrants further study. Mechanisms, causes, clinical signs, and recommended treatment of hypermagnesemia are summarized in Table 1.

Magnesium deficiency

A total body magnesium deficiency can exist in spite of a normal serum magnesium concentration. A magnesium loading test is an accepted method in people for diagnosing total body magnesium depletion.[18] While this test may be a more accurate means of determining a total body magnesium deficit, it is labor intensive and could place patients with underlying renal disease, respiratory insufficiency, and cardiac conduction abnormalities at risk.[18]

A diagnosis of ionized hypomagnesemia has been associated with a prolonged hospital stay in dogs,[65] ileus in horses following colic surgery,[8] as well as a prolonged hospital stay and a higher incidence of mortality in hospitalized cats.[10] The hospital length of stay for critically ill dogs with hypomagnesemia was reported to be twice as long as those with normal serum magnesium.[65] Hypomagnesemia was also associated with concurrent hyponatremia and hypokalemia in dogs.[65]

Hypomagnesemia is common in critically ill human patients. In a 1985 study, Reinhart and Desbiens[2] reported that 20% of people admitted to ICU had low serum magnesium, and hypomagnesemia was the most common abnormal serum electrolyte reported. Ryzen et al[3] found that 65% of human ICU patients with serum creatinine concentrations <97.2 μmol/L (<1.1 mg/dL) had hypomagnesemia at the time of ICU admission. A study[72] of 84 neonatal ICU and 33 newborn patients revealed that 31.1% of the newborns admitted to the neonatal ICU had low ultrafilterable serum magnesium (a combination of both ionized and anion complexed magnesium). The neonatal ICU patients with hypomagnesemia were more likely to have concurrent hypokalemia and require mechanical ventilation.

Although magnesium-depleted patients may represent a subset of patients with more severe disease, hypomagnesemia appears to be an independent predictor of outcome. In a 2003 human study by Soliman et al,[23] magnesium concentrations were measured in ICU patients at admission and daily until discharge. Patients who developed ionized hypomagnesemia had higher Acute Physiology and Chronic Health Evaluation II scores and higher Sequential Organ Failure Assessment scores, longer hospital stays, and significantly higher mortality rates.

Mechanisms, causes, clinical signs, and recommended treatment of magnesium deficiency are summarized in Table 2. Anticipated complications and proposed pathogenesis of problems associated with hypomagnesemia are listed in Table 2. When refractory hypokalemia and tachyarrhythmias exist, a total body magnesium deficit may be exacerbating the condition and prevent correction with conventional therapy.[73–75]

Table 2: Causes, clinical signs, and treatment of hypomagnesemia

Causes	Clinical signs	Treatment
Decreased intake	**Respiratory**	**Veterinary patients**
Anorexia	Bronchoconstriction	Emergency IV: 0.15–0.3 mEq/kg
Decreased intestinal absorption	**Cardiovascular**	CRI: 0.5–1 mEq/kg/24 h
Vomiting	Vasospasm	PO: 1–2 mEq/d (dog, no published data available for cats)
Chronic diarrhea	Hypertension	**Human patients**
Inflammatory bowel disease	Digoxin sensitivity	Emergency IV: 8–16 mmol immediately followed by 40 mmol over the next 5 hours
Other malabsorption syndromes	**ECG**	Severely ill: 48 mmol IM on day 1 followed by 17–25 mmol on days 2–5
Intestinal resection and anastomosis	Ventricular tachycardia	Mildly ill: 15 mmol PO daily
Severe cholestatic liver disease	Supraventricular tachycardia	**General**
Pancreatic insufficiency	Torsade de Pointes	Correct hypokalemia and hypocalcemia
Body compartment loss	Atrial tachycardia/fibrillation	
Insulin therapy	**Neuromuscular**	
Catecholamine excess (endogenous or exogenous)	Tetany	
Correction of acidosis		
Reperfusion injury		
Glucose administration	Muscle spasms/fasciculations	
Pancreatitis	Muscle weakness	
Excessive loss	Seizures	
Renal loss	Migraines: humans	
Saline diuresis	**Skeletal**	
Diuretics	Osteoporosis (chronic): humans	
Hyperphosphatemia*		
Hypocalcemia*		
Renal disease		
Post-obstructive diuresis		
Transplantation		
Hemodialysis		
Peritoneal dialysis		
Inherited renal tubular disorders (humans)		
Other tubular disorders such as ATN, RTA, interstitial nephritis		
Endocrine causes		
Primary hyperparathyroidism		
Hyperadrenocorticism		
Hypercalcemia		
Hyperthyroidism		
Hyperaldosteronism		
Diabetes mellitus		
Drugs		
Diuretics		
Cytotoxic drugs (ie, cisplatin and carboplatin)		
Aminoglycosides		
Cyclosporine		
Pamidronate		

