Rational treatments for mineral disorders in fresh cows

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Abstract

Hypocalcemia, hypophosphatemia, hypomagnesemia, and hypokalemia are important metabolic diseases of fresh dairy cows. Many dairy practitioners and dairy producers may need to update their approaches to these diseases based on current scientific information. Hypocalcemia in standing cows is best treated orally; intravenous calcium should be reserved for recumbent cases of milk fever because it may cause cardiac toxicity and rebound hypocalcemia. Glucose or additional electrolytes should not be included in intravenous solutions administered to cows with hypocalcemia. Hypophosphatemia is a less common mineral disorder that is usually secondary to hypocalcemia. Mild to moderate cases of hypophosphatemia are best treated with oral phosphorus; intravenous phosphorus should be reserved for severe cases. Hypomagnesemia may be a clinical problem in grazing herds or a subclinical problem in confinement dairies with cows fed stored feeds. Clinical hypomagnesemia may be treated intravenously or via rectal enema; subclinical cases are best managed by oral magnesium supplementation. Hypokalemia may follow prolonged periods of anorexia in early lactation cows and typically presents as severe, flaccid paralysis. Oral potassium supplementation is the preferred means for treating and preventing hypokalemia.

Key words: fresh cow mineral disorders, hypocalcemia, hypophosphatemia, hypomagnesemia, hypokalemia

Résumé

L'hypocalcémie, l'hypophosphatémie, l'hypomagnésémie et l'hypokaliémie sont des désordres métaboliques importants chez les vaches récemment vêlées. En se basant sur l'état actuel des connaissances, plusieurs praticiens et producteurs laitiers pourraient avoir besoin de mettre à jour leurs approches concernant ces maladies. L'hypocalcémie chez les vaches debout se traite le mieux oralement. Le calcium intraveineux devrait être réservé pour les cas de fièvre vitulaire chez les vaches à terre car il y un risque de toxicité cardiaque et ce calcium peut causer un rebond de l'hypocalcémie. Le glucose ou d'autres électrolytes ne devraient pas être inclus dans la solution intraveineuse administrée à des vaches en hypocalcémie. L'hypophosphatémie est un désordre minéral moins commun qui fait souvent suite à l'hypocalcémie. Les cas légers ou modérés d'hypophosphatémie se traitent le mieux avec du phosphore administré oralement tandis que le phosphore intraveineux devrait être réservé aux cas plus sévères. L'hypomagnésémie peut être un problème clinique dans les troupeaux au pâturage ou un problème subclinique dans les troupeaux confinés nourris avec des aliments entreposés. L'hypomagnésémie clinique peut se traiter par voie intraveineuse ou par lavement du rectum tandis que les cas subcliniques se traitent le mieux par la supplémentation orale en magnésium. L'hypokaliémie peut faire suite à une longue période d'anorexie chez les vaches en début de lactation et se présente le plus souvent sous forme de paralysie flasque sévère. La supplémentation orale en potassium est la façon désignée de traiter et de prévenir l'hypokaliémie.

Introduction

Despite the shift from veterinary to lay diagnosis and treatment of most mineral disorders on dairy farms, dairy practitioners still have a unique role in guiding the diagnostic and treatment protocols used by dairy producers. This makes it doubly important that dairy practitioners be aware of the best available science and clinical observations about these disorders. Unfortunately, some of the treatments for metabolic diseases recommended by veterinarians are less than optimal. My main concerns are the excessive use of intravenous (IV) mineral treatments that interfere with the cow's own attempts at homeostasis, the use of IV multiple electrolyte solutions that contain ineffective ingredients, and disregard for oral treatments that may be more effective than IV treatments.

New graduates may face opposition from older veterinarians regarding new or different methods of diagnosing and treating mineral disorders in fresh cows. My suggestions for those in this dilemma are: 1) it is fair to expect to be given the freedom to diagnose and treat fresh cows as you were trained to do; 2) be professional as you deal with situations in which there are differences; and 3) respect the long experience that older practitioners have with less than optimal treatments. There are more important issues than these for you, your colleagues, and your clients.

The purpose of this paper is to provide an overview of the current science and clinical reasoning for appropriate diagnostic and treatment protocols for hypocalcemia, hypophosphatemia, hypomagnesemia, and hypokalemia in fresh dairy cows.

Diagnosis and Treatment for Hypocalcemia

Pathophysiology of hypocalcemia. Dairy cows excrete very large amounts of colostrum into milk after calving.

Calcium outflow increases from about 10 grams per day into the fetal skeleton prior to calving[18] to excreting about 30 grams of daily calcium into colostrum.[39] On the day before calving, the cow must meet the demand for both fetal and colostral calcium. Colostrum is about twice as calcium-dense as milk (1.7 to 2.3 g calcium per kg of colostrum vs 1.1 g/kg calcium in milk).[11,39]

Because of the large increase in calcium outflow that occurs after calving, about half or more of all second and greater lactation cows develop subclinical hypocalcemia (SCH) following calving and about 2 to 6% of second and greater lactation cows develop clinical milk fever.[34] Producers surveyed by the 2002 dairy study of the US National Animal Health Monitoring System (NAHMS)[43] reported that 5.2% of their cows had clinical milk fever. The incidence of clinical milk fever appears to be declining; producers surveyed in 2007 reported 4.9% clinical milk fever[44] and those surveyed in 2014 reported 3.7% clinical milk fever.[45] Average risk for clinical milk fever is not the goal; herds can continue to improve and do better than average. A reasonable goal for clinical milk fever cases is <2% of calvings from second and greater lactation cows.[30]

The 2002 NAHMS dairy study reported that 47% of second and greater lactation cows had SCH, which was defined as serum total calcium <8.0 mg/dL (<2.0 mmol/L) measured within 48 hours of calving but without clinical signs of milk fever.[34] The risk for SCH increased substantially as parity increased.

