TREATMENT OF CALCIUM, PHOSPHORUS, AND MAGNESIUM BALANCE DISORDERS

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In food animal practice, the majority of the calcium (Ca), phosphorus (Phos), and magnesium (Mg) balance disorders are due to low blood concentrations of one or more of these minerals. The purpose of this article is to review methods that can be used to restore normal blood concentrations of these minerals. The theories on the pathophysiology and prevention of the diseases that result in these mineral imbalances are discussed in recent reviews.[9, 10, 21, 25, 28] Although low plasma Ca is often accompanied by changes in plasma Phos and Mg, the following sections will consider each mineral separately. The pros and cons of combined therapies will be discussed in the final section. In all cases the doses of the treatments described are those appropriate for the 600-kg cow. Doses for smaller animals and sheep or goats should be adjusted according to body weight.

TREATMENT OF CALCIUM DISORDERS

Plasma Ca concentration is normally maintained between 2.1 and 2.6 mmol/L (8.5–10.4 mg/dL). Nearly all dairy cows will experience subclinical hypocalcemia (<1.8 mmol/L, 7.5 mg/dL) within 24 hours of calving. Generally, cows that are recumbent and unable to rise as a result

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of low blood Ca will have plasma Ca concentration less than 1.25 mmol/L (5 mg/dL), and some will be down as low as 0.5 mmol/L (2 mg/dL); below this level is generally incompatible with life. About half of the plasma Ca is bound to plasma proteins, such as albumin; another 5% is bound to citrate, phosphate, and other organic anions. Ionized Ca constitutes from 40–45% of total Ca concentration. Ionized Ca concentration is closer to 45% of total Ca when blood pH is acidic and closer to 40% when blood pH is alkaline. While ionized Ca concentration is physiologically the most relevant Ca determination that can be made, our experience has been that total Ca determination is adequate to diagnose the metabolic disorders involving Ca in ruminants (i.e., ionized Ca remains at ~40–45% of the total Ca over a wide range of total plasma Ca concentrations).

Calcium Pool Sizes

In the 600-kg cow, the plasma volume will be ~6% of body weight or 36 L. Assuming normal plasma Ca concentration is 10 mg/100 mL plasma, there will be 3.6 g Ca in the plasma pool, half of which is ionized and the other half is bound to plasma proteins. Interstitial fluid volume is in equilibrium with the plasma but does not contain albumin-bound Ca. If interstitial fluids constitute 15% of body weight (90 L) and contain 5 mg Ca/100 mL, there will be 4.5 g Ca in the interstitial fluids. Total extracellular fluid Ca pool size is therefore about 8.1 g Ca in a 600-kg cow. Intracellular body fluids constitute about 40% of body weight or 240 L. Intracellular Ca concentration is estimated to be 0.004 mg/100 mL. Total intracellular Ca pool size is just 0.01 g.

Treatment of hypocalcemia should be done as early as possible, especially if recumbency is present. The pressure exerted by the massive weight of the cow can cause a "compartment-like" syndrome on the down side appendages in which ischemia of the muscles is followed by necrosis resulting in the downer syndrome cow.[7]

Intravenous Ca Treatments

The fastest way to restore normal plasma Ca concentration is to administer an intravenous injection of Ca salts. The first Ca solutions used to treat severe hypocalcemia were 10% calcium chloride solutions given at a rate of about 150 mL/cow.[18] Although effective, this treatment lost favor because any subcutaneous leakage of the calcium chloride solution tended to cause localized sloughing of the skin. Calcium gluconate has largely replaced calcium chloride because it is less injurious when injected subcutaneously. Boric acid is often added to the calcium gluconate forming calcium borogluconate, which improves the solubility and stability of the solution. Because pure calcium borogluconate solu-

tions are acidic (pH ~3.5), calcium oxide is often added to these solutions to increase the pH. In general, commercial preparations for intravenous use supply from 8.5 to 11.5 g Ca/500 mL. They may also contain sources of Mg, phosphite (not phosphate), and glucose (dextrose). Solutions containing calcium propionate, calcium lactate, calcium levulinate, and calcium formate have been used successfully as well. The source of Ca has no significant effect on clinical recovery from hypocalcemia.[17] All effectively raise total and ionized Ca concentrations in the blood. Calcium chloride solutions tend to increase ionized Ca content of blood to a greater extent than do other Ca salt preparations, especially when more than 20 mg/kg Ca is administered intravenously (~12 g Ca/600-kg cow).[14, 17]

How much Ca should be given intravenously? Assuming the 600-kg cow has 8.1 g Ca in the extracellular fluids, a cow with a blood Ca concentration of 4.5 mg/100 mL will have ~50% of the normal amount of Ca in her extracellular fluids and will require about 4 g Ca to restore normal extracellular fluid Ca concentrations; however, we also would like to supply her with a bit more Ca to give her a bit of a buffer against the continuing drain of Ca to production of milk. What is an effective dose?

An internordic field study examined the effect of the intravenous administration of 6, 9, or 12 g of Ca on the therapeutic result in cows with milk fever.[1] A variety of Ca preparations were used, and the cattle were primarily of the Nordic breeds (weighing approximately 500 kg). The 9-g Ca dose yielded significantly better results than did the 6-g dose, but there was no advantage observed by raising the dose to 12 g. These data suggest the effective intravenous Ca dose is just under 2 g Ca/100 kg body weight. A good rule of thumb is to administer the Ca at a rate of 1 g/min.

Fatal arrhythmia of the heart will occur when plasma total Ca becomes excessively high, beginning at about 28 to 32 mg Ca/100 mL.[19] Figure 1 is the plasma Ca profile of a Jersey cow with milk fever given 500 mL of a 26% calcium borogluconate solution (10.5 g Ca total) over a period of 12 minutes. Plasma Ca increased from 4.3 to 22 mg/100 mL during the course of treatment. Plasma Ca remained above normal (10 mg/100 mL) for about 4 hours after the treatment. One effect of this hypercalcemia is to shut off parathyroid hormone secretion vital to the Ca homeostatic mechanisms of the body. Parathyroid hormone has a half life of 3 to 4 minutes, and in this cow parathyroid hormone was quite high prior to treatment, 780 pg/mL, but was just 82 pg/mL 1 minute after treatment. Hypercalcemia also stimulates release of thyrocalcitonin, which inhibits renal Ca reabsorption and bone Ca resorption. The establishment of hypercalcemia during treatment has the negative effect of reducing the ability of the animal to establish Ca homeostasis. From 1 to 2 g Ca is typically lost to the urine within 30 minutes after treatment with intravenous Ca as the animal responds to the hypercalcemia.

