Magnesium Disorders in Horses

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KEYWORDS

• Hypomagnesemia • Hypermagnesemia • Calcium • Alkalosis
• Parathyroid hormone

Magnesium (Mg) is an essential macroelement that is required for cellular energy-dependent reactions involving ATP, including ion pump function, glycolysis and oxidative phosphorylation, and nucleic acid and protein synthesis. Mg has an important role in the regulation of calcium (Ca) channel function and therefore neurotransmitter release, neuronal excitation, skeletal muscle contraction, vasomotor tone, and cardiac excitability. Because of the importance of Mg in several physiologic processes, homeostatic mechanisms normally maintain intracellular and extracellular concentrations within narrow limits. Severe Mg deficiency results in neuromuscular disturbances, but such overt clinical signs are rarely documented in horses. In contrast, subclinical hypomagnesemia is common in critically ill humans and animals. Subclinical hypomagnesemia increases the severity of the systemic inflammatory response syndrome (SIRS); worsens the systemic response to endotoxins; and can lead to ileus, cardiac arrhythmias, refractory hypokalemia, and hypocalcemia.

CHEMISTRY

Mg concentrations in body fluids are reported as mEq/L, mg/dL, or mmol/L. Because the atomic weight of Mg is 24.3 and its valence is 2^+, 1 mEq (0.5 mmol) = 12.156 mg. The conversion factors are as follows:

mg/dL = mmol/L × 2.43
mmol/L = mg/dL × 0.411
mmol/L = mEq/L × 0.5
mg/dl = mEq/L

Dietary Mg levels are reported in g/kg of feed, in parts per million (ppm), which is expressed as mg/kg = g/kg × 1000 or as a percentage, by dividing by 10. Oral Mg is commonly available as magnesium oxide (MgO), MgO_x, which contains 60.25% elemental Mg. Magnesium carbonate ($MgCO_3$) and magnesium sulfate ($MgSO_4$) can also be fed. $MgSO_4$ for intravenous (IV) injection is commercially available as

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Vet Clin Equine 27 (2011) 149–163
doi:10.1016/j.cveq.2010.12.009 **vetequine.theclinics.com**
0749-0739/11/$ – see front matter

$MgSO_4 \cdot 7H_2O$ in a 50% solution. Although the $MgSO_4$ compound contains 20.2% elemental Mg, its solution contains only 9.9% elemental Mg. Each mL of 50% $MgSO_4 \cdot 7H_2O$ solution contains 99 mg (8 mEq = 4 mmol) of elemental Mg. The 50% solution (500 mg/mL = 4 mEq/mL) is hypertonic, with an osmolarity of 4000 mOsm/L and should be diluted to at least a 10% solution before IV administration.

MG DISTRIBUTION WITHIN THE BODY

Mg is the fourth most abundant cation in the mammalian body and the second most abundant intracellular cation after potassium. The body of domestic animals contains 0.05% Mg by weight, of which 60% is in bones, 38% is in soft tissues, and 1% to 2% is in extracellular fluids. Only 30% of the bone Mg is readily exchangeable and therefore available as a reservoir to maintain extracellular Mg concentrations. The remaining 70% of bone Mg has structural functions and is held within the hydroxyapatite lattice and released only during active bone resorption. Although most soft tissue Mg is in the intracellular compartment, intracellular and extracellular ionized Mg (Mg^{2+}) concentrations are similar, with only a very small transmembrane gradient compared with calcium ions (Ca^{2+}). Intracellular Mg^{2+} concentrations are variable, being proportional to the metabolic activity of the cell.

Less than 1% of the total body Mg is contained in the extracellular fluid, therefore serum Mg concentration may not adequately reflect the total body Mg stores. In equine serum, 30% of Mg is protein bound and 10% is complexed to weak acids, with the remaining 60% in the ionized form (Mg^{2+}).[1,2] Only the ionized form is biologically active, therefore it is preferable to measure the concentration of the ionized form in the serum rather than the total Mg (tMg) concentrations. Red blood cells contain approximately 3 times the concentration of Mg in serum; therefore hemolysis can elevate measured serum Mg concentrations.