The overall risk for SCH in dairy herds does not appear to be declining over time; this is the opposite of the trend for clinical milk fever. Recent studies that measured SCH [5,23,35] have reported higher rates of SCH – as high as 88% of cows tested. Unfortunately, it is not possible to compare risks for SCH across studies because of differences in herd selection criteria, parities of cows sampled, and cutpoints used for SCH.

Standing vs recumbent cases of hypocalcemia. Keen dairy producers may recognize very early signs of clinical milk fever in standing cows; this is Stage 1 clinical milk fever. Clinical signs of Stage 1 milk fever may include wobbliness, weight-shifting, dull appearance, cold extremities, hypothermia, reduced ruminal contractions, and mild tachycardia.[29]

Oral calcium is the preferred supplementation choice for Stage 1 clinical milk fever. Oral calcium supplementation causes a very rapid spike in blood calcium concentrations that peak within about 30 minutes of administration.[14] The increase in blood calcium concentration following oral calcium chloride administration is equivalent to IV administration of about 4 grams of calcium.[14] This is the equivalent of about half of a bottle of IV calcium and should provide more than enough calcium to help the cow overcome her Stage 1 milk fever.

Intravenous calcium is not recommended for standing cows, even if they are exhibiting clinical signs of Stage 1 milk fever. Oral calcium supplementation alone is recommended because it is much safer for the cow. Intravenous calcium infusion increases blood calcium to extremely high and potentially dangerous concentrations.[13] Hypercalcemia may induce a fatal arrhythmia starting at blood concentrations of about 28 to 32 mg/dL (7.0 to 8.0 mmol/L).[22] The routine administration of a single dose of IV calcium increases average blood calcium to about 19 mg/dL (4.8 mmol/L), with individual cows exceeding 22 mg/dL (5.5 mmol/L).[4] It is useful to remember that any IV calcium infusion puts cows dangerously close to a fatal arrhythmia. This precludes the use of IV calcium in standing cows, because they do not require immediate correction of their hypocalcemia and can be effectively treated with oral calcium instead.

Another complication associated with IV calcium infusion is a secondary hypocalcemia. Hypercalcemia quickly and directly impairs parathyroid hormone (PTH) secretion. This in an unfortunate metabolic consequence, because increased PTH secretion is the cow's primary response to hypocalcemia. Increased PTH enhances renal reabsorption of calcium from proximal renal tubular fluids, enhances osteoclastic bone resorption, and stimulates the production of the hormonal form of vitamin D.[11] These adaptations to hypocalcemia are necessary for the cow to survive the period of negative calcium balance that occurs during early lactation. Interrupting them has negative consequences.

Blood concentrations of PTH are very high in cows suffering from clinical milk fever (about 2,000 pg/mL).[4] However, blood PTH decreases to about 100 pg/mL within 10 minutes of IV calcium administration.[4] This effectively ends the cow's own efforts to mobilize calcium at the time she most needs it.

Hypercalcemia caused by IV calcium also stimulates the release of calcitonin (CT). This may be even more detrimental to the cow than impaired PTH secretion, because CT actively inhibits renal calcium resorption and bone resorption. This can be measured (at least in part) by urinary calcium loss, which is substantial (about 1 to 2 grams of calcium within 30 minutes of IV calcium treatment).[13]

A rebound hypocalcemia following IV calcium administration is caused by the combined effects of impaired PTH secretion and increased CT secretion. Cows given IV calcium typically return to hypocalcemia within about 8 hours and remain hypocalcemic until 24 to 48 hours after IV treatment.[4,13] About 25% to 38%[9,26] of cows treated successfully with IV calcium will suffer a hypocalcemic relapse and become recumbent again. Preventive measures (described later in the paper) can greatly reduce the risk. Relapses into recumbency typically occur about 12 to 18 hours after the initial IV treatment.[9]

Intravenous calcium is clearly necessary for cows with Stage 2 or Stage 3 milk fever because recumbent cows can quickly suffer irreversible musculoskeletal damage. About 4 to 30% of cows with clinical milk fever become alert downer cows, and about 20 to 67% of alert downer cows die.[41] The critical need for a recumbent cow is to get up; this need overshadows potential complications from IV calcium

administration.

Proper intravenous dose of IV calcium. The goal of IV calcium treatment should be to provide as little calcium as possible in order to get the cow up. Any IV calcium beyond the minimum required exposes the cow to additional risk for fatal cardiac complications, inhibits the cow's own attempts at calcium homeostasis, and increases the risk for a hypocalcemic relapse.

It is not possible to precisely determine the optimal dose of IV calcium for recumbent cases of milk fever. Nonetheless, physiological calculations provide a useful starting point. A dairy cow's entire extracellular pool of calcium is about 11 grams (3.5 grams dissolved in the bloodstream and 7.5 grams in the interstitial fluid).[11] A cow in Stage 2 clinical hypocalcemia typically has a blood calcium concentration around 4.5 mg/dL (about half of the normal blood calcium concentration). The total calcium deficit for this cow is 6.5 grams (making the reasonable assumption that blood and interstitial fluid have equal calcium concentrations). Blood calcium is typically lower (about 2.0 mg/dL) in severe cases of Stage 3 milk fever. This represents a loss of about 88% of the extracellular calcium – about 9.7 grams. A single bottle of calcium for IV infusion provides about 8 to 11 grams of calcium – an amount that replaces more than the cow's entire body deficit of calcium in almost all scenarios. Providing some calcium beyond the deficit is reasonable because calcium will continue to be lost in the colostrum. However, IV infusions of 2 or more 500 mL bottles of calcium provides 16 to 22 grams of calcium, which is an unreasonably high amount.