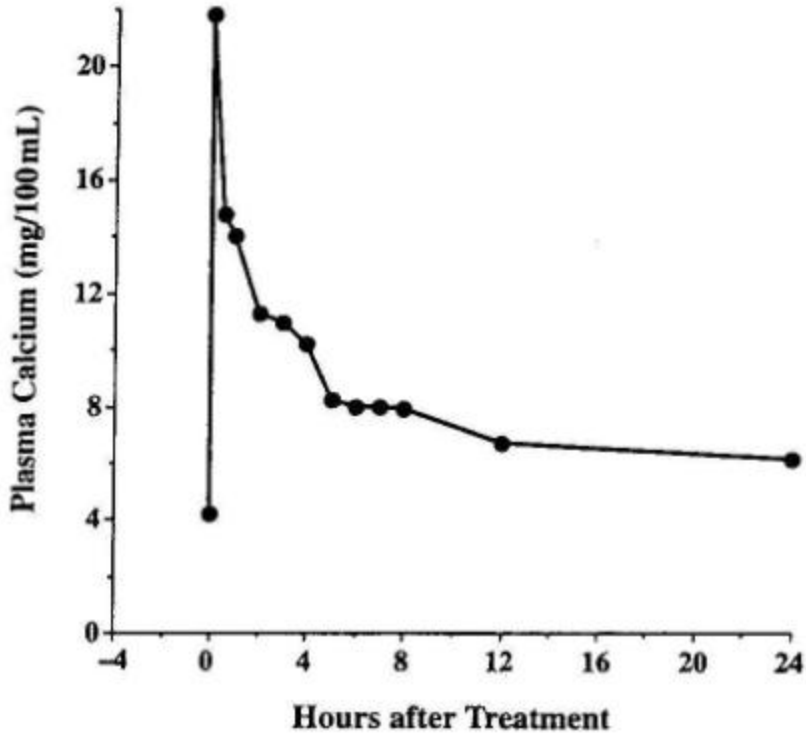

Figure 1. Plasma Ca concentration in a cow treated for milk fever with 10.5 g Ca as calcium borogluconate administered intravenously over a 12-minute period.

Subcutaneous and Intramuscular Ca Treatments

Ca salts can also be injected subcutaneously. Figure 2 presents the plasma Ca profile in 6 normal Jersey cows given 10.5 g Ca as 500 mL calcium borogluconate divided and injected into 10 subcutaneous sites. The degree of hypercalcemia achieved is not as great as with intravenous administration of the same dose of Ca. As with intravenous Ca injection, the subcutaneous injection of Ca increases Ca in the blood for 4 to 5 hours only.

The amount of Ca that can be injected into a subcutaneous site should be limited to 1 to 1.5 g Ca (50–75 mL of most commercial preparations). Greater amounts of Ca can cause local tissue necrosis. Ca is toxic to cells as high amounts of Ca extracellularly can overwhelm the ability of cells to maintain low intracellular Ca concentrations. Calcium chloride solutions are not at all well tolerated subcutaneously. Ca solutions containing glucose may also be slightly more injurious as the added glucose adds to the osmolarity of the solution.

Although subcutaneous Ca injection will not cause severe hypercalcemia, the subcutaneous injection of Ca may not result in a favorable clinical response in a severely hypocalcemic cow, as the circulation to the subcuticular tissues is often compromised during severe hypocalcemia. Occasionally cows with clinical milk fever that have been unsuccessfully treated with subcutaneous Ca solutions by producers have died within minutes of an intravenous injection of Ca administered by a veterinarian. The suspicion is that as the circulation was restored, the intravenous

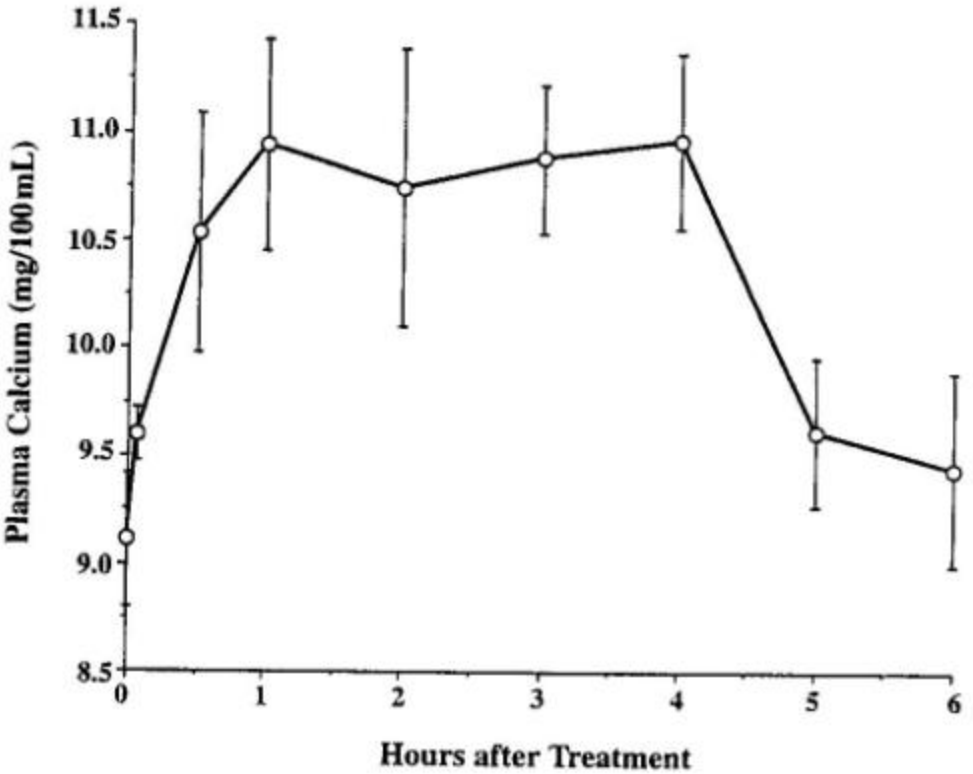

Figure 2. Mean ± SEM plasma Ca concentration in 6 Jersey cows given 10.5 g Ca as calcium borogluconate subcutaneously (500 mL in ten different sites).

and subcutaneously administered Ca entered the blood simultaneously, causing fatal hypercalcemia.

Preparations are available for intramuscular administration of Ca. Usually the Ca is supplied as calcium levulinate or calcium lactate, which tend to be less injurious to tissues than other forms of Ca and also tend to be more expensive. Most of these preparations must be limited to 0.5 to 1.0 g Ca per injection site to avoid tissue necrosis. To get an effective dose of Ca into the clinically hypocalcemic animal might therefore require 6 to 10 injections into widely separated sites.

Oral Ca Supplementation

Ca is absorbed across the intestinal mucosa by two methods. The first method is by the active transport of Ca across intestinal cells, a process mediated by the hormone, 1,25-dihydroxyvitamin D. The second method is by passive diffusion across the tight junctions that hold adjacent mucosal cells together. This paracellular Ca transport is concentration dependent. Theoretically, when the concentration of ionized Ca over the intestinal tract mucosa cells (including the rumen mucosa) is greater than the concentration in the blood, Ca will diffuse into the blood. Because of the electrical charge and molecular size of Ca relative to the tight junction, the actual concentration of ionized Ca that must

bathe the mucosa to get passive transport of Ca is ~6 mmol/L, about five times the ionized Ca concentration in blood.[5] Oral Ca supplements are available that effectively use this method to increase plasma Ca concentration rapidly following treatment.[15, 30]

Several efficacy and safety factors are important to consider when using and choosing an oral Ca supplement for treating hypocalcemia. To be effective, the Ca in the supplement must be readily soluble in water (digestive fluids) so elevated ionized Ca concentration over the mucosa will be rapidly achieved before the Ca concentration over the mucosa is diluted below the 6 mmol/L effective level during mixing with other intestinal digesta. Calcium chloride is the most soluble of the Ca salts; calcium propionate and calcium formate, calcium acetate, calcium gluconate, and calcium lactate are also soluble enough for this purpose; calcium hydroxide, calcium oxide, and calcium carbonate are relatively insoluble and unsuitable for treating hypocalcemia.[8] Ca that is not absorbed by passive diffusion is still available for absorption by active Ca transport in the small intestine, but this absorption is not rapid enough to be of aid in the treatment of hypocalcemia and will not be considered further in this review. Most of the commercial supplements available use calcium chloride or calcium propionate as the source of Ca.