The serum tMg concentration depends on the protein concentration, whereas the Mg^{2+} concentration depends on the acid-base status. Acidosis increases the Mg^{2+} concentration, whereas alkalosis reduces it. This property is clinically important when treating alkalotic conditions, such as exercise-associated metabolic alkalosis in endurance horses resulting from chloride loss, nasogastric reflux associated with small intestinal obstruction, or duodenitis/jejunitis and respiratory alkalosis associated with hyperventilation. Clinical signs of hypomagnesemia can develop because of low concentrations of Mg^{2+} despite normal tMg concentrations. Feeding an acidic diet with a low dietary cation-anion balance will increase the percentage of Mg^{2+}.[1]

PHYSIOLOGIC ROLE OF MG

Mg serves as an essential cofactor for more than 300 enzymatic reactions involving ATP, such as replication, transcription and translation of genetic information, and cellular energy metabolism reactions of glycolysis and oxidative phosphorylation.[3,4] Mg is necessary for membrane stabilization, nerve conduction, ion transportation, regulation of Ca channel activity, and normal functioning of the sodium-potassium–activated ATP (Na^+/K^+ ATPase) pump, which maintains the Na^+/K^+ gradient across all membranes as well as regulates the intracellular K^+ balance.[5] Ca ATPase and proton pumps also require Mg as a cofactor. Consequently, Mg plays an important role in excitable tissues. Defective function of ATPase pumps and ion channels may result in interference with the electrochemical gradient, alteration in resting membrane potential, and disturbances in repolarization, resulting in neuromuscular and cardiovascular abnormalities.[4,6–8] Mg's role in the regulation of movement of Ca into the

myocyte, gives it a pivotal role in cardiac contractile strength, peripheral vascular tone, and visceral peristalsis.[8]

MG ABSORPTION

Mg^{2+} is absorbed by passive, nonsaturable, and concentration-dependent paracellular diffusion and by saturable transcellular active transport. In horses, 25% of the ingested Mg is absorbed in the proximal half of the small intestine; 35% in the distal half of the small intestine; and only 5% in the cecum, large colon, and small colon.[9] Increased dietary Mg leads to increases in bone, tissue, erythrocyte, and serum Mg concentrations. Intestinal Mg absorption increases in proportion to the amount supplied in the diet, but the absorptive efficiency decreases as the dietary Mg content increases until a plateau is reached.[10] The average absorption of Mg from feed by horses is 49.5% (30%–60%),[9] which is higher than that in ruminants.[11] Alfalfa has the highest Mg digestibility of 50%; clover and meadow hay, 31%; and hay and grain, 38%.[12] The diet type does not affect the site of Mg absorption.[9] Oral MgO, $MgSO_4$, and $MgCO_3$ have equivalent digestibilities (50%–70%), with their absorption rates higher than those from organic sources. Mg digestibility is higher in foals.[13] Excessive amounts of fiber, oxalates, phosphates, and fatty acids decrease Mg absorption in horses, whereas phytates, Ca, and aluminum contents have little effect.[9]

MECHANISMS OF RENAL MG EXCRETION AND REABSORPTION

Mg is primarily excreted via the gastrointestinal tract, kidneys, and mammary gland during lactation, with smaller amounts lost in sweat and to the developing fetus.

In an effort to regulate Mg balance and maintain stable serum Mg concentrations, renal excretion of Mg varies directly with dietary changes. With low Mg intake, the kidney avidly conserves Mg and virtually no Mg is excreted into the urine. Conversely, when excess Mg is ingested, it is rapidly excreted into the urine because of diminished renal tubular reabsorption. Ionized and anion-bound fractions of Mg are filtered by the glomerulus (ultrafilterable), whereas protein-bound Mg passes directly through the renal efferent arteriole without passing into the glomerular filtrate. Approximately 70% of blood Mg is filtered by the glomeruli, with 70% to 90% reabsorbed in different segments of the nephron. The proximal tubule reabsorbs 5% to 15% and the thick ascending limb of the loop of Henle 70% to 80% of the Mg filtered by the glomerulus.[14] The distal convoluted tubule only absorbs approximately 10% of the filtered Mg, but this amount is 70% to 80% of that delivered from the loop of Henle. Because there is minimal absorption beyond the distal tubule, this segment is responsible for determining the final urinary Mg excretion.

MG REQUIREMENTS OF HORSES

Obligatory urinary and fecal Mg loss in horses was estimated at 2.8 and 1.8 mg/kg birth weight (BW)/d, respectively.[9] Maintenance Mg requirement for horses has been estimated at 13 mg/kg BW/d and can be provided by a diet containing 0.16% Mg (1600 ppm of feed).[9,10] Growing, lactating, and exercising animals have a higher requirement of dietary Mg. The mammary gland actively secretes 3 to 6 mg/kg/BW/d of Mg into the milk. During the first week of lactation the Mg concentration in milk is 120 to 300 mg/L; then it decreases to 50 to 70 mg/L for the next 2 to 3 months.[15] During lactation, mares require 15- to 30-mg/kg dietary intake of Mg.[16] Hypomagnesemia is more likely to occur in high-producing mares, especially if transported long distances without feed. Substantial amounts of Mg can also be lost in sweat. The

Mg intake should be increased 1.5 to 2 times for maintenance horses undergoing moderate to intense exercise.