Some empirical studies help us to define an optimal dose of IV calcium. A low dose of IV Ca (6.2 grams) was not as effective as 8.0 grams in treating clinical cases of milk fever.[27] Another field study reported that a high dose of IV calcium (12.4 grams of calcium) was no more effective in correcting clinical milk fever than a lower dose (7.4 grams of calcium).[10] Thus, a reasonable inference is that the optimal IV calcium dose is between about 7 and 10 grams of calcium.

The most commonly used IV calcium solution in the US is provided in a 500 mL bottle and contains 23% calcium gluconate. One bottle provides 10.7 grams of elemental calcium; this is sufficient to restore the entire calcium deficit of any hypocalcemic cow. Unfortunately, many veterinarians and producers routinely administer 2 or more bottles of IV calcium to cows with clinical milk fever. For example, a published field study used 2 bottles (1000 mL total) of calcium-containing solutions for all cases of clinical milk fever.[24] This equals as much as 21.6 grams of calcium per IV treatment, depending on the products used. This is physiologically unwarranted and potentially harmful. High doses of IV calcium could result in higher risks for iatrogenic death, hypocalcemic relapse, and alert downer cows.

Another potential complication of high doses of intravenous calcium is excessive systemic acidification. Intravenous calcium solutions are acidic because boric acid is added to calcium gluconate preparations to solubilize the calcium gluconate and stabilize the solution.[13] Intravenous calcium solutions in the US are typically labeled as containing calcium gluconate; however, boric acid has been added and the solution is technically calcium borogluconate. Calcium gluconate would precipitate at room temperature if the solution contained no boric acid and was more than about 10% calcium gluconate.[2] The actual concentration of calcium gluconate is typically 23% – much greater than 10%. In countries other than the US, IV calcium solutions are correctly labeled as calcium borogluconate and provide between about 8 and 12 grams of elemental calcium per standard dose of 400 to 500 mL. The standard US formulation of 500 mL of 23% calcium gluconate includes 17.5 grams of boric acid. One bottle of this solution lowers urinary pH substantially (from about 6.6 to 5.8 at 1 hour post-treatment).[3] The acid load from administering 2 bottles of 23% calcium gluconate has not been evaluated. It could be substantial and contribute to clinically relevant acidemia.

The amount of calcium required to restore depleted stores of intracellular calcium is not significant in determining the appropriate dose of intravenous calcium. Intracellular calcium concentrations are extremely low in dairy cows (about 0.004 mg/dL) and the total intracellular calcium pool is numerically insignificant (about 0.01 grams).[13]

Providing multiple electrolytes in addition to calcium for IV treatment. Many products marketed for treatment of hypocalcemia include phosphorus, magnesium, glucose, or potassium in addition to calcium. None of these additional electrolytes are necessary, and some could be harmful. Cows suffering from clinical milk fever typically have low blood phosphorus, high blood magnesium, high blood glucose, and normal to slightly low blood potassium.[21] This information alone indicates that including additional magnesium, glucose, and potassium is irrational. Low blood phosphorus during hypocalcemia suggests that treatment with additional phosphorus might be helpful. It is true that hypophosphatemia typically follows hypocalcemia; however, it does not require treatment unless it persists following the correction of the hypocalcemia. Another problem is that hypophosphites are commonly used as the phosphorus source in multiple electrolyte solutions; however, this form of phosphorus is not biologically available to the cow.

Hypermagnesemia often accompanies hypocalcemia because of the effect of PTH on the renal tubules. Administering additional magnesium to hypocalcemic cows is not necessary; however, there is no evidence of physiological basis for it to be harmful. One field trial reported that treating cases of clinical milk fever with either IV calcium alone (10.5 grams from calcium borogluconate) or an IV solution containing calcium (12.4 grams from calcium borogluconate) plus phosphorus (1.5 grams from glycerophosphate) and magnesium (2.6 grams from magnesium chloride) resulted in no difference in treatment response.[36] The addition of phosphorus or magnesium to IV calcium solutions for the treatment of hypocalcemia appears to be unnecessary.

Hyperglycemia accompanies hypocalcemia because calcium is required for glucose to simulate insulin secretion from the pancreas. Administering additional glucose IV to hypocalcemic cows that are already hyperglycemic is not necessary and could prolong the cow's period of hyperglycemia if her hypocalcemia is not corrected and her insulin secretion restored. The effect of a bolus dose of IV glucose on a cow that is already hyperglycemic has not been formally evaluated to my knowledge. Prolonged hyperglycemia from continuous glucose infusions lowers GI motility and may increase the risk for displaced abomasum.[17]

The amount of potassium contained in multiple electrolyte products marketed to treat milk fever is quite small (1 to 2 grams) relative to the extracellular pool of potassium (19 to 20 grams). Even if hypokalemia were present along with hypocalcemia (which it usually is not), providing enough potassium in an IV solution to correct a clinically significant hypokalemia is nearly impossible. Administering more than about 2 grams of potassium as an IV bolus causes very high risk for cardiac side effects and sudden death.[13]

The addition of a small amount of potassium to an IV solution for the treatment of clinical milk fever may reduce the risk for cardiac problems secondary to hypercalcemia. Potassium is known to counteract the toxic effects of calcium on the electrical potential of cardiac muscle.[13] However, there is no empirical evidence that the addition of potassium to IV solutions to treat clinical milk fever is actually safer or improves the clinical response to treatment.[13] It is quite likely that the very small dose of potassium found in multiple electrolyte solutions marketed for IV milk fever treatment at least does no harm.