The greater the amount of soluble Ca in the preparation, the greater the amount of ionized Ca that will be available for absorption (Fig. 3).

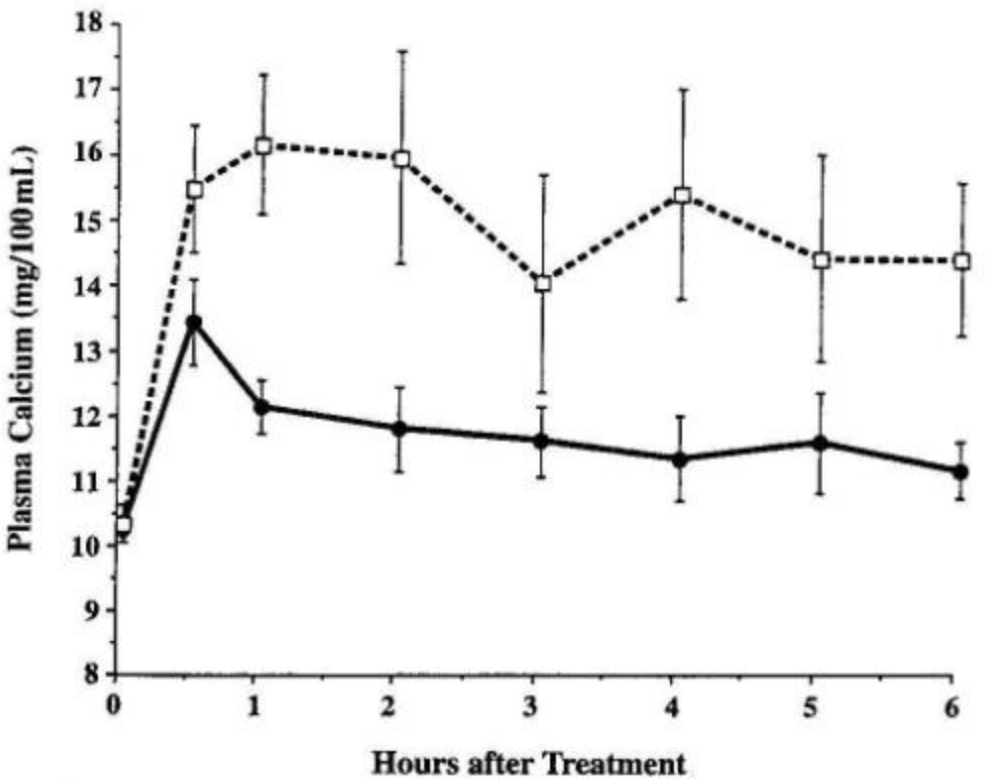

Figure 3. Mean ± SEM plasma Ca concentration profiles from Jersey cows (n = 6/treatment) treated with 50 g (circle) or 100 g (square) Ca (supplied by calcium chloride) in an oral drench.

Administering small amounts of Ca may never achieve the 6 mmol/L Ca concentration over the mucosa necessary for passive absorption. Administering larger amounts of Ca will rapidly achieve the 6 mmol/L level over a section of mucosa, and all the Ca above 6 mmol/L will rapidly diffuse into the blood. Administering 50 g Ca from calcium chloride as a drench in 250 mL of water is roughly equivalent to administering 4 g Ca intravenously.[8] Giving the same amount of Ca in 1000 mL water greatly reduces the amount of Ca absorbed by passive absorption.[8] Giving 100 g Ca as calcium chloride in 500 mL water (doubling the dose) results in much greater blood Ca concentrations so that it is roughly equivalent to giving 10 to 12 g Ca intravenously.

When Ca solutions are administered as a drench, at least a portion of the dose will bypass the rumen and enter the abomasum. This enhances passive Ca absorption because the volume of fluid in the rumen will rapidly dilute the Ca concentration to a value below the 6 mmol/L required for passive absorption. The abomasal and duodenal fluids will not dilute Ca concentration as rapidly. Calcium chloride may be more effective than calcium propionate in terms of eliciting the esophageal groove reflex.[8, 11] Incorporating the Ca into a gel or paste reduces the amount of Ca likely to bypass the rumen. Pastes and gels can be effective as they release Ca in a localized area of mucosa, but, in general, more Ca must be administered by gel or paste to get the same rise in plasma Ca as is achieved by an oral Ca drench.

Unfortunately, hypocalcemic cows have poor swallowing and gag reflexes, making them vulnerable to aspiration pneumonia. Drenches of Ca solutions suffer one distinct disadvantage: some cows will aspirate the solution, which leads to a severe aspiration pneumonia. The risk increases with the volume of the drench. Gels and pastes are much less likely to cause aspiration pneumonia, the risk decreasing with the viscosity of the preparation. Various definitions of "gel" exist; the safer preparations have a consistency close to that of toothpaste.

Another consideration is whether it is better to use calcium chloride or calcium propionate as the source of Ca. Calcium chloride is slightly more effective and takes up less volume than calcium propionate. It also is an acidifying agent. This could be good if the herd is not being fed anionic salts prior to calving to induce a mild metabolic acidosis to prevent milk fever. The calcium chloride may induce a mild acidosis to enhance Ca homeostasis. Unfortunately, the acidifying activity of calcium chloride also means that it is possible to induce a severe metabolic acidosis when repeated treatments of calcium chloride are administered. In herds where cows are already being fed prepartal anionic salts, this is likely to be a bigger problem. Calcium chloride is very irritating to mucous membranes, and treatment has been known to cause lesions in the rumen and abomasum.[34] Incorporating the calcium chloride into an oil emulsion effectively eliminates the tissue damage induced by calcium chloride (and also improves the palatability),[34] but it also reduces the availability of the Ca for passive absorption.[11] One such preparation has been used in Europe for a number of years and effectively improves

plasma Ca concentration.[32] Because the calcium is not readily available to improve calcium concentration immediately, the efficacy of these oil-calcium chloride emulsions suggests that the chloride in the preparation may be an active component of the preparation. Perhaps the chloride is inducing a slight metabolic acidosis, simulating the beneficial effects observed when anions are added to the diet to prevent milk fever. Calcium chloride boluses have also been made. Unfortunately, the solubilization of calcium chloride in water is an exothermic process, and these boluses have caused severe esophageal and rumen mucosa damage in some animals.