(*Continued*)

Table 2: Continued

Causes	Clinical signs	Treatment
Amphotercin B		
ACE inhibitors		
Beta agonists		
Chelation therapy		
Massive citrated blood infusion		
Mannitol		
Digoxin		
Metabolic acidosis		
Other		
Severe burn injury		
Growth		
Pregnancy		
Lactation		
Familial and congenital abnormalities (humans)		

ATN, acute tubular necrosis; RTA, renal tubular acidosis.

*Unclear if hypercalcemia and hyperphosphatemia are causes of hypomagnesemia or are concurrently associated with hypomagnesemia.

Refractory hypokalemia

Hypokalemia can become refractory to standard potassium replacement therapy as a consequence of magnesium deficiency.[18,23,72,76] The continuous loss of potassium ions into the extracellular compartment because of impaired magnesium-dependent potassium transport mechanisms can eventually result in urinary potassium wasting.[77] Magnesium replacement may be necessary before potassium supplementation is effective.

Impaired insulin sensitivity

Magnesium serves as a cofactor for insulin release and function, as well as in maintenance of appropriate cellular sensitivity to insulin.[78,79] Insulin resistance may develop secondary to magnesium deficiency, as reported in both human patients and the rat model, with higher blood glucose concentrations reported in human patients having low total body magnesium.[78–81] Supplementing with oral magnesium will restore the ability of pancreatic beta cells to compensate for acquired changes in insulin sensitivity.[80]

Hypomagnesemia is a common finding in diabetic ketoacidotic people.[82] Ketoaciduria and glucosuria promote urinary magnesium excretion, which can be exacerbated with fluid diuresis. In addition, significant cellular redistribution of magnesium occurs as insulin moves from the extracellular space to the intracellular compartment with insulin therapy.[18] Close monitoring for clinical signs of a magnesium deficit is necessary since a total body deficit may not be reflected in the measured serum magnesium concentration.

Concurrent hypocalcemia

Calcium and magnesium are both divalent cations affected in a similar manner by hormones including PTH, vitamin D, and vasopressin.[23] Additionally, the CaSR senses both calcium and magnesium, resulting in increased or decreased calcium or magnesium reabsorption.[44] As many as one-third of human patients with low serum magnesium may concurrently have low serum calcium.[3]

PTH levels were found to be inappropriately low in one dog with concurrent hypocalcemia and hypomagnesemia.[83] Both the PTH and calcium concentrations increased after treatment with an IV magnesium solution.[83] Bone responsiveness to PTH can be markedly diminished in dogs fed a magnesium-deficient diet, resulting in both low serum magnesium and calcium.[84] Correction of magnesium deficiencies may be required with refractory hypocalcemia.[18,85,86]

Gastrointestinal effects

Magnesium deficiency has been shown to affect gastrointestinal function and motility. Weglicki et al[87] noted increased leukocyte infiltration and loss of gut mucosal barrier function after 3 weeks feeding a magnesium-deficient ration to rats. Hypomagnesemia has been reported in horses after colic surgery, suggesting a potential causal relationship between hypomagnesemia and strangulating lesions and ileus of the bowel.[8] Horses with lower ionized magnesium and calcium concentrations were found to have more severe lesions at the time of surgery necessitating euthanasia compared to survivors. Magnesium deficiency should be considered a differential in any patient with decreased stomach or intestinal motility.