The use of multiple electrolyte solutions containing additional phosphorus, magnesium and glucose for the treatment of clinical milk fever is irrational. Veterinarians should actively discourage dairy producers from using such products. Additionally, dairy practitioners should push against the notion that adding more ingredients to an IV solution makes it better. Stage 2 and Stage 3 cases of milk fever should be treated with a single bottle of a solution that provides 7 to 10 grams of calcium from calcium borogluconate. Nothing else is needed and anything else could be detrimental.

Preventing hypocalcemic relapses following successful IV treatment. About 25%[26] to 38%[9] of cows successfully treated with IV calcium will become recumbent again within about 12 to 24 hours. It is likely that an even higher percentage will return to biochemical hypocalcemia but remain standing.

Oral calcium supplementation is the preferred method of preventing hypocalcemic relapses following successful IV calcium treatment. The efficacy of oral calcium drenches in preventing relapses in cows successfully treated for clinical milk fever is about 50 to 60%.[42] Bolus formulations of oral calcium, which are safer to administer, were developed later and have not been directly evaluated for the prevention of hypocalcemic relapses. In theory, they should be just as effective in reducing the risk for hypocalcemic relapses. A reasonable recommendation is to administer one oral bolus after the cow is standing, alert and able to swallow, followed by a second bolus about 12 hours later.[28,42]

Subcutaneous calcium administration is a second-choice approach to preventing hypocalcemic relapses following successful IV treatment of cases of clinical milk fever. It reduces the risk for a clinical relapse by about half compared to cows not given any source of slower-release calcium after IV calcium administration.[9] Important practical limitations of subcutaneous calcium administration are tissue irritation and abscessation. High amounts of extracellular calcium may overwhelm the ability of cells to maintain low intracellular calcium concentrations and lead to cell death.[13] The amount of solution per injection site should be limited to 1.0 to 1.5 grams of calcium, which equals about 50 to 70 mL per site for a typical IV calcium preparation.[13] Solutions that contain glucose should never be given subcutaneously due to the high risk for swelling, tissue irritation, and abscessation. Glucose requires active uptake by cells; however, there is not much cellular activity in the subcutaneous space. This leads to poor absorption of the glucose, prolonged high osmolarity in the subcutaneous space,[13] swelling, and tissue irritation. Glucose also supports bacterial growth in the subcutaneous space, which increases the risk for abscessation.

Managing subclinical hypocalcemia in early lactation. Individual treatment of cows for SCH is not possible, because cows with SCH (by definition) do not exhibit clinical signs and thus cannot be diagnosed. This leaves either blanket or strategic supplementation as the only options. Oral calcium is the most commonly used form of calcium supplementation for mitigating the effects of SCH on fresh cows.[28] Blanket oral calcium supplementation for second and greater lactation cows reduced the risk for health events in lame cows and increased milk yield in cows with higher previous lactation milk production.[31] The herds that participated in this large field study were fed supplemental anions and had an extremely low incidence of clinical milk fever. Nonetheless, they still had positive results in subgroups of cows. In this study, it is also notable that neither the age of the cow at calving nor her blood calcium concentration at calving had any effect on her response to oral calcium supplementation.[31]

Blanket use of IV calcium for the management of SCH is clearly contraindicated due to the risk for cardiac complications and rebound hypocalcemia. This concept is well illustrated by a field trial in which cows that were given a blanket, single-dose treatment of IV calcium at calving had lower blood calcium concentrations by 48 hours after calving than cows given no supplemental calcium at all.[3]

Treating secondary hypocalcemia in early lactation cows. Transient hypocalcemia may occur whenever a dairy cow goes off feed or has periods of decreased intestinal motility. This principle is illustrated by the results of a study in which cows were induced to have hypocalcemia. This resulted in severe ruminal stasis.[20] Gastrointestinal stasis

from other causes could lead to hypocalcemia, or at least make it worse. Whatever the underlying cause, oral calcium supplementation is indicated for any off-feed cows in early lactation. Most oral fresh cow drench products (or recipes) contain an effective dose of oral calcium. Sick cows that are still standing should not be exposed to the risks of IV calcium administration.

Diagnosis and Treatment for Hypophosphatemia

Overview of hypophosphatemia. Primary hypophosphatemia in dairy cattle is extremely unusual; almost all dairy cows are fed diets that provide excessive amounts of dietary phosphorus. Phosphorus is an important environmental pollutant, and dairy nutritionists have appropriately focused on reducing dietary phosphorus intakes. Even with reductions, dairy cattle diets are well over minimum phosphorus requirements.

Hypophosphatemia can occur in early lactation cows for metabolic reasons rather than overt phosphorus deficiency. Milk production requires a significant phosphorus outflow, and colostrum is higher in phosphorus than milk.[15] Thus, the greatest challenges to phosphorus homeostasis occur in early lactation.

Most hypophosphatemia is secondary to hypocalcemia. Blood calcium and phosphorus concentrations are highly correlated; 90 to 100% of cows with clinical milk fever will be hypophosphatemic.[4] The known physiology of calcium and phosphorus metabolism explains this relationship. The first principle is that PTH, which increases during hypocalcemia, causes renal excretion of phosphorus in order to retain calcium. The second principle is that salivary phosphorus, in the form of phosphate buffers, pools in the rumen during periods of hypomotility caused by hypocalcemia. The amount of ruminal phosphorus that is transiently unavailable may be substantial. Saliva contains about twice the concentration of phosphorus as blood, and salivary production of phosphorus is between 25 and 100 grams per day.[13] Phosphorus that is pooled in the rumen cannot be absorbed across the rumen wall; it must pass on to the small intestine before it can be absorbed back into circulation.

