MINERAL DISORDERS OF THE TRANSITION PERIOD: ORIGIN AND CONTROL

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1. INTRODUCTION

Inadequate blood calcium (Ca), phosphorus (P), magnesium (Mg), or potassium (K) concentrations can cause a cow to lose the ability to rise to her feet as these minerals are necessary for nerve and muscle function. Less severe disturbances in blood concentrations of these minerals can cause reduced feed intake, poor rumen and intestine motility, poor productivity, and increased susceptibility to other metabolic and infectious disease.

Mechanisms for maintaining blood Ca, P, Mg and K concentrations perform efficiently most of the time but occasionally these homeostatic mechanisms fail and metabolic diseases such as milk fever occur. An understanding of how and why these mechanisms fail may arise from a thorough understanding of how these mechanisms work under normal circumstances and then exploring the possible sites for breakdown of homeostasis. Strategies to avoid these disorders can then be developed.

2. FACTORS IMPAIRING CA HOMEOSTASIS TO CAUSE HYPOCALCEMIA AND MILK FEVER

2.1 Metabolic Alkalosis

Metabolic alkalosis predisposes cows to milk fever and subclinical hypocalcemia. Metabolic alkalosis blunts the response of the cow to PTH (Goff et al. 1991). In vitro studies suggest the conformation of the PTH receptor is altered during metabolic alkalosis rendering the tissues less sensitive to PTH (Bushinsky, 1996). Lack of PTH responsiveness by bone tissue prevents effective utilization of bone canaliculi fluid Ca, sometimes referred to as osteocytic osteolysis, and prevents activation of osteoclastic bone resorption. Failure of the kidneys to respond to PTH reduces renal reabsorption of Ca from the glomerular filtrate. More importantly, the kidneys fail to convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Therefore enhanced intestinal absorption of dietary Ca that normally would help restore blood Ca to normal, fails to be instituted. Metabolic alkalosis is
largely the result of a diet that supplies more cations (K, sodium (Na), Ca, and Mg) than anions (chloride (Cl), sulfate (SO₄), and phosphate (PO₄)) to the blood.

2.1.1 Strategy 1: reducing diet cation-anion difference

The difference between the number of cation and anion particles absorbed from the diet determines the pH of the blood. The cation-anion difference of a diet is commonly described in terms of mEq/kg (some authors prefer to use “mEq/100 g” diet) of just Na, K, Cl, and SO₄ (traditionally calculated on S% reported when diet is analyzed by wet chemistry) as follows:

\[
\text{Dietary Cation-Anion Difference (DCAD)} = (\text{mEq } Na^+ + \text{mEq } K^+) - (\text{mEq } Cl^- + \text{mEq } SO_4^-)
\]

This equation is useful, although it must be kept in mind that Ca, Mg, and P absorbed from the diet will also influence blood pH. Evaluation of the relative acidifying activity of dietary Cl vs. SO₄ demonstrate SO₄ is only about 60% as acidifying as Cl (Tucker et al. 1991). The DCAD of a diet and its acidifying activity is more accurately described by the following equation: \((Na^+ + K^+) - (Cl^- + 0.6 S^-)\). While DCAD equations provide a theoretical basis for dietary manipulation of acid-base status they are not necessary for formulation of mineral content of prepartum dairy cow rations because, with the exception of K and Cl, the rate of inclusion of the other macrominerals can be set at fixed rates based on the requirements of the cow. Diet sodium should be set at 0.12% and P at 0.35-0.40%.

At least two studies have clearly demonstrated that inclusion of Ca in the diet at NRC required levels or several fold above NRC required levels does not influence the degree of hypocalcemia experienced by the cow at calving (Goff and Horst, 1997; Beede et al. 2001). Beede et al. (2001) fed 0.47, 0.98, 1.52, and 1.95 % Ca diets to cows in late gestation being fed a high Cl diet to prevent milk fever. Cows fed 1.5% Ca diets had slightly reduced feed intake when compared to control cows while those fed the 1.95% Ca diet had significantly lower feed intake. Dietary Ca did not influence the degree of hypocalcemia experienced at calving or milk production in the subsequent lactation. It appears from this study that close-up diet Ca concentration should be maintained between 0.85 and 1.0% Ca.