Calcium propionate is effective[12, 27] and less irritating to tissues than is calcium chloride. It does not induce a metabolic acidosis, so larger amounts of Ca can be given. It supplies the cow with a gluconeogenic precursor, which is generally a good idea, as most hypocalcemic cows are in negative energy balance. Calcium propionate's main disadvantage is the large volume of material that must be used to raise plasma Ca. Drenches and gels commonly used exceed 700 mL to achieve an effective dose. Another option is to stomach tube the cow (or use an esophageal pump system) and pump larger volumes of calcium propionate into the rumen. This bypasses problems with swallowing large volumes. Calcium propionate costs ~$1.55/kg whereas calcium chloride is ~$0.30/kg; however, the cost of the Ca source is a minor component of the overall price of commercially available oral Ca supplements.

Care must be taken when administering oral Ca supplements not to injure the back of the throat, especially with animals resisting treatment.[16] Long nozzles at the end of the gel tubes were common but have been shortened, and that seems to have reduced the incidence of injury. Animals should have a good swallowing reflex to avoid aspiration pneumonia; recumbent and wobbly cows should not be treated with oral Ca supplements. Oral treatment increases Ca within 30 to 60 minutes of administration, and plasma Ca concentrations remain elevated for about 6 hours. Calcium chloride acts a little faster, but calcium propionate may act a little longer. Figure 4 presents the plasma Ca concentration profile of a Jersey cow with moderate hypocalcemia after calving that was treated with an oral calcium propionate drench supplying 94 g Ca.

Summary

Intravenous, subcutaneous, and oral treatment of hypocalcemia result in rapid increases in plasma Ca that last about 5 to 7 hours, and any method can be used to buy the cow the time she needs to establish her Ca homeostatic mechanisms. In cows that are recumbent, slow intravenous Ca injection is the only choice that should be recommended. Combining intravenous, subcutaneous, and oral treatments is not a good idea. It risks inducing fatal hypercalcemia, it further shuts off the endocrine system needed to achieve Ca homeostasis, and it does not improve the clinical response, as you are unlikely to be raising plasma

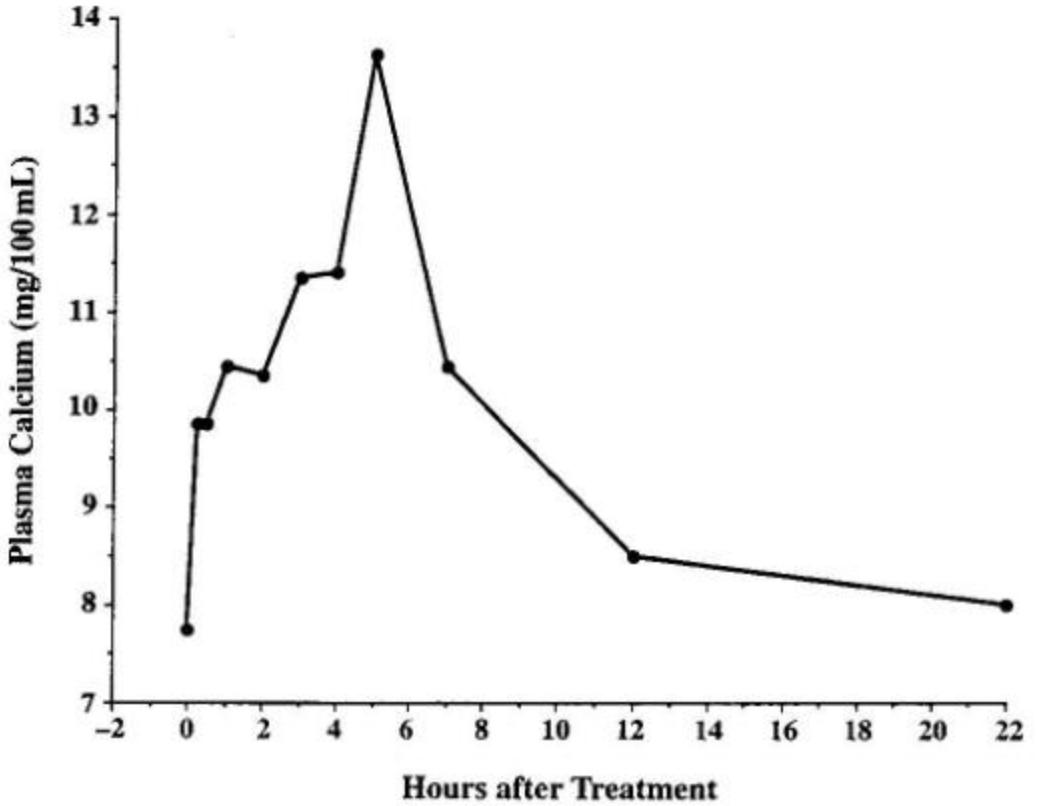

Figure 4. Plasma Ca concentration following treatment of a moderately hypocalcemic Jersey cow within 12 hours of calving with 94 g Ca orally supplied in a calcium propionate drench.

Ca for longer than the 5 to 7 hours achieved with any single treatment. A more reasonable approach is to administer a second treatment 8 to 12 hours after the first treatment.

TREATMENT OF MAGNESIUM DISORDERS

Mg is a major intracellular cation that is a necessary cofactor for enzymatic reactions vital to every major metabolic pathway. Extracellular Mg is vital to normal nerve conduction, muscle function, and bone mineral formation. Hypomagnesemia generally leads to hyperexcitability, tetany, convulsion, and, too often, death. Hypomagnesemia is often accompanied by and complicated by hypocalcemia and hypophosphatemia.

Bovine plasma Mg concentration is normally 0.75 to 1.0 mmol/L (1.8 to 2.4 mg/dL). Normal plasma Mg concentration in sheep is 0.90 to 1.15 mmol/L (2.2 to 2.8 mg/dL). Moderate hypomagnesemia of 0.5 to 0.75 mmol/L (1.1 to 1.8 mg/dL) is associated with reduced feed intake, nervousness, and reduced milk fat and total milk production. This can be a chronic problem in some dairy herds that often goes unnoticed. It can also predispose these animals to milk fever. Because moderate hypomagnesemia is not an emergency situation and is generally treated

by increasing dietary Mg, treatment of this condition will not be discussed further in this review.

When plasma Mg concentration falls below 0.5 mmol/L (1.1 mg/dL), twitching is sometimes seen in the muscles of the face, shoulder, and flank. As hypomagnesemia progresses, tetanic spasms of the muscles become more common, which eventually cause the cow to stagger and fall. Clonic convulsions may follow with chomping of the jaws and frothy salivation. Hypomagnesemic tetany in calves is clinically similar to that in adults and is often accompanied by moderate hypocalcemia. Affected ewes are generally hypocalcemic and hypomagnesemic.[9]

Cerebrospinal fluid Mg concentrations less than 0.4 mmol/L (1 mg/dL) are responsible for the clonic convulsions seen in animals with hypomagnesemic tetany.[2, 26] Blood samples obtained during or shortly after an episode of tetany may have near normal levels of Mg as a result of muscle damage and leakage of Mg from intracellular pools. CSF Mg concentration will remain low during tetany, and also can be a reliable indicator of Mg status for up to 12 hrs after death.