Hypophosphatemia secondary to hypocalcemia almost always self-corrects once the hypocalcemia is corrected. Restored blood calcium improves ruminal motility and allows pooled salivary phosphorus to exit the rumen and be absorbed back into the bloodstream at the small intestine. Correcting the hypocalcemia also lowers blood PTH, which decreases renal phosphorus excretion. These theoretical assertions have been supported by field study results. For example, adding IV sodium phosphate to IV calcium for the treatment of cows with clinical milk fever did not improve response to treatment, despite the finding of hypophosphatemia in almost all of the affected cows.[4]

A small proportion of cows with secondary hypophosphatemia remain hypophosphatemic following correction of the hypocalcemia. Blood phosphorus concentrations in these cows are quite low - typically about 0.5 to 0.9 mg/dL (0.15 to 0.30 mmol/L).[3] This is well below the normal range of about 4.0 to 8.0 mg/dL (1.3 to 2.6 mmol/L). Some cows with persistent hypophosphatemia may remain recumbent but alert. The exact causes for persistent hypophosphatemia are unknown, and the role that hypophosphatemia might play in the continued recumbency of these cows is unclear and controversial. There is no empirical evidence that hypophosphatemia actually causes prolonged recumbency.[15] Persistent recumbency may be secondary to hypocalcemia-related musculoskeletal damage, gastrointestinal stasis, and inappetance.

Hypophosphatemia may also be secondary to IV administration of glucose. A bolus dose of IV glucose lowers blood phosphorus concentrations quickly and dramatically.[16] This effect is mediated by insulin, which moves phosphorus from the extracellular space into the cells.[15] Insulin increases dramatically following IV glucose administration.

Several unique features of phosphorus metabolism complicate our ability to diagnose it. For example, blood collected from the jugular vein contains less phosphorus than blood collected from the coccygeal vein.[25,46] This happens because the salivary glands, located just above the jugular vein, harvest large amounts of phosphorus to buffer the rumen. Therefore, jugular blood samples may cause a false positive diagnosis of hypophosphatemia. Blood samples collected to diagnose recumbency in parturient dairy cows should always be collected from the coccygeal vein. Blood samples should also be collected prior to any treatment. If the cow was recently given IV glucose, her blood phosphorus will be depressed (as described above).

It is reasonable to attempt to correct hypophosphatemia whenever it is diagnosed, whether hypophosphatemia directly contributes to prolonged recumbency or not.[13,15] Treating the primary cause of the hypophosphatemia (hypocalcemia or hyperglycemia) is always the first consideration. There are no empirical data to support the value of phosphorus therapy for recumbent cows with hypophosphatemia.[15] Phosphorus therapy likely does no harm if it does not interfere with correction of the cow's primary condition and if it is not seen as a replacement for excellent management of downer cows (humane handling, prompt flotation, and excellent nursing care).

Intravenous treatment for hypophosphatemia. Intravenous treatment for hypophosphatemia is controversial. One author suggests reserving it for unusual cases, such as when severe intravascular hemolysis may be resulting from the hypophosphatemia.[15] Another author is more open to wider use.[13]

A precise dose of phosphorus needed for IV treatment cannot be known.[15] Nonetheless, a reasonable dose can be estimated from the calculated phosphorus deficit in the cow. The entire extracellular pool of inorganic phosphorus for a dairy cow is about 6 grams.[13] Using the reasonable assump-

tions that blood phosphorus is a valid surrogate for extracellular phosphorus[15] and that the phosphorus concentration in extracellular fluid decreases from about 5 mg/dL to 1 mg/dL (1.6 to 0.3 mmol/L) during hypophosphatemia, the calculated extracellular phosphorus deficit in a hypophosphatemic cow is about 4.8 grams. It would also be reasonable to provide a modest amount of additional phosphorus to help cover for continued phosphorus loss in the milk. Therefore, a reasonable dose for IV phosphorus therapy is about 5 to 7 grams of phosphorus.[13] Intracellular phosphorus is unlikely to be depleted during short periods of hypophosphatemia and is not considered in the dosage calculations.[13]

No commercial products are available in the US that can be recommended for the IV correction of hypophosphatemia. The only recommended IV treatment for hypophosphatemia is 30 grams of sodium phosphate (monobasic, monohydrate, reagent grade) mixed in 300 mL sterile water.[13] This formulation provides 6.7 grams of phosphorus. It should be infused slowly, over a 10 minute or longer period of time. Intravenous phosphorus supports blood phosphorus concentrations for only 3 to 4 hours.[13] Therefore, oral supplementation of phosphorus should follow IV phosphorus treatment for most cases. An exception could be made for cows that are able to get up and begin eating well on their own.

Intravenous infusions of phosphorus should not be regarded as innocuous. Blood phosphorus concentrations rise well above the normal range soon after IV infusion. This apparently does not cause overt clinical signs or problems with rebound hypophosphatemia, because phosphorus is a poorly regulated mineral. However, hyperphosphatemia is associated with transient reductions in blood calcium. The formation of insoluble calcium phosphate crystals in the bloodstream could explain the secondary hypocalcemia.[15] The value of IV phosphorus infusions must be weighed against risks associated with subsequent hypocalcemia.

Sodium phosphate cannot be mixed with calcium salts prior to IV administration, as the phosphates immediately form insoluble calcium phosphate crystals in the bottle. The same phenomena may occur in the bloodstream of the cow; giving IV phosphorus concurrent with or soon after IV calcium will simply favor the formation of insoluble calcium phosphate crystals and not correct either the calcium or phosphorus deficit. Wait at least 2 hours after giving IV calcium before administering IV phosphorus.[13]

Some saline enemas that are available over the counter for human use contain a reasonable dose of phosphorus (6 to 7 grams) that comes from reasonable sources (monobasic and dibasic sodium phosphate). These have been used for IV treatment of hypophosphatemia in dairy cattle. The use of these formulations in dairy cattle involves some risk. First, the enema solution should first be diluted with water to 1000 mL in order to reduce the tonicity of the IV infusion.[13] Second, the amounts and effects of other ingredients in these human enema solutions (benzalkonium chloride and disodium EDTA, for example) are unknown.