Reproductive system effects

Magnesium has been successfully used in the treatment of preeclampsia and eclampsia in women since 1912.[31]

The anticonvulsant of choice for treating seizures due to eclampsia is magnesium.[88] Hollenberg[89] and Guerrera et al[90] have proposed that magnesium may reduce cerebral or umbilical vasospasms. Hypomagnesemia may also be a factor in dogs presenting with eclampsia[135] and should be considered when managing dogs with signs of eclampsia.

Cardiac effects

Cardiac conduction abnormalities are one of the most common and serious manifestations of magnesium deficiency. Cardiac arrhythmias associated with hypomagnesemia include ventricular tachycardia, ventricular fibrillation, supraventricular tachycardia, atrial fibrillation, digitalis toxicity associated arrhythmias, and torsades de pointes (TdP).[28,91]

Magnesium's role in the pathogenesis of arrhythmias is difficult to ascertain since magnesium deficits often coexist with potassium and calcium deficiencies. Cardiomyopathic injury has been noted in rats fed a magnesium-deficient diet.[92] Magnesium supplementation has been shown to increase the energy required to induce arrhythmias and cause a prolongation of the effective refractory period.[93] Multiple studies in both human and veterinary patients have documented resolution of TdP after magnesium sulfate infusion.[59,94,95] Magnesium supplementation decreases the incidence of ventricular arrhythmias and atrial fibrillation following cardiopulmonary bypass and coronary artery bypass in humans with magnesium deficiency.[96]

Hypomagnesemia predisposes to the development of toxic side effects of digitalis administration, and digitalis administration predisposes to hypomagnesemia.[18] Digitalis glycosides and hypomagnesmia both inhibit sodium–potassium ATPase and increase intracellular calcium levels. Digoxin also increases urinary excretion of magnesium.[18] A variety of arrhythmias can develop with digitalis toxicity, and these can be responsive to magnesium sulfate administration.[18,88,97]

Vascular effects

In people and in animal research models, magnesium deficit is associated with hypertension and vasospasm. Chronic magnesium deficiency is potentially a predisposing factor for left ventricular hypertrophy[98] and chronic systemic hypertension.[98,99] Both coronary and cerebral vasospasm appear to be potentiated by magnesium deficit and can be abrogated by magnesium administration.[70,89,100–106]

Central and peripheral nervous systems

Magnesium is involved in neurotransmitter release, modulation of inflammatory cytokines, and reduction in excitotoxicity.[107–110] It has been proposed that magnesium may block *N*-methyl-D-aspartate (NMDA) receptors in the spinal cord, helping to modulate wind-up, prevent substance P release, and reduce sensitivity to pain.[111] Intrathecal administration of magnesium sulfate (1.6, 3.2, 4.8, and 6.6 μmol) is equally as effective as an NMDA receptor antagonist in abolishing hyperalgesia caused by magnesium deficiency.[112]

Immunologic and anti-inflammatory effects

Magnesium may play a role in modulation of inflammation. A multiorgan system tissue inflammatory response has been reported in magnesium-deficient animals,[63,82,102] and significant intestinal leukocyte infiltration and intracellular adhesion molecule-1 (ICAM-1) expression has been reported in magnesium-deficient rats.[113] Lung polymorphonuclear leukocytes were found to be increased in control rats that had been given endotoxin as compared to rats given endotoxin that were also treated with magnesium sulfate.[69] A magnesium-deficient state is also associated with reduced circulating red blood cell glutathione concentrations, and increased mediators of inflammation, lipid peroxidation, substance P, calcitonin gene related peptide, myeloperoxidase, and tumor necrosis factor alpha (TNF-α).[69,92,113] Additionally, magnesium deficiency can lead to substance P receptor activation, which causes neutrophil activation in rats.[114]

Treatment of Magnesium Disorders

The decision to treat a suspected or diagnosed magnesium disorder will depend on the severity of the clinical signs and the magnitude of change from normal range of the serum magnesium level of the patient. Treatment options for hypermagnesemia and hypomagnesemia are provided in Tables 1 and 2.