To ensure adequate concentrations of Mg in the blood of the periparturient cow the dietary Mg concentration should be 0.35-0.4% to take advantage of passive absorption of Mg across the rumen wall. The details behind this rationale are discussed in the section on Mg.

Dietary S must be kept above 0.22% (to ensure adequate substrate for rumen microbial amino acid synthesis) but below 0.4% (to avoid possible neurological problems associated with S toxicity). Calcium sulfate and Mg sulfate are good sources of sulfur that may also supply Mg and Ca if needed. Sulfuric acid may also be used to increase diet sulfur to 0.4% if proper handling precautions are observed, which includes a respirator as the fumes are very hazardous!

Now, with the exception of K and Cl, the “variables” in the various proposed DCAD equations have become “fixed”. The key to milk fever prevention (at least with Holstein cows) is to keep K as close to the NRC requirement of the dry cow as possible (about 1.0% diet K). The key to reduction of subclinical hypocalcemia, not just milk fever, is to add Cl to the ration to counteract the effects of even low diet K on blood alkalinity. For formulation purposes the concentration of Cl required in the diet to acidify the cow is approximately 0.5% less than the concentration of K in the diet. In other words, if diet K can be reduced to 1.3% the Cl concentration of the diet should be increased to 0.8%. If dietary K can only be reduced to 2.0% the diet Cl would need to be roughly 1.5% to acidify the cow. This level of Cl in the diet is likely to cause a decrease in dry matter intake. Chloride sources differ in their palatability and since achieving low dietary K can be difficult it is prudent to
use a palatable source of Cl when formulating the diet. Ammonium chloride (or ammonium sulfate) can be particularly unpalatable when included in rations with a high pH. At the higher pH of some rations the ammonium cation is converted to ammonia, which is highly irritating when smelled by the cow. Prilling the Cl (and SO₄) salts can reduce the unpleasant taste of the salts. In our experience hydrochloric acid has proved the most palatable source of anions. As with sulfuric acid, hydrochloric acid can be extremely dangerous to handle when it is procured as a liquid concentrate. Several companies now manufacture hydrochloric acid based anion supplements, which are safe to handle.

These are simply guidelines for anion supplementation used by this author and are based on inclusion of Ca, Na, S, Mg, and P at the levels outlined above. Urine pH of the cows provides a cheap and fairly accurate assessment of blood pH and can be a good gauge of the appropriate level of anion supplementation (Jardon, 1995). Urine pH on high cation diets is generally above 8.2. Limiting dietary cations will reduce urine pH only a small amount (down to 7.5-7.8). For optimal control of subclinical hypocalcemia the average pH of the urine of Holstein cows should be between 6.2 and 6.8, which essentially requires addition of anions to the ration. In Jersey cows the average urine pH of the close-up cows has to be reduced to between 5.8 and 6.3 for effective control of hypocalcemia. If the average urine pH is between 5.0 and 5.5, excessive anions have induced an uncompensated metabolic acidosis and the cows will suffer a decline in dry matter intake. Urine pH can be checked 48 or more hrs after a ration change. Urine samples should be free of feces and made on midstream collections to avoid alkalinity from vaginal secretions.

**Preventing hypomagnesemia to avoid hypocalcemia**

Hypomagnesemia affects Ca metabolism in two ways:

- by reducing PTH secretion in response to hypocalcemia, and,
- by reducing tissue sensitivity to PTH.

PTH secretion is normally increased greatly in response to even slight decreases in blood Ca concentration. However hypomagnesemia can blunt this response (Rude et al. 1978).

Field evidence suggests that blood Mg concentrations below 1.6 mg/dl in the periparturient cow will increase the susceptibility of cows to hypocalcemia and milk fever (van de Braak et al. 1987).

### 2.1.2 **Strategy 2: feed a Ca deficient diet to stimulate PTH secretion pre-calving**

When cows are fed a diet that supplies less Ca than they require, the cows are in negative Ca balance. This causes a minor decline in blood Ca concentration stimulating PTH secretion, which in turn stimulates osteoclastic bone resorption and renal production of 1,25-dihydroxyvitamin D. This increases bone Ca efflux and the intestine is ready to absorb Ca efficiently once it becomes available in the lactating ration. At parturition the cow’s osteoclasts are already active and in high numbers and the lactational drain of Ca is more easily replaced from bone Ca. If provided with Ca in the lactation ration, the previous stimulation of enterocytes by 1,25-dihydroxyvitamin D will allow efficient utilization of dietary Ca and the cow avoids hypocalcemia (Green et al. 1981).