Dietary Mg deficiency in horses is very rare unless extreme conditions combine to result in decreased consumption and increased demand, such as long distance transportation of unfed lactating mares or prolonged administration of enteral or parenteral fluid or nutrition solutions deficient in Mg.

MG HOMEOSTASIS

Although the extracellular concentration of Mg depends on gastrointestinal absorption, renal excretion, and bone exchange, there is no precise homeostatic regulating system for Mg.[17] However, parathyroid hormone (PTH), PTH-related protein, arginine vasopressin (AVP, antidiuretic hormone), aldosterone, insulin, and β-adrenergic agonists increase renal reabsorption of Mg.[18] In vitro and in vivo studies have demonstrated that insulin may modulate the shift of Mg^{2+} concentration from the extracellular to intracellular space. Activation of the Ca-sensing receptor in the thick ascending loop of Henle by hypercalcemia increases urinary Ca^{2+} and Mg^{2+} excretion.[16] Reabsorption of Mg^{2+} is impaired with osmotic diuresis (volume expansion), hyperglycemia, hypercalciuria, hypercalcemia, hypermagnesemia, hypophosphatemia, hypokalemia, tubular acidosis, metabolic acidosis, and toxicities caused by amphotericin B or aminoglycosides.[18] Administration of furosemide and induction of hypercalcemia causes reduction in serum tMg and Mg^{2+} concentrations in healthy horses by inhibition of the $Na^+/K^+/2Cl^-$ transporter, which reduces the transepithelial voltage gradient[19] and directly decreases the reabsorption of Ca and Mg. PTH indirectly increases Mg^{2+} release from bone during bone resorption. PTH, vitamin D, calcitonin, AVP, glucagon, and Ca concentrations influence Mg absorption and excretion to some degree.

PTH acts on the renal tubules to increase Mg reabsorption.[20] Micropuncture studies have shown that PTH changes the cortical thick ascending limb of the loop of Henle potential difference, which increases the transepithelial voltage gradient to enhance paracellular Mg reabsorption.[14,21]

PATHOPHYSIOLOGICAL CONSEQUENCES OF HYPOMAGNESEMIA AND INFLAMMATION

Mg has a role in protection against neurotoxicity, cardiotoxicity, inflammation, and free radical damage.[22–25] Hypomagnesemia is associated with increased cytokine production and systemic inflammation.[26,27] Subclinical hypomagnesemia is common in the intensive care unit and is associated with increased risk of death. Experimental endotoxin administration in horses results in an acute decrease in tMg and Mg^{2+} concentrations.[28] It seems that endotoxemia induces acute hypomagnesemia and that Mg administration may have a protective effect in hypomagnesemic endotoxemic patients. Endotoxemic humans with concurrent hypomagnesemia have a worse outcome compared with normomagnesemic endotoxemic patients.[22] Considering that approximately 40% of horses with colic have endotoxemia, and that free radical injury is an important mechanism in intestinal ischemia-reperfusion injury, the role of Mg and its therapeutic importance in equine disease warrants investigation.

INCIDENCE AND OUTCOME OF HYPOMAGNESEMIA IN EQUINE PATIENTS

Hypomagnesemia is commonly observed in the critically ill patient, but whether it contributes to mortality or is merely associated with severe disease is unknown.

A retrospective study found that 48.7% (401/823) of hospitalized horses had tMg values below the reference range.[29] Hypomagnesemia was associated with gastrointestinal disease, infectious respiratory disease, and multiorgan disease.[29] Although there was no association with mortality, the length of hospitalization was longer for horses with hypomagnesemia.[29] In equine surgical colic patients, 54% had low serum Mg^{2+} levels and 17% had low tMg concentrations. Horses with ionized hypomagnesemia had a significantly greater prevalence of postoperative ileus than normomagnesemic equine surgical colic patients.[30] Surgical colic patients that were euthanatized at the time of surgery (7/35) had significantly lower preoperative serum concentrations of Mg^{2+} compared with horses that survived, but the serum Mg concentration did not predict hospitalization time or survival.[30] A low Mg^{2+} concentration was documented in 78% (50/64) of horses with enterocolitis.[19] In other species, a clear association has been made between hypomagnesemia, severity of disease, and mortality, but larger studies in severely ill horses may be required to determine if similar associations exist in horses. Although 15% of critically ill foals were found to have low serum Mg^{2+} concentrations, no association between hypomagnesemia and mortality was detected.[31] Hypomagnesemia is also commonly seen in blister beetle toxicosis[32] and horses with synchronous diaphragmatic flutter (SDF).