Magnesium excess

A suspicion or diagnosis of hypermagnesemia necessitates that any magnesium-containing medications or crystalloid fluid (eg, Plasmalyte-A[a] and Normosol-R[b]) be substituted with magnesium-free crystalloid fluids such as Ringer's lactate or 0.9% NaCl. Acute magnesium toxicity from iatrogenic overdose can be treated with 100 mg/kg 10% calcium gluconate administered IV over 20 minutes.[68] Promoting urinary excretion and inhibiting renal tubular reabsorption of magnesium are the mainstays of treatment for moderate to severe hypermagnesemia and when clinical signs are apparent (eg, cardiac arrhythmia, hypotension). Sodium chloride diuresis will increase the tubular flow rate, decreasing

reabsorption of magnesium in the DCT.[38,91] Mannitol and other osmotic diuretics have been reported to increase urinary magnesium excretion.[51] Loop diuretics will decrease magnesium reabsorption in the TAL but can also cause excessive loss of sodium, chloride, and potassium loss. Thiazide diuretics and spironolactone have been shown to increase magnesium absorption in the DCT and should be avoided in patients with suspected magnesium excess.[44,115] Hemo- or peritoneal dialysis using magnesium-free dialysate may be necessary to treat symptomatic magnesium excess resulting from kidney disease or iatrogenic overdose.

Magnesium deficiency

If the magnesium deficit is mild, dietary changes and oral magnesium salts such as magnesium carbonate or oxide may be sufficient to increase magnesium intake.[18] Oral magnesium supplementation (see Table 2) should be considered in small animal patients at risk for chronic mild magnesium deficit, for example, those with GI malabsorptive diseases or chronic digoxin or loop diuretic therapy.

Animals symptomatic for low magnesium should be treated with an IV infusion of magnesium sulfate or magnesium chloride. Plasmalyte[a] and Normosol[b] contain 1.5 mmol/L (3 mEq/L) of magnesium, which should be taken into consideration when calculating magnesium supplementation doses. The optimum dosage and rate of magnesium administration has not been defined for veterinary patients. In a study of healthy anesthetized Beagles, Nakayama et al[28] found that a cumulative dose of 0.5–1.0 mmol/kg (1.0–2.0 mEq/kg) magnesium sulfate (resulting in plasma magnesium concentrations of 4.25–6.1 mmol/L [8.5–12.2 mEq/L]) caused an increase in heart rate, lusitropy, inotropy, and cardiac output. Above a 1.0 mmol/kg (2.0 mEq/kg) dose, hypotension and cardiac arrhythmias were observed, and a dose-dependent deterioration of hemodynamic parameters occurred with increasing magnesium dose. No change in hemodynamic parameters was found with a 0.050–0.1 mmol/kg (0.1–0.2 mEq/kg) dose. This has been the basis for a magnesium sulfate dose recommendation in dogs and cats of 0.1–0.15 mmol/kg (0.2–0.3 mEq/kg) IV at a rate of 0.06 mmol/kg/min (0.12 mEq/kg/min) for treating acute, life-threatening problems associated with magnesium deficiency (ie, TdP and other cardiac arrhythmias).[28] A constant rate infusion (0.1–0.5 mmol/kg/day [0.2–1 mEq/kg/day]) may be required to treat magnesium-deficient animals that have ongoing magnesium loss or chronic magnesium deficiency.[28,116]

Magnesium chloride and magnesium sulfate are available in different concentrations (12.5–50% solutions). Because these are hyperosmolar solutions, it is recommended that the infusion be diluted to a concentration below 20% using 0.9% sodium chloride or 5% dextrose in water.[91] Calcium-, bicarbonate-, and lactate-containing solutions are incompatible with magnesium salt solutions. Clinical signs of magnesium toxicity during magnesium replacement therapy include vomiting, diarrhea, hypotension, weakness, and respiratory depression. The electrocardiogram and blood pressure of the animal should be monitored during IV magnesium infusion. ECG abnormalities may include bradycardia, QT interval prolongation, PR interval prolongation, and QRS complex widening.

In addition to monitoring plasma magnesium concentrations, plasma potassium, sodium, calcium, and chloride should also be monitored. Magnesium replacement in patients with kidney failure should be done carefully, as they are more at risk for magnesium toxicity.[44,51] Treatment of acute magnesium toxicity is described in the previous section.