Magnesium Pool Sizes

In a 600-kg cow there is about 0.84 g Mg in the blood, 3 g Mg in all extracellular fluids, 84 g Mg inside cells, and 204 g Mg within bone mineral. Blood and extracellular fluid Mg is in equilibrium with Mg concentration in the cerebrospinal fluids. CSF Mg concentration is similar to plasma Mg concentration, although changes in CSF Mg concentration will lag behind changes in plasma Mg concentration as the blood brain barrier slows diffusion. It is generally believed that the reduction in CSF Mg level is responsible for the tonic-clonic convulsions typical of severe hypomagnesemia.[2, 26, 33] No depletion of the Mg content of soft tissues has been demonstrated in hypomagnesemic cattle[33]; thus, intracellular Mg does not serve as a significant readily mobilizable store of Mg for replenishment of extracellular Mg.

Intravenous Treatment of Hypomagnesemia

Animals exhibiting hypomagnesemic tetany need immediate treatment. If normal plasma Mg concentration is about 2 mg/100 mL and clinical signs requiring immediate treatment occur when plasma Mg declines to 0.5 to 1.0 mg/100 mL, we can assume that 50% to 75% of the extracellular fluid Mg must be administered intravenously to return plasma Mg to "normal" levels. This will require from 1.5 to 2.25 g Mg; however, as with Ca, we would like to supply her with a bit more Mg to give her a bit of a buffer against the continuing drain of Mg. Most of the commercially available intravenous Mg preparations supply from 1.5 to 4 g Mg, usually as the chloride, borogluconate, or hypophosphite salts of Mg; usually these include calcium salts and are primarily meant

for IV calcium therapy. No research has been done to titrate the most effective dose for treatment of hypomagnesemia. A dose of 2 to 3 g of Mg administered intravenously over a 10-minute period should be a safe and effective means of treating hypomagnesemia. Most of the commercial preparations are combined with Ca because hypomagnesemia is often accompanied by hypocalcemia. Also, intravenous administration of a solution containing Mg only carries a risk of inducing respiratory failure as a result of medullary depression and increased cardiac failure during treatment.[23]

When plasma Mg exceeds the renal threshold for reabsorption of renal tubule fluid Mg (approximately 1.8 mg/100 mL in cattle and 2.2 mg/100 mL in sheep), the excess plasma Mg is rapidly excreted into the urine. Plasma Mg concentrations of 4 to 7 mg/100 mL result in muscle weakness, and the deep tendon reflexes are decreased. When plasma Mg is increased to 11 mg/100 mL, the deep tendon reflexes are absent. At 14 to 18 mg, Mg/100 mL plasma respiratory paralysis becomes a real threat. Higher concentrations of plasma Mg can induce cardiac arrest in diastole. Hypocalcemia exacerbates these effects; addition of Ca to Mg-containing solutions reduces the severity of these effects.[24] Figure 5 presents the plasma Mg profile of a normal cow treated with 2.5 g Mg as $MgSO_4$ intravenously over an 8-minute period. One minute after intravenous treatment, plasma Mg was 6.4 mg Mg/100 mL in the systemic circulation (sample taken from the opposite jugular vein). We can

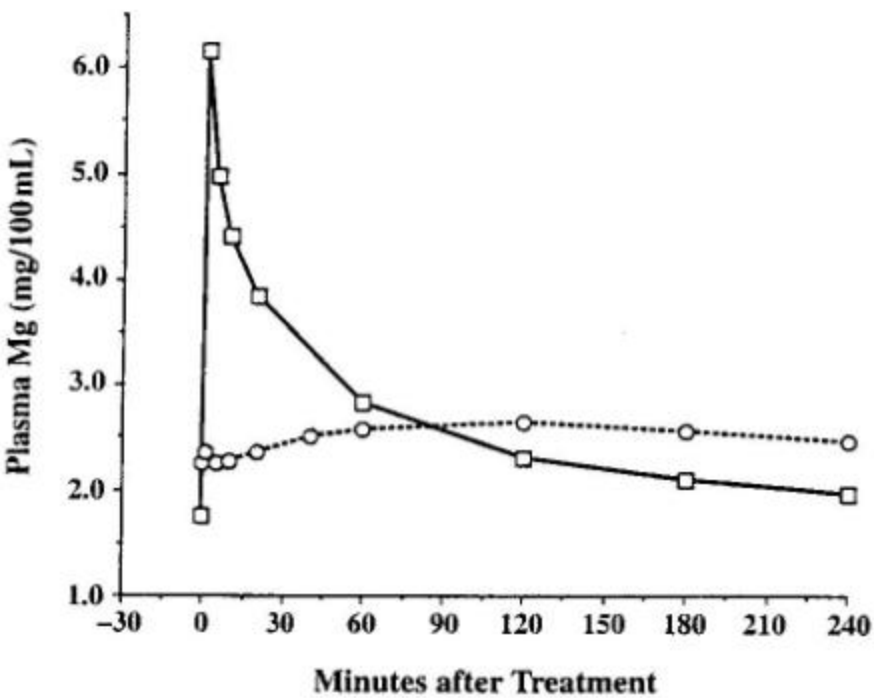

Figure 5. Plasma Mg concentration in Jersey cows following intravenous or oral treatment with 2.5 g Mg supplied by magnesium sulfate (2.5 g Mg in 500 mL intravenously administered over an 8-minute period versus 2.5 g Mg in 100 mL SQ). Square = intravenously; circle = subcutaneously.

assume that the Mg concentration within the heart was much higher during jugular infusion!

Hypermagnesemia was commonly used as part of anesthesia protocols involving chloral hydrate years ago. Hypermagnesemia induces a neuromuscular blockade and flaccid paralysis. Unfortunately it does not quickly induce central nervous system depression, reducing its ability to block pain.[4] This property also eliminates induction of hypermagnesemia as a humane means of euthanasia.

Treatment of these animals can be challenging, as insertion of the IV needle will often initiate another tetanic episode. Some veterinarians use intramuscularly administered tranquilizers or sedatives such as Acepromazine to reduce the risk of injury to the cow and themselves from continuous clonic convulsions prior to intravenous treatment. Intravenous administration of tranquilizers is not advisable, as it has been associated with sudden hypotension and death.

Clinical response to Mg therapy can be disappointing, and success is related to the interval between onset of tetany and treatment. Cows should not be stimulated to rise for at least 30 minutes after treatment to avoid initiating tetany and convulsion. Cattle that will recover do so about an hour after treatment, as it takes that long for CSF Mg concentration to return to normal. Many of these cows will relapse and require further treatment within 12 hours.

Subcutaneous Treatment with Magnesium Solutions

The difficulty of treating an animal during a convulsion can sometimes be overcome by the subcutaneous administration of Mg. Injecting 200 to 400 mL of a 25% magnesium sulfate ($MgSO_4 \cdot 7\ H_2O$) solution to supply 5 to 10 g Mg subcutaneously (50–100 mL per injection site) will increase plasma Mg to normal levels in about 30 minutes, provided peripheral blood flow has not been compromised. Solutions of higher concentrations are essentially fully saturated and hyperosmotic and can cause tissue damage. Figure 5 presents the plasma Mg profile of a cow given 2.5 g Mg as magnesium sulfate in 100 mL water subcutaneously. Although this dose is low and does not increase blood Mg very much, it demonstrates that the response to subcutaneous Mg will be much slower than the intravenous response, but it may be safer for the cow and the veterinarian.