Sepsis-induced hypocalcemia and hypomagnesemia may be associated with intracellular ionic shift, hemodilution, or sequestration. Mg may function as a Ca antagonist, and low Mg concentrations may enhance intracellular entry of Ca in sepsis and endotoxemia.[22] It is undetermined if Mg administration to acutely hypomagnesemic patients is beneficial in the reduction of mortality or length of hospitalization, but it seems reasonable to therapeutically maintain serum concentrations within reference range during times of severe illness when homeostatic mechanisms are overwhelmed.

ASSOCIATION OF HYPOMAGNESEMIA WITH HYPOKALEMIA

Hypomagnesemia is frequently associated with hypokalemia and kaliuresis in other species.[33–37] Mg deficiency has been associated with the loss of cellular potassium stores, and as is the case in hypocalcemic patients, it may be difficult to restore normokalemia until the concurrent Mg deficiency is corrected.[38] Hypomagnesemia affects the ability of Mg to act as a coenzyme for the Na^+/K^+ ATPase pump, resulting in decreased intracellular K^+ and increased intracellular Na^+ concentrations that lower the resting membrane potential, predisposing cells to spontaneous depolarization and impairment of transmission of electric impulses. Hypomagnesemia can result in the blockade of voltage-gated K^+ channels,[39] which interferes with electric repolarization and the propagation of the action potential. Hypomagnesemia can also lead to increased Purkinje fiber excitability, which predisposes to arrhythmia generation.[40] Clinically, concurrent hypomagnesemia and hypokalemia leads to hyperexcitability, cardiac arrhythmias, seizures, muscle fasciculations, and weakness.

ASSOCIATION OF HYPOMAGNESEMIA WITH HYPOCALCEMIA

Hypocalcemia and hypomagnesemia are concurrently observed in horses with blister beetle poisoning, endotoxemia, enterocolitis, intestinal strangulation, ileus, and SDF; in transported horses; and in lactating mares.[19,28,30,32] Hypocalcemic patients with concurrent hypomagnesemia are often refractory to Ca therapy unless the low serum Mg concentrations are identified and corrected.[41–44] Although the mechanisms by which hypomagnesemia results in hypocalcemia are not completely understood, low serum Mg concentrations can impair PTH synthesis and secretion and induce target tissue resistance to PTH. This mode of action affects renal resorption of Ca^{2+}

and Mg^{2+}, decreases bone resorption, and reduces renal synthesis of 1,25-dihydroxyvitamin D_3.[45] Consequently, parallel determination of Ca and PTH concentrations is important in the investigation of Mg and Ca homeostasis.

Mg is considered nature's physiologic Ca blocker because it reduces the release of Ca from and into the sarcoplasmic reticulum and protects the cell against Ca overload under conditions of ischemia.[46] Mg's Ca channel blocking effect seems to be decreased in the hypomagnesemic state with a subsequent increase in intracellular Ca concentration, leading to enhanced cellular sensitivity to cardiotoxic drugs or ischemic events.

ASSOCIATION OF MG AND ENDOTOXEMIA

Hypocalcemia and hypomagnesemia are common in horses with sepsis and endotoxemia.[19,29,30] Experimental endotoxin infusion in horses resulted in electrolyte abnormalities that included hypomagnesemia, hypocalcemia, hypokalemia, hypophosphatemia, and increased serum PTH and insulin concentrations, but no changes in serum sodium or chloride concentrations.[28] Correction of electrolyte abnormalities is well recognized as part of the care of the critically ill equine patient, and it seems that correction of serum Mg^{2+} concentrations is warranted. Experimental murine studies have implicated Mg in cell messaging and cytokine production. Hypomagnesemic rats exhibit elevated circulating cytokine concentrations (interleukin [IL] 1, IL-6, tumor necrosis factor [TNF]) indicating a generalized inflammatory state.[26,27] Hypomagnesemic rats are acutely sensitive to the effects of experimentally administered endotoxin, and this vulnerability is correlated with higher plasma TNF concentrations.[27] In a murine model, progressive Mg deficiency led to increasing mortality rates from the effects of endotoxin administration, whereas Mg supplementation reduced the endotoxin-induced mortality.[22] Hypomagnesemia also predisposed animals to free radical–associated injury,[23,24] leading to the formation of cardiomyopathic lesions and altered vascular tone.[25,47] These murine studies were performed after chronic dietary-induced hypomagnesemia, and care must be taken when extrapolating this information to the critically ill patients, which have redistribution of serum and cellular Mg rather than a state of whole body Mg depletion.