Infusing more than about 8 grams of phosphorus IV will cause severe and unnecessary hyperphosphatemia. High blood phosphorus by itself is apparently not a clinical problem; however, it could trigger a profound, secondary hypocalcemia.[15]

Ineffective sources of parenteral phosphorus. Hypophosphites (PO_2) such as calcium hypophosphite may be added to commercially-available multiple electrolyte solutions labeled for the correction of hypocalcemia or hypophosphatemia. Hypophosphites are chosen as the source of supplemental phosphorus because they do not precipitate with calcium, as phosphates would. Unfortunately, phosphites are biologically unavailable to the cow.[6] Phosphates (PO_4) are the dominant form of phosphorus in the body and are biologically available.[13] Phosphite forms of phosphorus are not biologically available, are not metabolized, and are simply excreted in the urine. They do no apparent harm, but have no value whatsoever in correcting hypophosphatemia. It is unfortunate and misleading that hypophosphites are added to multiple electrolyte IV solutions. Any label indication for these products indicating that they may be used to treat phosphorus deficiency is false.

Organic phosphorus compounds may be included in products that are labeled for parenteral use to correct phosphorus deficiencies. Examples of organic phosphorus sources include sodium glycerophosphate, butafosfan, toldimfos, and aminoethyl dihydrogen phosphate. This category of products is not recommended for correcting hypophosphatemia. They either use a metabolically useless form of phosphorus, or they provide much less phosphorus than is needed to be metabolically useful in hypophosphatemic cows.[15]

Oral treatment for hypophosphatemia. Oral supplementation of phosphorus is the preferred approach to correcting and sustaining blood phosphorus in mild to moderate cases of hypophosphatemia.[15] An example recipe for oral phosphorus supplementation is 200 to 300 grams of feed grade monosodium phosphate (NaH_2PO_4) mixed with about 1.5 L warm water.[13,16] This solution can be administered by pumping it through an oro-gastric tube or as a drench. Pumping is preferred, as oral drenching results in about a 13% loss of product due to spillage.[19] Extreme care must be used to prevent pharyngeal trauma or regurgitation with aspiration when administering oral supplements to recumbent cows.

Oral administration of 200 to 300 grams of monosodium phosphate provides 45 to 67 grams of elemental phosphorus. This dose appears adequate to support blood phosphorus concentrations for about 12 to 24 hours and does not cause hyperphosphatemia.[13,19] Monopotassium phosphate (KH_2PO_4) is similarly effective in supporting blood phosphorus when administered at a similar dose (263 grams, which provides 60 grams of phosphorus).[19] Monopotassium phosphate provides an effective dose of available potassium as well as phosphorus; this could be useful for cows with anorexia in early lactation. Monocalcium phosphate ($Ca(H_2PO_4)_2$) does raise blood phosphorus concentrations,

but not as much as monosodium or monopotassium phosphate.[19] Dicalcium phosphate ($CaHPO_4$) has little to no effect on blood phosphorus concentrations. It is not considered an effective oral phosphorus supplement.[19,40]

Oral monosodium phosphate or monopotassium phosphate may be administered to cows in gelatin capsules.[13] A number 7 gelatin capsule (1.5-ounce size) has a 24 mL capacity and should hold about 49 grams of monosodium phosphate (assuming 2.03 grams per cubic centimeter) or about 56 grams of monopotassium phosphate (assuming 2.34 grams per cubic centimeter). Thus, about 4 to 6 capsules per cow would be a reasonable dose for either compound.

This author is not aware of any commercially available paste, gel, or bolus formulations in the US that provide a reasonable amount of supplemental phosphorus from monosodium phosphate. Oral products in the US that contain phosphorus are typically combined with other nutrients and provide relatively small amounts of phosphorus from less available sources. The labels for these products may create the false impression that they are useful for correcting hypophosphatemias.

Subcutaneous treatment for hypophosphatemia. There are no commercially available phosphorus supplements in the US that are labeled for subcutaneous administration. The subcutaneous administration of monosodium phosphate solutions is strongly discouraged. Unbuffered preparations of monosodium phosphate have a very low pH (< 3.5); this would be expected to cause severe tissue irritation if given subcutaneously.[15] Buffering a monosodium phosphate solution to a reasonable pH (above about 5.8) would unfortunately impair its solubility.[13]

Diagnosis and Treatment for Hypomagnesemia

Clinical hypomagnesemia. Clinical hypomagnesemia (grass tetany) is mostly a disease of pastured animals; it is uncommon in dairy cattle housed in confinement and fed stored feeds. Grazing dairies do encounter hypomagnesemia during the spring months, when pasture is relatively high in potassium and low in magnesium. Potassium, as for all monovalent ions, is highly soluble in water and is readily taken up by plant tissue during the wet, early spring months. Grass tetany may be seen year-round in the southern US, when dairy cattle may be grazed on cool-season pasture grasses during periods of high moisture.

Potassium unfortunately competes with magnesium for plant uptake from the soil and for ruminal absorption. Thus, hypomagnesemia may develop when pastures are low in magnesium, high in potassium, or both.

Cows have minimal ability to regulate blood magnesium. They also have no readily available body stores of magnesium. Thus, they must consume adequate amounts of available magnesium from the diet each day.