Magnesium Infusion as an Adjunct to Therapy

The multifaceted role of magnesium in cells has led researchers and clinicians in human medicine to explore the effects of infusing magnesium as an adjunct to therapy for various conditions. Chaudry[11] recommended the infusion of magnesium chloride-adenosine triphosphate solution during resuscitation from shock. Current studies of brain injury, spinal injury, pain, sepsis and systemic inflammatory response syndrome, hypercoagulable states, eclampsia, tetanus, and ischemia have demonstrated potential beneficial effects from magnesium administration. In these situations, magnesium administration is not given to replace a documented magnesium deficiency but instead given for its beneficial effects in specific cells. Though all syndromes reported in people may not be common in veterinary patients, knowledge of the possible mechanisms of action of magnesium infusion on various tissues may allow extrapolation into the veterinary population of patients.

Reduce vasospasms

Magnesium sulfate is the therapy of choice for preventing eclampsia in women.[89,117,118,134] One proposed mechanism of action is the reduction in cerebral ischemia secondary to vasospasm.[89,117] In one study, magnesium sulfate was more effective than the calcium channel blocker nimodipine in preventing seizures in women with severe preeclampsia.[89] IV magnesium sulfate therapy may dampen vasospasm following subarachnoid hemorrhage in people. A 2006 study by Stippler et al[70]

showed a trend toward improved outcome and a lower frequency of symptomatic vasospasm in patients with subarachnoid hemorrhage who were treated with a daily magnesium infusion compared to those who did not receive the magnesium sulfate therapy. A randomized controlled trial by Westermaier et al[103] documented a significant decrease in delayed ischemic cerebral infarction in human patients treated with magnesium sulfate compared to placebo.

Early studies by Altura and Turlapaty[100] in 1982 showed that canine coronary artery contractile sensitivity to the stimulants 5-hydroxytryptamine, angiotensin II, and KCl was enhanced with magnesium-free perfusate and attenuated with magnesium supplementation. The ratio of magnesium to other ion concentrations, such as potassium, is a factor in determining basal vascular tone. Acute withdrawal of extracellular magnesium in isolated perfused canine coronary arteries produced vasospasm.[101] Small changes in extracellular magnesium concentration caused significant changes in sensitivity of vascular smooth muscle cells as the extracellular potassium concentration was lowered. These findings warrant further investigation in veterinary patients when establishing treatment protocols for diseases known to have vasospasms or ischemia as part of the pathology (eg, gastric-dilatation and volvulus, acute trauma associated intestinal ischemia, renal transplantation, and patients experiencing ischemic forms of acute renal failure).

Neuroprotection

Magnesium therapy has been shown to provide neuroprotection in human patients[119] as well as in laboratory models of traumatic brain injury.[120] Magnesium sulfate administration in severe closed traumatic brain injured people has been shown to significantly reduce mortality[121] and reduce the degree of intraoperative brain swelling.[121] Administration of either mannitol or polyethylene glycol with parenterally infused magnesium salts has been advocated to improve the bioavailability of magnesium to the central nervous system.[122–124] In addition to being an NMDA receptor antagonist, magnesium modulates several pathways significant in the pathology of secondary brain injury. Magnesium therapy will decrease glutamate release, decrease calcium channel blockade, and downregulate proinflammatory and proapoptotic signals.[91,123,124]

Magnesium appears to have a direct, positive, neuroprotective effect in the spinal cord. Using a rat model of acute spinal cord injury, Kwon et al[124] found that histological lesions were decreased by 27–33% after magnesium sulfate or magnesium chloride infusion compared to saline controls. A trend toward improved locomotion was also demonstrated in the magnesium-treated group.

Analgesia

Although magnesium sulfate decreased the duration of local anesthesia attained during sciatic nerve block,[125] other studies have found advantageous responses when magnesium administration was added to analgesic protocols. DeRossi et al[126] found that the addition of magnesium sulfate to ketamine lumbosacral epidural increased the duration of analgesia by over twice the amount obtained with either drug alone. Ouerghi et al[112] found that when magnesium sulfate was added to morphine-fentanyl spinal analgesia in human patients undergoing elective thoracotomy, there was a 57% reduction in the IV morphine requirement compared to the saline additive group. Ryu et al[127] found that when an IV bolus and continuous infusion of magnesium sulfate was used in human patients undergoing gynecological surgery, there was a reduction in the dose of neuromuscular blocker required, postoperative pain score, and total amount of postoperative analgesic required.