ASSOCIATION OF MG AND INSULIN RESISTANCE

Although a great deal of controversy exists about the role of Mg in human diabetes, there have been epidemiologic studies linking low Mg status with insulin-dependent and non–insulin-dependent diabetes mellitus.[48] Intracellular Mg^{2+} concentration has been shown to modulate insulin action, and there is an increased incidence of low intracellular Mg^{2+} concentrations in human patients with non–insulin-dependent diabetes mellitus.[49] There have been suggestions that this incidence may result in defective tyrosine kinase activity at the insulin receptor level, resulting in increased intracellular Ca^{2+} concentrations, which can contribute to worsening insulin resistance.[48,49] Daily oral Mg supplementation to human patients with non–insulin-dependent diabetes mellitus has resulted in the restoration of intracellular Mg^{2+} concentrations and improvement of insulin-mediated glucose uptake.[48]

Care should be taken when making inferences from humans to horses because human epidemiologic data are often confounded with poor dietary intake and alcoholism. There has been some discussion as to the usefulness of Mg supplementation to horses with insulin resistance with either equine metabolic syndrome or pituitary pars intermedia dysfunction. It seems unlikely that horses would develop chronic whole body Mg deficiency because efforts to induce Mg depletion have required

long-term feeding of severely Mg-deplete artificial diets in young growing animals.[1,9,10] It is the author's opinion that dietary Mg supplementation to horses is infrequently required when a normal diet is fed. However, oral Mg supplementation is unlikely to be harmful because of rapid renal elimination of excessive Mg if renal function is normal. There are anecdotal reports from veterinarians that Mg supplementation in addition to previously attempted dietary modifications to horses with equine metabolic syndrome has been beneficial in reducing neck crestyness and the frequency of laminitis episodes. However, there are no published reports or experimental substantiation of such claims.

EXPERIMENTAL DIETARY MANIPULATION OF MG IN HORSES

Hypomagnesemia was induced in mature ponies by feeding 5 to 6 mg/kg BW/d of Mg (using a 370 ppm diet) while 20 mg/kg BW/d met Mg requirements.[50] A deficiency state can be more readily induced in growing animals because of their higher dietary requirement of Mg. Foals fed an extremely Mg-deficient diet (7–8 ppm or 0.0007%) developed severe mineralization of the aorta, with severe clinical signs of hypomagnesemia becoming apparent after 90 days in 2 of 11 foals.[51]

Urinary excretion of electrolytes is useful for assessing the dietary supply of minerals. The urinary Mg concentration decreased from a baseline of 30 mg/dL to 4 mg/dL after 6 days on a Mg-deficient diet (370 ppm) and increased to more than 300 mg/dL on a high Mg diet supplemented with 36 g of MgO/d.[50] Increasing the Mg content of a diet from 3100 ppm to 8600 ppm increased Mg digestibility, retention, and excretion in urine and feces and increased serum concentrations from 2.21 mg/dL to 3.39 mg/dL.[10] In foals fed a severely Mg-deficient diet (7–8 ppm), serum Mg concentration decreased rapidly from a baseline of 0.78 mmol/L to 0.53 mmol/L after 7 days and then decreased steadily to 0.26 mmol/L after 150 days. The slower rate of reduction in serum Mg concentrations was presumed to be caused by the mobilization of Mg from bone. Bone Mg content decreased in response to Mg depletion, however, there was no effect on tissue (brain, liver, kidney, spleen, lung, cardiac, or skeletal muscle) concentrations of Mg, Ca, or P after 71 to 180 days.[52]

CLINICAL SIGNS AND CONSEQUENCES OF MG DEFICIENCY

In comparison to cattle, clinical signs of hypomagnesemia are rarely reported in horses, but include weakness, muscle fasciculations, ventricular arrhythmias, seizures, ataxia, and coma. Hypocalcemic tetany complicated by hypomagnesemia was reported in Welsh mountain ponies.[53,54] Similar signs were experimentally induced after 90 days in 2/11 foals fed an extremely Mg-deficient diet (7–8 ppm). Signs of hypomagnesemic tetany were precipitated by loud noises, with foals initially exhibiting nervousness, muscular tremors, and ataxia followed by collapse, with profuse sweating, hyperpnea, and convulsions. One foal died during its third seizure on day 150 of the deficiency trial.[51]

Concurrent hypocalcemic and hypomagnesemic tetany was reported in 2 thoroughbred broodmares that had been transported for breeding. The mares were nursing foals that were aged 4 and 7 weeks. Their serum total Ca (tCa) concentration was 4.0 mg/dL and 5.4 mg/dL, whereas their tMg was 1.0 mg/dL and 1.9 mg/dL, respectively. The mares responded to IV calcium borogluconate and magnesium chloride.[55]