Magnesium Enemas

This treatment was also developed as an alternative to intravenous treatment in the convulsing patient. It is easier for the producer and does not require sterile equipment. An enema for an adult cow consisting of 60 g magnesium chloride or 60 g magnesium sulfate dissolved in 200 mL water can be administered into the descending colon. This treatment

will increase plasma Mg concentration within 10 minutes.[3, 29] It can cause some mucosal sloughing, especially if more highly concentrated solutions are used.

Oral Magnesium Administration

Oral administration of Mg salts can provide longer maintenance of plasma Mg concentration once the animal has regained good esophageal reflexes so that the risk of aspiration pneumonia is reduced. They are not recommended for initial treatment because of the relatively slow rate of absorption of orally administered Mg. They are most effective as a means of preventing relapse following intravenous Mg treatment. Drenching the cow with a slurry of 100 g magnesium oxide in water has been reported to be effective. This provides about 50 g Mg to the animal. It may be easiest to give via stomach tube, and the addition of 100 g calcium chloride, 100 g sodium phosphate, and 50 g sodium chloride may enhance the effectiveness of the slurry, especially if hypocalcemia and hypophosphatemia accompanied the hypomagnesemia. The addition of sodium may enhance rumen Mg absorption. Alternatively, 200 to 400 mL of a 50% magnesium sulfate solution can be administered by drench. Magnesium sulfate is more available for absorption than magnesium oxide.

Summary

Cows exhibiting clinical hypomagnesemia must be treated quickly. The intravenous administration of Mg is preferred, and this is most safely done when the Mg solution also contains Ca as well. Clinical signs may not subside until cerebrospinal fluid Mg concentrations increase, which may require 30 to 60 minutes following treatment. Subcutaneous or rectal administration of Mg salts can be an effective alternative, although problems with peripheral blood flow and premature evacuation of enemas may compromise the effectiveness of these treatments. When using solutions containing Mg only, it may be wisest to give 1/2 the IV dose of magnesium (1 g) and 5 to 10 g Mg subcutaneously to safely get initial correction of blood magnesium and sustained increase in blood Mg from the subcutaneous dose. All of these treatments only increase plasma Mg to normal concentrations for 3 to 6 hours. Oral administration of Mg salts at the time of initial treatment (once it can be given safely) will help maintain normal plasma Mg concentration for up to 12 hours and is highly recommended. Unless management practices are instituted to increase dietary Mg intake (or in some cases, decrease potassium and nitrogen intake[9]), relapses to treatment are almost inevitable. Remember too that if hypomagnesemic tetany has occurred in one cow or ewe in a herd or flock, steps should be taken immediately to increase Mg intake to prevent further losses.

TREATMENT OF PHOSPHORUS DISORDERS

The biologically active form of Phos is the phosphate anion. Phosphate is a component of phospholipids, phosphoproteins, nucleic acids, and energy-transferring molecules, such as ATP. The phosphate anion is an essential component of the acid-base buffer system. It is second only to Ca as the major component of bone mineral. Plasma inorganic Phos concentration is a measure of the amount of phosphate anion in the blood, and is normally 1.3 to 2.6 mmol/L (4–8 mg/100 mL) in adult animals and 1.61 to 2.74 mmol/L (5 to 8.5 mg/100 mL) in young growing animals.

Chronic mild hypophosphatemia with plasma Phos concentrations between 2 and 4 mg/100 mL is generally associated with reduced growth and productivity and, in time, will result in rickets in young animals and osteomalacia in adult animals.[10] Because this is not an emergency situation and is generally treated by increasing dietary Phos, treatment of moderate hypophosphatemia will not be discussed further in this review.

Animals recumbent as a result of severe acute hypophosphatemia will have plasma Phos concentrations below 0.3 mmol/L or 1 mg/dL, and often closer to 0.15 mmol/L or 0.5 mg/100 mL. Hypocalcemia, hypomagnesemia, and hypoglycemia are also often present in these animals as well. Why these cows are recumbent is essentially unknown. It seems reasonable to believe that depletion of intracellular phosphate in the form of ATP or creatine phosphate in muscle is involved in the "downer cow" syndrome; however, because about 170 g Phos (as phosphate anion) is in the total intracellular pool, and often cows respond clinically to the relatively small intravenous dose of 5 to 6 g Phos as phosphate, it is difficult to believe that the cause of the downer cow syndrome is intracellular phosphate depletion. We can speculate that the extracellular phosphate concentration is restored by the intravenous dose accounting for the clinical response, but the only known role for extracellular phosphate anion is in acid-base physiology. Perhaps extracellular phosphate plays a critical role in myoneural transmission or muscle strength.

Beef cows and ewes fed a diet marginal in Phos will have a chronic hypophosphatemia of 0.6 to 1.1 mmol/L (2–3.5 mg/100 mL). Then, in late gestation plasma, Phos can decline precipitously as the growth of the fetus accelerates and removes substantial amounts of Phos (and energy) from the maternal circulation. These animals often become recumbent and are unable to rise, although they appear fairly alert and will eat feed placed in front of them. Cows carrying twins are most often affected. Plasma Phos concentration in these recumbent animals is often less than 0.3 mmol/L (1 mg/100 mL). The syndrome usually is complicated by concurrent hypocalcemia, hypomagnesemia, hypoglycemia, and in some cases, hypokalemia.

In dairy cows and goats, the production of colostrum and milk at the onset of lactation draws large amounts of Phos out of the extracellu-

lar Phos pools. This alone will often cause an acute decline in plasma Phos levels at parturition. Downer cow syndrome is an occasional sequelae to milk fever in dairy cows. Cows with milk fever are severely hypocalcemic (plasma Ca < 5 mg/dl) and usually hypophosphatemic (plasma inorganic Phos < 2 mg/dL) at the time of initial treatment for milk fever. In most cases, intravenous administration of Ca salts raises blood Ca concentrations immediately, followed within a few hours by a rise in blood Phos concentration.[13] This rapid recovery of plasma Phos is due to a reduction in parathyroid hormone secretion reducing urinary and salivary loss of Phos, and resumption of gastrointestinal motility accompanied by increased plasma concentrations of 1,25-dihydroxyvitamin D, which allows absorption of dietary Phos and reabsorption of salivary Phos secretions; however, in some animals plasma Phos concentrations fail to increase following therapy for milk fever, and it is believed that this results in a failure to rise after treatment, which can be one cause of the "downer cow" syndrome.[7, 10, 22] Effective methods to restore normal plasma Phos concentrations could be of aid in treatment and prevention of the downer cow syndrome.

Phosphorus Pool Sizes

About 1 to 2 g Phos is present in the plasma inorganic Phos pool, and 4 to 7 g Phos is normally present in the extracellular Phos pool of a 600-kg cow. Intracellular Phos concentration is about 25 mmol/L (78 mg/dL), and total intracellular Phos content is about 170 g, with 5 to 6 g located within erythrocytes. Salivary secretions represent another important pool, which removes between 30 and 90 g Phos from the extracellular Phos pool each day, with higher amounts secreted when dietary Phos is high.