Reduction of inflammatory response

Lee et al[69] compared the effect of endotoxin challenge alone and endotoxin challenge with different doses of magnesium sulfate. They found that rats moderately dosed (50 and 100 mg/kg) with magnesium sulfate had reduced leukocyte infiltration, myeloperoxidase, nitric oxide levels, IL-6, PGE_2, and cyclooxygenase-2 (COX-2) levels after endotoxin challenge compared to magnesium-deficient mice challenged with endotoxin alone. Magnesium deficiency contributes to tissue inflammation and an increase in circulating inflammatory cytokines.[92] It may be partially through NMDA receptor activation and substance P receptor stimulation.[92,128] Magnesium infusion as an adjunct to more standardized sepsis therapy may be an appropriate clinical research focus in veterinary patients.

Platelet inhibition

The effect on coagulation of adding magnesium sulfate to a rapid crystalloid infusion in people was followed by thromboelastography.[129] In the group that received magnesium-deficient saline, hypercoagulability was induced. This effect was abrogated when magnesium concentrations were maintained within a low-normal range. Magnesium may inhibit platelet activation and aggregation and has been shown to inhibit fibrinogen binding to the platelet glycoprotein IIb/IIIa (gpIIb/IIIa) receptor.[130] The concept that magnesium may play a role in the treatment of hypercoagulable states is intriguing and deserves further exploration.

Tetanus autonomic dysfunction

Magnesium sulfate has been utilized in the treatment of autonomic dysfunction associated with severe

generalized tetanus in both people and dogs.[131,132] Treatment was associated with a decrease in epinephrine, norepinephrine, and dopamine concentrations.[131] The administration of magnesium as an adjunctive therapy in the tetanus patients has not been associated with adverse side effects.[131,132]

Ischemia and reperfusion

Magnesium chloride-ATP solutions have been studied in models of both shock and reperfusion injury. In a porcine model of endotoxic shock, magnesium chloride-ATP infusion increased portal blood flow and blunted the endotoxin-induced decrease in hepatic lactate clearance.[133] Hirata et al[134] studied isolated rat lung during cold ischemia following perfusion of the samples with either saline or magnesium chloride-ATP solution. The magnesium chloride-ATP group had lower peak airway pressure, a lower intrapulmonary shunt fraction, and a lower wet to dry lung weight ratio, findings supportive of reduced ischemia–reperfusion damage. The mechanism of action is currently unknown and recommendation for use in clinical patients is lacking.

Clinical cases

The following cases present clinical examples of the potential value of IV magnesium infusions in the treatment of small animal patients with refractory hypokalemia and ventricular tachycardia.

Case 1

A 14-year-old female spayed domestic longhair cat was presented with a 3-day history of a decreased appetite and lethargy and a 1-day history of vomiting. The patient had a past diagnosis of diabetes mellitus and was receiving 1.5 units of glargine insulin subcutaneously twice daily. Abnormalities found on physical examination included poor perfusion (82 mm Hg indirect systolic arterial blood pressure), 5% dehydration, grade I–II left parasternal systolic heart murmur, generalized weakness, and depressed mentation. Hypotension was responsive to rapid IV infusions of crystalloid and colloid. Initial CBC and biochemistry laboratory tests revealed an increase of the white blood cell count, alanine aminotransferase, blood urea nitrogen, cholesterol, and glucose (500 mg/dL [27.75 mmol/L]; normal range 76–145 mg/dL [4.22–8.05 mmol/L]). Urine ketones were positive. Venous blood gas results at presentation demonstrated a compensated metabolic acidosis. Electrolyte values drawn at presentation revealed hypermagnesemia (0.85 mmol/L [1.7 mEq/L], normal range 0.43–0.7 mmol/L [0.86–1.4 mEq/L]) and hypokalemia (3.07 mEq/L [3.07 mmol/L], normal range 3.5–4.8 mEq/L [3.5–4.8 mmol/L]). Patient history, clinical signs, abdominal ultrasound, and laboratory findings were consistent with a working diagnosis of diabetic ketoacidosis and pancreatitis. The patient was treated with isotonic balanced crystalloid (Plasma-Lyte A,[a] containing 3 mEq/L of magnesium) and 6% hetastarch (600/0.75) fluid therapy, a constant rate infusion of regular insulin, analgesia (buprenorphine), and supportive care. A transfusion of stored whole blood was required on day 2 of hospitalization and the cat received 2 doses of furosemide (1 and 2 mg/kg) on day 3.