Severe hypomagnesemia can lead to ventricular arrhythmias, supraventricular tachycardia, or atrial fibrillation. Characteristic findings on electrocardiogram (ECG) include prolongation of the PR interval, widening of the QRS complex, ST segment depression, and peaked T waves.[56]

Hypomagnesemia and hypocalcemia are common perioperatively in horses requiring exploratory celiotomy for colic, particularly in horses with strangulating intestinal lesions and ileus. Significantly lower serum concentrations of Mg^{2+} occurred in horses that developed postoperative ileus.[30] Horses with strangulating lesions were more likely to be hypomagnesemic and hypocalcemic and have more ECG changes than horses with nonstrangulating lesions.[30] There are probably multiple factors that contribute to the observed ECG disturbances, but the routine detection and correction of electrolyte abnormalities (including Mg^{2+} and Ca^{2+}) is recommended.

Hypomagnesemia and hypocalcemia can contribute to SDF, also known as "thumps." Horses with dehydration; electrolyte derangements; and especially hypochloremic metabolic alkalosis associated with prolonged endurance exercise, gastric outflow obstruction, and sometimes after inappropriate bicarbonate administration are predisposed. Irritation of the phrenic nerve causes unilateral or bilateral contraction of the diaphra\ synchronous with the heartbeat. A state of alkalosis because of massive chloride and hydrogen ion loss caused by prolonged sweating or reflux of gastric origin or inappropriate bicarbonate administration can result in hydrogen ion shifts and exposure of negative charges on serum protein molecules, which subsequently bind Ca^{2+} and Mg^{2+} resulting in a relative ionized hypocalcemia and hypomagnesemia. The tCa and tMg levels are normal, but Mg^{2+} and Ca^{2+} concentrations are low. The condition may resolve spontaneously after resolution of the primary cause or after the correction of electrolyte and acid-base imbalance and rehydration. IV administration of calcium gluconate and $MgSO_4$ often speeds recovery.

MG AND BRAIN INJURY

Mg is important in the regulation of neuroexcitation by blocking signal transmission via inhibition of Ca^{2+} -dependent presynaptic excitation-secretion coupling.[57–60] Depletion of Mg contributes to tetany by increasing acetylcholine release from neuromuscular junction and delaying degradation by acetylcholinesterase. Mg infusions have been advocated in the treatment of human and equine brain and spinal trauma patients, but the efficacy of such treatments is still uncertain.[58–60] Based on evidence from human medicine, Mg infusions are also used in the empiric treatment of hypoxic ischemic encephalopathy (HIE) in neonatal foals.[61]

Cerebral hypoxia impairs maintenance of ionic gradients across cell membranes, resulting in an influx of Ca and glutamate. Intracellular Ca and glutamate overload results in neuronal cell death. Traumatic brain injury induces the activation of the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor[62] and has been implicated in the pathophysiology of HIE.[63] Mg is important in the voltage-dependent blockade of NMDA Ca channels, preventing Ca entry into the cell and decreasing neurotransmitter release. Mg also blocks the entry of Ca through the voltage-gated Ca channels in the presynaptic membrane.[64] Normal blood-brain vessel vasodilation is also dependent on Mg.[65] Lower Mg concentrations increase vascular smooth muscle tone, potentiating vasospasm with reduction of oxygen and substrate delivery to tissues. Focal traumatic brain and spinal cord injury in rats can reduce free Mg concentrations in the brain by as much as 60%, with the reduction proportional to the extent of the injury.[64] Therefore, brain injury reduces brain Mg concentration, which will result in the loss of Mg's protective role and potentiate further brain injury.

The reduction in the voltage-dependant Mg^{2+} blockage of NMDA current in mechanically injured neurons can be restored by increasing extracellular Mg

concentration. $MgSO_4$ has been shown to dramatically improve the immediate recovery of rats from hypoxia[66] and improve the motor outcome in rats treated after severe traumatic axonal brain injury.[67] $MgSO_4$ has also been shown to protect the fetal brain during severe maternal hypoxia.[68] The available experimental literature and reasoning suggests that in most cases, Mg therapy may be advantageous in protecting against, and in the treatment of, HIE in foals and horses with traumatic brain injury, but further evidence is still required before the benefits, if any, can be proven.[59,61]

DIAGNOSTIC TESTING

The clinical laboratory evaluation of Mg status is primarily limited to the measurement of serum Mg concentration, 24-hour urinary excretion, and percentage retention after parenteral Mg loading. However, results for these tests do not necessarily correlate with intracellular ionized concentrations. There is no universally accepted, validated, and readily available test to determine the intracellular/total body Mg status.