Intravenous Treatment of Hypophosphatemia

Assuming that about 6 g inorganic Phos exists in the extracellular pool of a 600-kg cow and that plasma inorganic Phos concentration is normally 5 mg/100 mL, the cow with a plasma inorganic Phos concentration of 1 mg/100 mL will require about 4.8 g of inorganic Phos to restore normal plasma inorganic Phos concentration. The author is aware of no studies that have examined the intracellular phosphate levels in "downer cows," and because plasma phosphate is generally restored to normal with the treatments outlined later, we must assume that intracellular inorganic phosphate concentration is not altered dramatically, even when extracellular phosphate concentration is reduced by as much as 80%! As with treatment of Ca and Mg deficits, we would like to supply her with more than 4.8 g Phos to give her a bit of a buffer against the continuing drain of Phos.

The majority of the products available to veterinarians in the United

States for intravenous treatment of hypophosphatemic cattle use phosphite (PO_2) salts as the source of Phos. Phosphite salts are used because they are very soluble in water and remain soluble even in the presence of Ca and Mg, allowing preparation of solutions to treat low blood Ca, Mg, and Phos conditions with the same product; however, Phos found in blood and body tissues is almost exclusively in the form of the phosphate anion (PO_4). To our knowledge, no pathway exists for the conversion of phosphite to phosphate salts in body tissues. Phosphite salts are incapable of increasing plasma inorganic phosphate concentration.[6]

Sodium phosphate (monobasic, monohydrate) is a soluble form of phosphate that can be administered intravenously. The pH of the solution must be slightly acidic (pH ~5.8) to ensure solubility of the phosphate. Ca salts cannot be included in these solutions, as insoluble Ca phosphate salts will form. Intravenous sodium phosphate treatment (7 g Phos from 30 g reagent grade monosodium phosphate in 300 mL water administered over a 10-minute period) initially causes a hyperphosphatemia (plasma phosphate above 10 mg/100 mL) for a short time and will maintain normal plasma Phos concentration for 3 to 4 hours (Fig. 6). How deleterious the initial hyperphosphatemia is to the cow is unknown, although it seems likely that some Ca phosphate precipitates are likely to form as plasma Phos rises, especially if the animal has recently been treated with Ca intravenously. A product using 30 g

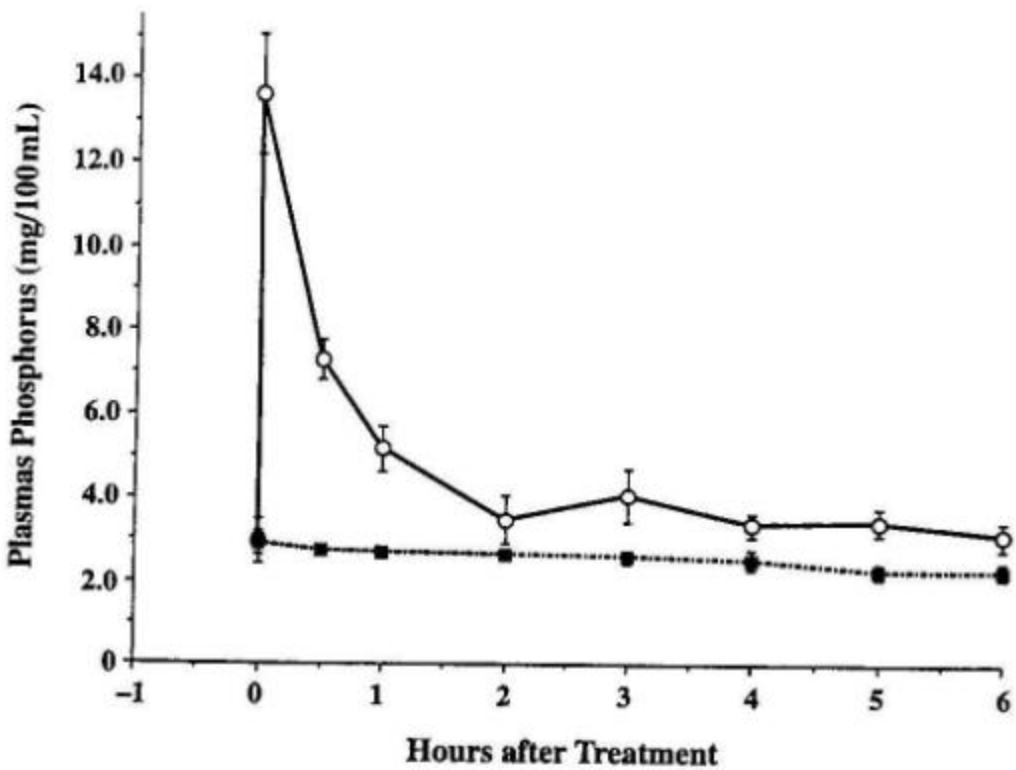

Figure 6. Mean ± SEM plasma Phos concentration (mg/dL) in cows receiving 7 g Phos intravenously supplied by sodium phosphate (circle) or sodium hypophosphite (square). *n* = 6/treatment.

monosodium phosphate in 300 mL water with no pH adjustment so the pH is less than 3.0 is available in Australia and is believed to be effective.[20] Some of the sodium phosphate enemas designed for use in humans contain 5 to 6 g Phos in each treatment with the pH adjusted to ~5.8 (very similar to the formula described above) and have been used for intravenous treatment of cattle after diluting to 1000 mL in water to reduce the tonicity.

Oral Treatment of Hypophosphatemia

Because the intravenous phosphate effect is short lived, most animals will require oral administration of phosphate to achieve more prolonged elevation of plasma phosphate. An effective dose is 50 to 60 g Phos supplied by 200 to 300 g feed grade monosodium phosphate in warm water administered as a drench or via stomach tube. Bone meal or dicalcium phosphate may also be used (0.5 kg), but they are only poorly soluble, difficult to administer, and do not increase plasma Phos rapidly enough to be very useful (Fig. 7).[6] Sodium phosphate can also be put into gelatin capsules and administered as boluses or incorporated into a paste or gel, which reduces the risk of aspiration pneumonia from drenches.