Table 3: Case 1 blood ionized potassium and magnesium levels

Hospitalization day	Day 1	Day 2	Day 2	Day 3[#]	Day 4	Day 4
Time of blood test	9 pm	7 am	9 pm	9 pm	8 am	8 pm
IV fluid supplement	KCl	KCl K_2HPO_4	KCl K_2HPO_4	KCl K_2HPO_4	KCl K_2HPO_4 $MgSO_4$	KCl K_2HPO_4 $MgSO_4$
Potassium* (mEq/L)	3.07	3.22	2.48	2.64	2.64	3.25
Ionized magnesium** (mmol/L)	0.85	0.64	0.46	0.43	Not available	0.78

[#]Furosemide administered (dose) at 11 pm.

KCl: potassium chloride; K_2HPO_4: potassium phosphate; $MgSO_4$: magnesium sulfate.

*Potassium normal reference range 3.5–4.8.

**Ionized magnesium normal reference range 0.43–0.7.

The IV maintenance fluids were supplemented with KCl on day 1 after initial fluid resuscitation. Table 3 presents serum potassium and magnesium values as well as any treatment specific for the electrolyte disorders. Hypokalemia persisted despite parenteral potassium supplementation. Parenteral magnesium supplementation was initiated on day 4 of hospitalization, after which the potassium concentration finally increased to near normal values. This case demonstrates the importance of evaluating serial ionized serum magnesium concentrations, particularly when hypokalemia is refractory to potassium supplementation. The addition of magnesium to IV fluids may be warranted as part of the treatment for hypokalemia when ionized serum magnesium values are low or low normal.

Case 2

A 7-year-old male neutered Labrador Retriever was presented with a 2-day history of lethargy and decreased appetite. He was coughing, breathing heavily, and excessively salivating on the day of presentation. Physical examination revealed tachycardia of 130–240/min and an indirect systolic blood pressure of 250 mm Hg. His hydration was normal. An ECG revealed ventricular tachycardia (Figure 3). Initial treatment for the ventricular arrhythmia consisted of IV infusion of magnesium sulfate (10 mL of 12.5% solution or 0.3 mEq/kg) over 5 minutes. Within 2 minutes of the start of the infusion

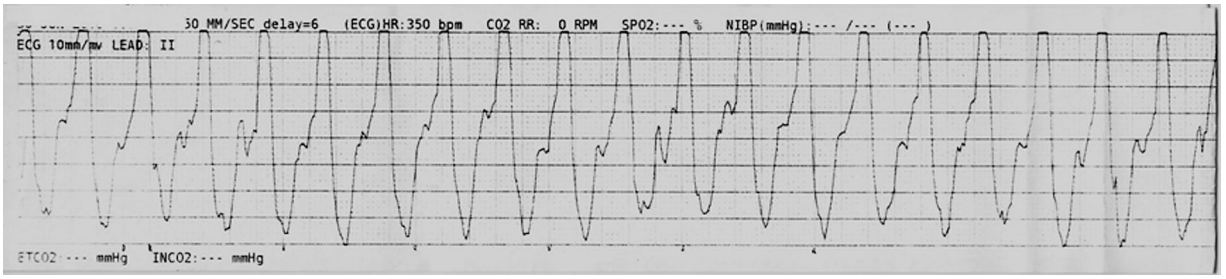

Figure 3: Excerpt from lead II (10 mm/mv, 50 mm/s) electrocardiographic rhythm strip showing ventricular tachycardia present upon presentation.