The easiest way to assess Mg status is using serum tMg or Mg^{2+} concentrations. Serum Mg^{2+} is more useful because it is the active form and is minimally affected by serum protein concentrations. Hypoalbuminemia results in a low measured serum tMg concentration (pseudohypomagnesemia) and does not require Mg supplementation if the serum Mg^{2+} concentration is normal. Formulas to correct tMg concentration based on adjustment for protein concentrations are not accurate, and Mg^{2+} concentration should be measured. pH can affect the availability of serum Mg and the percentage in the active ionized form. Similar to Ca, Mg binds to anionic (negatively charged) protein binding sites, with the binding affinity depending on the pH. During acidosis, the increased hydrogen ion concentration displaces Ca^{2+} and Mg^{2+} from their protein binding sites, increasing the percentage of these cations in their ionized form, resulting in increased serum Ca^{2+} and Mg^{2+} concentrations. In animals with respiratory or metabolic alkalosis, (often observed after prolonged strenuous endurance exercise), Ca^{2+} and Mg^{2+} concentrations may be low because of increased protein binding. Because Mg^{2+} is the physiologically active component, with ionized hypomagnesemia, supplementation is recommended, especially if clinical signs of SDF (thumps); ileus; or rarely muscle fasciculations, ataxia, or tetany are observed. Although not likely to be of consequence in an animal with adequate renal function, resolution of the alkalosis may result in elevations of the serum Mg^{2+} concentration. In contrast, animals with metabolic acidosis secondary to sepsis, SIRS, and severe gastrointestinal disease rarely have serum ionized hypermagnesemia, rather their serum Mg^{2+} concentration tends to be low from altered Mg homeostasis, cellular or third space redistribution, gastrointestinal loss of Mg, or diuresis secondary to aggressive fluid therapy with IV fluids unsupplemented with Mg.

Renal excretion of Mg may be used to evaluate Mg balance. With low dietary Mg intake, urinary Mg excretion decreases to negligible levels.[1] Renal Mg excretion is measured in urine collected over 24 hours (mg/kg/d). The fractional clearance of Mg (FMg) is determined by expressing the renal Mg clearance relative to creatinine clearance. FMg in healthy horses fed grass hay ranges from 15% to 35%,[1,28] and values less than 6% indicate inadequate dietary Mg intake.[1] The Mg retention test to assess thev total body status has been evaluated in horses receiving Mg-deficient diets using 10 mg/kg of elemental Mg (100 mg/kg of a 50% $MgSO_4$solution diluted to 10%) administered intravenously over 60 minutes. Percentage retention (%Ret) is calculated as % Ret = (1 − [Mg excretion in 24 h]/[Mg infused]) × 100.

However, in the study validating the Mg retention test in horses, the 24-hour excretion of Mg was found to be a more sensitive indicator of reduced Mg intake than the Mg retention test, and the spot FMg reflected the 24-hour excretion of Mg, providing a simple method to assess the Mg status in horses.[1]

Muscle Mg content has been used as an estimate of total body Mg stores in horses.[1,15] In horses fed a moderately Mg-deficient diet, no differences were found in muscle Mg content compared with controls, but intracellular Mg^{2+} concentrations were lower in Mg-deficient horses.[1]

TREATMENT OF HYPOMAGNESEMIA

When supplementing Mg, it is important to carefully determine whether the dose reported is for elemental Mg or for the salt. For $MgSO_4$ solution (9.7% Mg), a dose of 100 mg/kg provides 9.7 mg/kg of elemental Mg, whereas for $MgCl_2$ (25.5%), a dose of 100 mg/kg provides 25.5 mg/kg of elemental Mg. Confusion and subsequent overdose may be fatal.

Recommended dose rates for $MgSO_4$ in adult horses are 25 to 150 mg/kg/d (0.05–0.3 mL/kg of a 50% solution) diluted to a 5% solution in normal saline, dextrose, or a polyionic isotonic solution and given by slow IV infusion. An IV constant rate infusion (CRI) of 150 mg/kg/d of $MgSO_4$ solution (0.3 mL/kg/d of the 50% solution) would provide the horse's daily requirements.[69] For a 500-kg horse receiving 30 L/d of IV fluids, 25 mL of a 50% $MgSO_4$ solution should be added to each 5 L bag, whereas for a horse receiving 60 L/d, 12 mL of $MgSO_4$ solution should be added per 5 L bag. Such therapy should also be considered in horses with postoperative ileus and SDF.

Plasmalyte-A and Normosol-R contain 3 mEq/L (3.6 mg/dL) of elemental Mg. If a horse received 60 mL/kg/d of the replacement fluid, it would receive 2.16 mg/kg/d of elemental Mg (equivalent to 20 mg/kg of $MgSO_4$). Additional Mg is required for long-term fluid support of an animal with inappetence.