The absorbable Ca requirement of the late gestation cow is from 14 g/day in Jerseys to about 22 g in large Holsteins (National Research Council, 2000). A truly low Ca diet capable of stimulating PTH secretion supplies considerably less absorbable Ca than required by the cow.

Recently two methods have been developed to reduce the availability of dietary Ca for absorption. The first method involves incorporation of zeolite (a silicate particle) into the ration, which binds
Ca and causes it to be passed out in the feces. At present the method is unwieldy because very large amounts of zeolite must be ingested each day (1 kg) and the effects of zeolite on P and trace mineral absorption are not clear (Thilsing-Hansen et al. 2002). By chemically modifying the zeolite it is theoretically possible to increase the affinity and the specificity of the zeolite for Ca, which may allow it’s practical use. The second method involves administration of vegetable oils which bind Ca to form an insoluble soap preventing absorption of diet Ca (Wilson, 2003). These have been successfully used in cattle fed reduced Ca diets containing 30-50 g/day. However they irreversibly bind enough dietary Ca to cause the reaction typically seen when diet Ca is < 15 g absorbable Ca/day.

2.1.3 Strategy 3: oral Ca treatments at calving

Ca administered to the fresh cow may arguably be called a treatment rather than a preventative measure for hypocalcemia. Contrasts between the effects observed with intravenous, subcutaneous, and oral Ca treatments have been described elsewhere (Goff, 1999). Briefly, the concept behind oral supplementation is that the cow’s ability to utilize active transport of Ca across intestinal cells is inadequate to help her maintain normal blood Ca concentrations. By dosing the animal with large amounts of very soluble Ca it is possible to force Ca across the intestinal tract by means of passive diffusion between intestinal epithelial cells. Best results are obtained with doses of Ca between 50 and 125 g Ca/dose. Ca chloride has been used but can be very caustic. Ca propionate is less injurious to tissues and has the added benefit of supplying propionate, a gluconeogenic precursor. For best control of hypocalcemia a dose is given at calving and again 24 hrs later. Toxic doses of Ca can be delivered orally - about 250 g Ca in a soluble form will kill some cows (Goff et al. 2002). The benefit of adding oral Ca on top of a properly formulated low DCAD program does not seem to warrant the added expense (Melendez et al. 2002).

2.2 Magnesium: homeostasis and tetany

Mg is well absorbed from the small intestine of young calves and lambs. As the rumen and reticulum develop these sites become the main, and perhaps the only, sites for net Mg absorption. In adult ruminants the small intestine is a site of net secretion of Mg (Martens & Schweigel, 2000).

Mg absorption from the rumen is dependent on the concentration of Mg in solution in the rumen fluid and the integrity of the Mg transport mechanism, which is a Na-linked active transport process. The active transport mechanism for Mg absorption across the rumen wall is critical to the survival of the animal when dietary Mg concentration is less than 0.25%. Unfortunately there are several known factors, such as dietary K, and several unknown factors that prevent efficient Mg absorption by this pathway.

A second pathway for absorption of Mg exists which operates only at high rumen fluid Mg concentrations. At high rumen Mg concentration the Mg will flow down its concentration gradient into the extracellular fluids of the cow (Martens & Schweigel, 2000). This passive transport mechanism is not subject to poisoning by K and is only subject to the solubility of the Mg in the rumen. The concentration of Mg in rumen fluid needed to utilize concentration gradient driven absorption of Mg is greater than 4 mmol/l which is approximated by a diet that is 0.35% (Ram et al. 1998). Mg content of the close-up dry cow ration and the early lactation ration should be between 0.35 and 0.4% as insurance against the possibility that the active transport processes for Mg absorption are impaired.

Sampling the blood of several cows within 12 hrs after calving is a simple, effective index of Mg status of the periparturient cows. If serum Mg concentration is not at least 2.0 mg/dl in 9 of 10 cows
sampled, it suggests inadequate dietary Mg absorption from either lack of diet Mg or interferences with absorption.