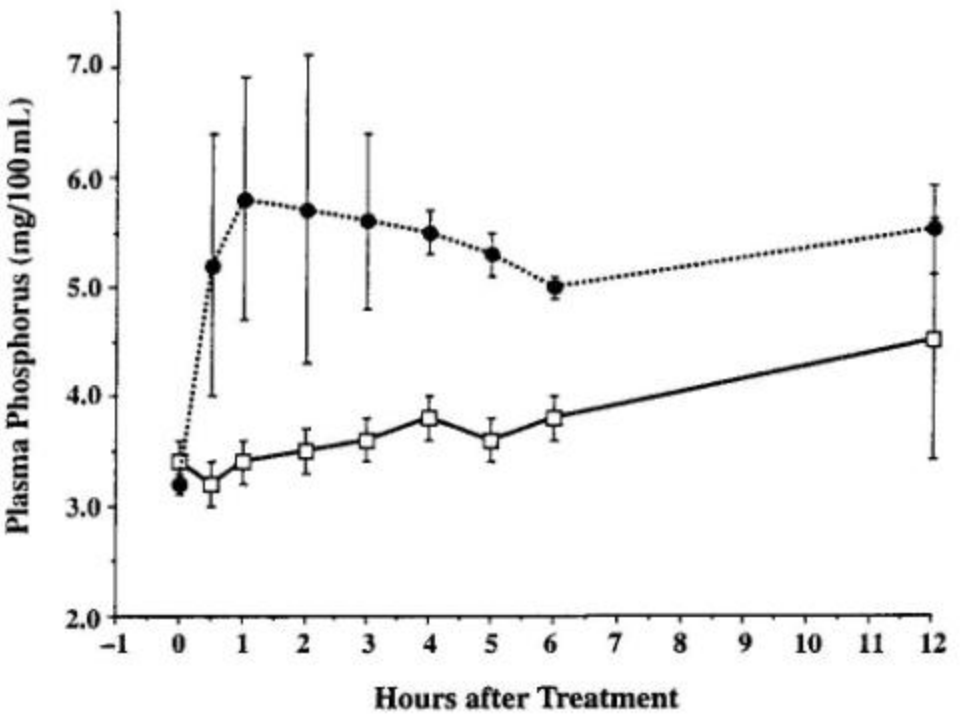

Figure 7. Mean ± SEM plasma Phos concentration (mg/dL) in cows receiving an oral drench containing 50 g Phos supplied by sodium phosphate (circle) or dicalcium phosphate (square). *n* = 4/treatment.

Summary

Oral sodium phosphate treatment (50 g Phos) causes a more prolonged increase in plasma Phos than does intravenous treatment (6 g Phos). One could give more phosphate intravenously, but there is a possibility that this might result in excessive formation of calcium or Mg phosphate precipitates within the blood, as plasma Phos concentrations immediately after treatment are well above physiological levels of plasma Phos. Intravenous phosphate solutions should not be given immediately before or after intravenous Ca treatment for this same reason. The two types of treatment should be spaced at least 2 hours apart. No such restrictions would be necessary for the oral sodium phosphate treatment. Monosodium phosphate is more soluble than dicalcium phosphate, which probably accounts for its greater ability to raise plasma Phos concentrations. The speed with which the oral sodium phosphate treatment raised plasma Phos concentration suggests that phosphate is being absorbed from the rumen or that a significant proportion has bypassed the rumen.[31]

Gastrointestinal motility and phosphate absorption may be poor in some downer cows, which actually is the precipitating cause of the hypophosphatemia. If true, it would suggest that oral treatment with the sodium phosphate drench may not be effective in these downer cows. Though this has not generally been our experience, the intravenous administration of sodium phosphate may be necessary to correct plasma Phos followed by an oral sodium phosphate treatment to maintain normal plasma Phos over a longer period.

The clinical response of the downer cows to the intravenous or oral sodium phosphate can be disappointing if not treated early in the course of the syndrome because muscle and nerve damage secondary to prolonged recumbency and the "crush" or "compartment" syndrome may keep the cow down despite correction of plasma Phos concentration. Although routine treatment of milk fever cows with phosphate solutions is unwarranted, on those farms with a historical record of hypophosphatemia and downer cows, the clinician could routinely follow intravenous Ca treatment with oral sodium phosphate treatment as initial treatment of the cow.

COMBINATION TREATMENTS AND CONCLUSIONS

Intraperitoneal administration of solutions containing Ca, Mg, or phosphate is an effective means of raising plasma mineral concentration and results in plasma pofiles that are nearly as high as with intravenous treatment. Unfortunately, this procedure carries a very high risk of inducing adhesions within the abdominal cavity. This risk can be reduced by using solutions with near neutral pH and using solutions that are only slightly hypertonic.

In most cases, combining Ca and Mg salts together is not harmful

and can be beneficial, especially when hypomagnesemia is the primary problem. Most hypomagnesemic animals also are hypocalcemic, and treatment with Mg alone can be lethal because the increasing Mg:Ca ratios in the heart during infusion into the jugular vein can cause heart failure. Phosphate cannot be put into solutions containing Ca or Mg without causing precipitates to form. Therefore, hypophosphatemia must be addressed separately.

Potassium is often incorporated into parenteral Ca solutions for two reasons. Most milk fever cows exhibit hypokalemia, and the idea is to help restore normokalemia. This probably is unnecessary, as potassium increases in the blood shortly after gastrointestinal motility is restored following intravenous Ca treatment. The second reason may be to protect the heart from the deleterious affects of hypercalcemia. Potassium can counteract the toxic effects of calcium on the electrical potential of the heart muscles. The potassium content of the entire extracellular pool of our 600-kg cow with a blood potassium concentration of 4 mEq/L is about 19 to 20 g potassium. The addition of 1 to 2 g potassium to these calcium-containing products would seem to offer little protection, as this is not enough to raise plasma potassium content of the extracellular pool by very much; however, because these products usually are administered into the jugular vein, the potassium concentration may confer some protection at the level of the heart before it is diluted within the systemic circulation. Including much more than 2 g potassium risks inducing cardiotoxicity from potassium. Although theoretically an interesting concept, it is not clear whether potassium-containing products are actually safer or result in an improved clinical response.

Glucose is often incorporated into intravenous treatments for cattle. In general, the glucose does no harm and can be used by the animal (milk fever cows are hyperglycemic because hypocalcemia prevents insulin secretion, and Ca administration will allow insulin to be released). Hypophosphatemic beef cattle are almost always hypoglycemic, suggesting that glucose should always be included in treatments for the recumbent beef cow in late gestation. Some glucose will be lost to urine, which might exacerbate dehydration in some animals, but this effect is relatively small. Glucose-containing solutions do cause more tissue necrosis when injected subcutaneously, perhaps because they increase the tonicity of the solution.

An oral cocktail that includes Ca, Mg, phosphate, and a glucogenic source can benefit the fresh cow to help prevent problems or can be given to the alert (good swallowing reflexes) recumbent cow. Many of the gels and pastes that are available for treating hypocalcemia also contain some Mg or Phos. Inclusion of Mg is generally a good idea. Inclusion of phosphate will reduce Ca absorption slightly.

A recipe we have used consists of 0.5 to 0.75 kg calcium propionate, 0.25 to 0.35 kg $MgSO_4 \cdot 7\ H_2O$, 0.2 to 0.3 kg monosodium phosphate (feed grade), and 0.5 L of propylene glycol dissolved in 6 L of warm water and administered via stomach tube or esophageal feeder. Varia-

tions might include the addition of 0.075 to 0.1 kg potassium chloride, or 1 kg alfalfa meal to help restore potassium in cows that are not eating.

Cardiotoxicity is the main problem during intravenous administration of any mineral solution, as jugular infusion causes very high blood mineral concentration in the heart. Give the solutions slowly! Use the subcutaneous abdominal vein (16-gauge needle) in animals that are at greatest risk (toxic cows, etc.) so the solution is diluted prior to reaching the heart.

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