$MgSO_4$ is also used to treat refractory ventricular arrhythmias, including those caused by idiosyncratic quinidine reactions (especially torsades de pointes). For ventricular arrhythmias, the intravenous administration of 2 to 6 mg/kg/min of $MgSO_4$ (1.8–5.4 mL of 50% $MgSO_4$/450 kg horse/min) to effect is recommended. Some investigators recommend a maximum dose of 25 g (56 mg/kg) of $MgSO_4$, but the author's studies in normal horses indicate that 100 mg/kg of $MgSO_4$ can be safely administered over 60 minutes, with mild sedation being occasionally noted.[1]

For the treatment of HIE in neonatal foals, Wilkins[61] suggests a CRI of $MgSO_4$ at an initial intravenous dose of 50 mg/kg/hour for 1 hour followed by a 25-mg/kg/h CRI for 24 hours. For a 50-kg foal, 62 mL of 50% $MgSO_4$ solution should be added to a 1 L bag of isotonic fluids and run at 85 mL/h for 1 hour, which is then decreased to 42 mL/h. This dose provides 600 mg/kg/d of $MgSO_4$ and is higher than that required for maintenance. Therapy has been continued for up to 3 days without visible detrimental effects other than possible trembling.[61] $MgSO_4$ has also been recommended as a muscle relaxant as an adjunctive treatment of tetanus. $MgSO_4$ can be infused with a high therapeutic safety index, with the safety depending on the dose and infusion rate, but is contraindicated with undiagnosed disturbances in cardiac conduction, renal failure, or elevated serum Mg concentrations.

The typical equine diet contains sufficient Mg for maintenance, with supplementation rarely required. If necessary, oral Mg can be provided with MgO, $MgCO_3$, or $MgSO_4$, which have equivalent digestibilities of approximately 70%. The maintenance requirement of 13 mg/kg/d of elemental Mg could be provided by 31 mg/kg/d of MgO,

64 mg/kg/d of $MgCO_3$, or 93 mg/kg/d of $MgSO_4$. This information may be important when formulating oral replacement fluids for horses that are inappetent.

$MgSO_4$ x H_2O (Epsom salt) is commonly used as an osmotic cathartic in the treatment of large colon impactions. A dose of 0.5 to 1.0 g/kg of $MgSO_4$ in 6 to 8 L of water can be administered by a stomach tube when the horse is metabolically stable. A second dose can be administered 24 to 36 hours later in severe cases only if serum Mg concentrations have returned to normal. Hypermagnesemic neuromuscular paralysis has been reported after the administration of 1.5 to 2 g/kg of $MgSO_4$.[31]

HYPERMAGNESEMIA

Hypermagnesemia is rare in all species and is commonly the result of iatrogenic Mg overdose or excessive supplementation to a patient with renal failure. Serum hypermagnesemia (with hyperkalemia and hyperphosphatemia) occurs after severe cellular damage (rhabdomyolysis, tumor lysis syndrome, hemolysis, severe sepsis).

Hypermagnesemia was reported in 2 horses given excessive Epsom salt in addition to dioctyl sodium sulfosuccinate (DSS) for the treatment of large colon impaction.[31] The 450-kg and 500-kg horses were reportedly given 750 g and 1000 g of Epsom salt, respectively. Four to six hours after the Epsom salt overdose, the horses showed signs of agitation, sweating, muscle tremors followed by recumbency, and flaccid paralysis. Tachycardia and tachypnea developed, peripheral pulses were undetectable, and capillary refill time was prolonged at 4 seconds. Serum tMg concentrations increased to 5 times the reported reference range. The horses were treated with 250 mL of a 23% solution of calcium gluconate (diluted in 1 L of 0.9% NaCl) administered slowly intravenously. One horse was able to stand 10 minutes after the completion of infusion. IV fluids were given to induce diuresis. A second Ca infusion was required when muscle tremors reoccurred 1 hour later in this horse. The second horse remained weak for several hours, being only able to stand for short periods. These 2 horses were given Epsom salt at 1.5 to 2 times the recommended maximum dose, but it is unlikely that this dose of Epsom salt alone would normally be able to induce such severe clinical signs. The investigators suggested that the concurrently administered DSS may have increased the intestinal permeability and the Mg absorption, with exacerbation of the signs of hypermagnesemia because of the concurrent low serum Ca concentration. Epsom salt should only be given to treat large colon impactions after correction of dehydration and metabolic imbalances. Simultaneous administration of excessive doses of Epsom salt with DSS should be avoided.[31]

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