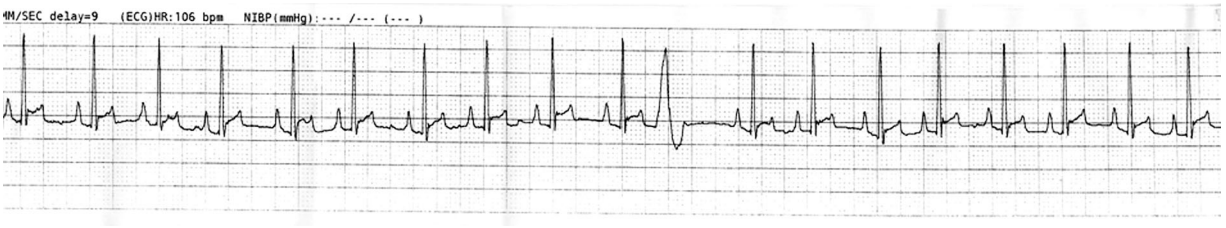

Figure 4: Excerpt from lead II (10 mm/mv, 25 mm/s) electrocardiographic rhythm strip obtained 2 minutes after the magnesium sulfate infusion. The rhythm is now a sinus rhythm with an occasional ventricular premature contraction.

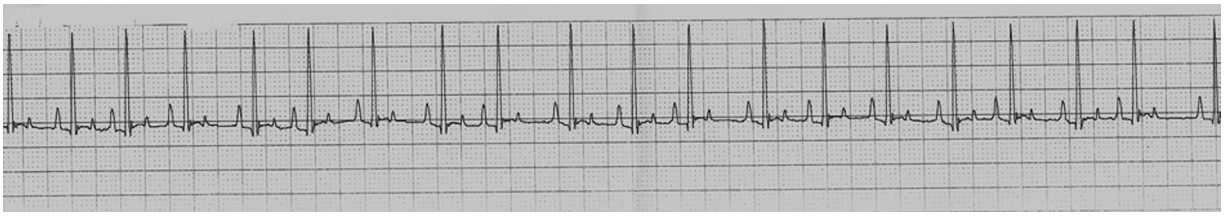

Figure 5: Excerpt from lead II (10 mm/mv, 50 mm/s) electrocardiographic rhythm strip obtained several minutes after the magnesium sulfate infusion with a heart rate of 115 beats/min.

of magnesium sulfate, the patient's rhythm converted to sinus rhythm with occasional ventricular premature contractions (Figure 4). The rhythm disturbance resolved completely following administration of the full dose (Figure 5). Indirect systolic blood pressure was 101 mm Hg and the patient's heart rate was 112/min following cardioversion. Ionized magnesium concentration prior to magnesium sulfate administration was 0.5 mmol/L (normal range 0.43–0.6) and following administration was 0.97 mmol/L. This case demonstrates that IV magnesium sulfate can be a viable option for treating ventricular tachycardia. An intracellular magnesium deficit may exist despite a normal serum ionized magnesium concentration.

Conclusion

Magnesium is an important intracellular cation required for energy production and cell function in every organ. Changes in magnesium homeostasis have consistently been correlated with increases in morbidity and mortality in veterinary and human critical patients.[10,23,66] Assessment of serum magnesium concentration should become a routine part of critical patient evaluation since the clinical signs and conditions associated with magnesium disorders can be nonspecific and varied. Equipment to measure serum ionized or total magnesium Is readily available in-hospital. However, measurement of serum magnesium may not reflect total body magnesium concentration. The serum magnesium concentration combined with clinical signs and conditions associated with magnesium disorders are used to make the diagnosis and to monitor treatment. Research is exploring the role of magnesium infusions as an adjunct to standard therapy for clinical disorders such as head trauma, reperfusion injury, and vascular disease. Future studies are expected to better define the role of magnesium in critical illness and investigate potential benefits of magnesium infusion in veterinary patients.

Footnotes

[a] Plasma-Lyte-A, Abbott Laboratories, Abbott Park, IL.
[b] Normosol-R, Hospira, Lake Forest, IL.

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