The clinical signs of grass tetany are easily recognized in grazing cows. Affected cows initially have mild anorexia. They soon develop hyperexcitability and may separate from the rest of the herd. If observed closely, they may display ear twitching, muscle fasciculations and hyperesthesia around the head. Some cows become maniacal and aggressive. Clinical signs then often progress to more severe whole-body tremors, ataxia, and recumbency with seizure activity. Low magnesium concentrations in the cerebrospinal fluid (CSF) are regarded as the primary cause for the clinical signs of grass tetany.[1,32] A clinical diagnosis of hypomagnesemia can be confirmed by pre-treatment blood magnesium below 1.1 mg/dL (0.5 mmol/L), or preferably by CSF magnesium below 1.0 mg/dL (0.4 mmol/L).[13] Blood magnesium concentrations may occasionally be falsely elevated (and thereby considered normal) because severe tetany may damage muscle cells enough to cause leakage of magnesium from the cells into circulation. Note that cells have relatively high magnesium concentrations compared to extracellular fluid. Magnesium concentration in the CSF is not affected by muscle damage and is therefore the preferred sample for diagnosing hypomagnesemia. Magnesium concentrations in CSF are low during episodes of tetany and for up to 12 hours after death.[13]

Hypomagnesemic cows that exhibit signs of tetany will almost certainly have concurrent hypocalcemia. Clinical manifestations of tetany may not even be possible unless the cow is also hypocalcemic.[11]

Treatment of clinical hypomagnesemia. Cows with clinical hypomagnesemia require immediate treatment with parenteral magnesium and calcium. Calcium is included in the treatment for 2 reasons: 1) affected cows are also hypocalcemic, and 2) IV calcium reduces the severity of side effects associated with IV magnesium, such as respiratory paralysis and cardiac arrest. An appropriate magnesium dose is between 1.5 and 2.25 grams of elemental magnesium. This allows for 50 to 75% replacement of all of the cow's extracellular magnesium.[13] Multiple electrolyte preparations available in the US typically contain about 1.6 grams of magnesium from magnesium borogluconate; this is a reasonable dose.

Multiple electrolyte preparations are often the only practical IV treatment for hypomagnesemia. Other components of some multiple electrolyte solutions may be unnecessary (phosphorus and potassium) or potentially harmful (glucose – since cows with clinical hypomagnesemia are most likely already hyperglycemic). Nonetheless, a multiple electrolyte solution that contains both magnesium and calcium may be the most practical choice for the initial correction of severe hypomagnesemia.

Intracellular magnesium represents about 29% of total body magnesium, and intracellular magnesium concentrations are very high relative to extracellular magnesium.[38] Fortunately, intracellular magnesium does not appear to be depleted during hypomagnesemia.[13] Correction of the extracellular magnesium deficit should be sufficient.

Cows with clinical grass tetany need immediate magnesium supplementation and should be treated IV whenever practical.[13] Once IV treatment is started, the infusion should

be given as slowly as possible, with careful monitoring of heart and respiratory rates.

Some cows affected with clinical grass tetany are too aggressive to be restrained for IV treatment. In these cases, supplemental magnesium may be administered by safer routes. Magnesium sulfate (about 200 to 400 mL of a 25% solution of $MgSO_4 \cdot 7\ H_2O$) can be given subcutaneously (50 to 100 mL per injection site).[13] This provides 4.9 to 9.9 grams of magnesium, which is reasonable to correct the cow's magnesium deficit. However, subcutaneous absorption will obviously be slow compared to IV magnesium administration. Cows with cold extremities may have poor peripheral perfusion and are not good candidates for subcutaneous magnesium.[13] There are no commercially available magnesium solutions for subcutaneous injection marketed in the US; therefore, the magnesium sulfate solution described above must be made up and sterilized by the veterinarian.

Expect the response to IV or subcutaneous treatment to be slower for cows with clinical grass tetany compared to cows with clinical milk fever. Additional time is required for magnesium to cross into the CSF; cows cannot recover until CSF magnesium is restored. Treated animals should not be stimulated to rise during or soon after treatment; this could trigger fatal convulsions. Instead, cows should be left in a quiet location after treatment and allowed at least 30 minutes to respond on their own without any stimulation to rise.[13]

Rectal administration is the route of choice for delivering supplemental magnesium to hypomagnesemic cows with severe convulsions and/or poor peripheral perfusion.[13] This route is safer both for the cow and for the person administering the treatment. Example magnesium-containing enema formulations are 60 grams of magnesium chloride or 60 grams of magnesium sulfate dissolved in 200 mL warm water. Administer the solution into the descending colon via a short tube.[3] Rectal absorption of magnesium is very good; blood magnesium concentrations increase within 10 minutes and CSF magnesium concentrations increase in about 30 minutes.[24] Cows should be observed for premature evacuation of the magnesium enema. Do not overdose the rectum with magnesium solutions, as this could cause severe rectal mucosal sloughing.[13]

Preventive measures are needed to prevent hypomagnesemic relapses following initial treatment of clinical grass tetany. Options include subcutaneous administration of magnesium sulfate (200 mL of a 50% solution, which provides 9.9 grams magnesium) or oral administration of 400 mL of a 50% magnesium sulfate solution (200 grams of magnesium sulfate in 400 mL of water, which provides 19.7 grams of magnesium).[13] Extreme caution should be exercised if any oral supplement is given to a recumbent cow; the best approach is to defer oral magnesium administration until the cow is standing, alert, able to swallow, and not aggressive. This could be 30 to 90 minutes after the initial treatment.[13]

Commercial oral gel preparations containing magnesium (typically packaged in 300-mL tubes) are available in the US. Most of these preparations source their magnesium primarily from magnesium chloride, which is a very available source of magnesium. Some products provide about 6 grams of magnesium per tube; 2 or 3 tubes would provide a reasonable dose for prevention of hypomagnesemic relapses. Some multiple nutrient oral tubes provide only about 3 grams of magnesium per tube; it would require too many of these tubes to reach an effective dose of magnesium. The other nutrients present in these tubes may be helpful, depending on the clinical situation.

Another reasonable source of oral magnesium is a fresh cow drench formulation. These typically provide about 200 grams of magnesium sulfate (19.7 grams of magnesium), along with other nutrients such as calcium, a glucose precursor, phosphorus, or potassium. These drench formulations are appropriate for preventing hypomagnesemic relapses.

Subclinical hypomagnesemia. Dairy cattle managed in confinement rarely develop clinical hypomagnesemia, but may have its subclinical form. Subclinical hypomagnesemia may be diagnosed at the herd level by evaluating blood magnesium concentrations in apparently healthy cows. The cutpoint that defines subclinical hypomagnesemia has not been formally characterized but appears to be around 1.8 mg/dL (0.74 mmol/L). Unfortunately, there has been no formal evaluation of the highest risk period for subclinical hypocalcemia and no formal evaluation of appropriate alarm levels for herd-level diagnosis of subclinical hypomagnesemia. The author's limited clinical experience suggests that the highest risk period for subclinical hypomagnesemia in confinement dairies may be about 4 to 14 days-in-milk, and that a reasonable alarm level may be over about 15% of the herd affected with subclinical hypomagnesemia.

Blanket supplementation with oral magnesium could be used to mitigate subclinical hypomagnesemia in dairy herds shown to be at high risk. There is no cowside test for diagnosing subclinical hypomagnesemia, so blanket treatment strategies are the only option available. Unfortunately, no studies have evaluated the effectiveness of blanket oral magnesium supplementation strategies. An oral drench that provides about 200 grams of magnesium sulfate (19.7 grams of elemental magnesium) would be a reasonable supplement to mitigate the impact of subclinical hypomagnesemia.[13] Magnesium sulfate at this dose, which is well below a cathartic dose, is very appropriately included in many fresh cow drench products.

Diagnosis and Treatment for Hypokalemia

Hypokalemia overview. Hypokalemia may occur in early lactation dairy cows due to prolonged anorexia. It is often associated with chronic ketosis or another primary condition that impairs appetite. Additional risk factors for hypokalemia include repeated administration of isoflupredone acetate, IV glucose, or insulin.[12] Depletion of total body potassium leads to severe muscle weakness and flaccid pa-

ralysis.[37] The flaccid paralysis associated with hypokalemia can be so severe that cows have a complete inability to keep their head in a straight position and cannot eat unless their head in placed into a feed bucket.[37]

Hypokalemia is confirmed by low serum or plasma potassium concentration. Samples must be separated from the red blood cells within about an hour after calving; otherwise, potassium from the red blood cells (which concentrate potassium about 30 times greater than serum or plasma[12]) could falsely elevate the measured potassium concentration and cause the diagnosis to be missed. Hypokalemia starts whenever blood potassium falls below the normal range (<3.9 mEq/L); however, most cows with clinical signs of hypokalemia have blood potassium concentrations below about 2.5 mEq/L.[7,37] There is no consensus on the exact cut point for blood potassium concentration that should be used to define hypokalemia.[37]

About 25 to 40% of cases of hypokalemia also have low blood phosphorus.[37] These conditions may both be related to prolonged anorexia.

Intravenous treatment of hypokalemia. Intravenous correction of hypokalemia requires slow infusion, due the risk for sudden cardiac death, and daily monitoring of blood potassium.[37] This is rarely practical in the field. An IV infusion should not provide more than 0.5 mEq of potassium per kg bodyweight per hour.

Oral treatment of hypokalemia. Oral potassium chloride is the treatment of choice for clinical cases of hypokalemia. Potassium is needed to correct the whole-body potassium depletion, and chloride is needed for cows that may be alkalemic and have a pH-induced compartmental shift of potassium into the intracellular space.[7]

The current recommendations for oral potassium chloride supplementation for clinical cases of hypokalemia is 0.4 g/kg body weight, which equals 300 grams of potassium chloride for a 1650 lb (750 kg) cow. This dose should be divided into 2 or more treatments during a 24-hour period.[8] In practice, this translates to an initial treatment of about 150 grams of potassium chloride (79 grams of potassium and 71 grams of chloride) that is repeated 12 hours later. There is no advantage to dividing this dose into 8 smaller doses administered every 3 hours.[8] Higher doses of oral potassium chloride are dangerous due to the risk for diarrhea, convulsions, or death; they should be reserved for cows with severe hypokalemia. Oral supplementation with potassium chloride is often necessary for 3 to 5 days.[8,33]

Prevention of hypokalemia. Essentially all cases of hypokalemia are preventable. This can be accomplished by: 1) avoid repeated administration of isoflupredone acetate, IV glucose, or insulin; and 2) supplement all early lactation cows that are anorectic more than 3 days with oral potassium chloride. The suggested preventive dose of oral potassium chloride is 100 grams per day; this dose appears to be safe and effective.[37] Oral potassium chloride may be pumped as part of a fresh cow drench package (100 grams of potassium chloride is a standard dose of potassium chloride in fresh cow drench packages marketed in the US) or administered orally in gelatin capsules. A number 7 gelatin capsule (1.5-ounce size) has a 24 mL capacity and thus should hold about 48 grams of potassium chloride (assuming 1.98 grams per cubic centimeter). Thus, a reasonable dose is 2 capsules of this size per cow per day.

Conclusions

Prevention of mineral disorders in fresh dairy cows is obviously superior to treating them. Nonetheless, clinical and subclinical cases of mineral disorders will still occur, even with the best of transition cow management. Dairy practitioners can work with dairy producers to implement the most effective programs for early detection and optimal treatment of mineral disorders.

Acknowledgments

Dr. Oetzel has served as a consultant and speaker for Boehringer Ingelheim Animal Health and Zoetis Animal Health. He has conducted research projects sponsored by AgSource, Boehringer Ingelheim Animal Health, and Zoetis Animal Health.

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