2.3 Phosphorus

Maintaining the extracellular P pool involves replacing P removed for bone and muscle growth, endogenous fecal loss, urinary P loss, and milk production with P absorbed from the diet or resorbed from bone. During late gestation fetal skeletal development can withdraw up to 10 g P/day from the maternal P pools. About 0.3 g P is incorporated into each kg of body tissue (muscle) gained during growth of the animal (National Research Council, 2000). Production of milk removes about 1 g P from the extracellular pool/kg of milk produced. Salivary secretions remove between 30 and 90 g P from the extracellular P pool each day. Factors affecting salivary phosphate secretion include the time spent ruminating (chewing activity) and the PTH status of the animal. PTH stimulates parotid salivary P secretion and can increase salivary phosphate concentrations 2-3 fold (Wright et al. 1984).

At the onset of lactation the production of colostrum and milk draws large amounts of P out of the extracellular P pools. This alone will often cause an acute decline in plasma P levels. In addition if the animal is also developing hypocalcemia, PTH will be secreted in large amounts, increasing urinary and salivary loss of P. In dairy cows, plasma P concentrations routinely fall below the normal range at parturition and in cows with milk fever plasma P concentrations are often between 0.3 and 0.6 mmol/l or 1 and 2 mg/dl. Plasma P concentrations usually increase rapidly following treatment of the hypocalcemic cow with intravenous Ca solutions. This rapid recovery is due to reduction in PTH secretion which reduces urinary and salivary loss of P. Administration of Ca generally causes resumption of gastrointestinal motility, which allows absorption of dietary P and re-absorption of salivary P secretions that were sequestered within the rumen (Goff, 1998).

Some dairy cows developing acute hypophosphatemia do not spontaneously recover normal plasma P concentration. This is sometimes the case in cows that are classified as “downer cows”. This syndrome often begins as milk fever but unlike the typical milk fever cow, plasma P remains low (below 1 mg/dl in most of these cows) despite successful treatment of the hypocalcemia. Protracted hypophosphatemia in these cows appears to be an important factor in the inability of these animals to rise to their feet, but why plasma P remains low is unclear. Treatment of cows with phosphate containing solutions can effect a recovery in some animals. For oral treatment the dose is 50 g P supplied in a 200 g monosodium phosphate drench. Intravenous treatment consists of 6 g P supplied by 23 g monosodium phosphate dissolved in 1 liter of saline. Oral treatment restores normal blood P slightly slower than intravenous treatment but the effect lasts much longer. Phosphite sources of P do not restore physiologic function to the cow and though they are commonly found in treatment solutions for cattle they are totally ineffective (Cheng et al. 1998).

The hypophosphatemic downer cow syndrome does not appear to be caused by low P diets as affected cows are often receiving diets containing 0.4% dietary P. The best preventative measure seems to be to avoid development of hypocalcemia.

2.4 Potassium

Hypokalemia has been associated with muscle weakness and recumbency in cows. The majority of cases present with severe hypokalemia (plasma K below 2.5 mmol/l) and most cases occur secondary to prolonged inappetance, often secondary to other illnesses. Ketosis is commonly the factor precipitating the inappetance.

K metabolism is very complex. Understanding K homeostasis can shed light on the etiology of this syndrome and perhaps suggest more effective treatments for this disorder. Extracellular K
concentration is normally 3.9-5.8 mmol/l and plays a vital role in osmotic equilibrium, and maintenance of acid-base balance. Intracellular K concentration is 150-160 mmol/l. Intracellular K is a co-factor of enzymes involved in protein synthesis and carbohydrate metabolism, and K plays a major role in intracellular osmotic and acid-base equilibrium. The ratio of intracellular:extracellular fluid K concentration is the main determinant of resting cell membrane potentials, which affects nerve and muscle cell excitability.

K can move between extracellular and intracellular fluid compartments. Unfortunately this movement is not always very predictable- a normal blood K concentration may not indicate normal intracellular stores of K, and abnormal blood K concentration does not necessarily indicate abnormal store or concentration of K inside cells.

2.5 Hypokalemia and “downer cows”

As a general rule, K homeostasis will effectively prevent severe hypokalemia, if the animal is only off feed for a few days (before muscle is severely depleted of K). In most reports concerning clinical cases of hypokalemia and recumbency in cows the plasma K concentration is less than 2.5 mmol/l. In many of the affected cows plasma K concentration is less than 1.8 mmol/l. The degree of hypokalemia observed simply from inappetence of just 4-5 days is unlikely to be severe enough to cause flaccid paralysis in the cow. The severely hypokalemic cow tends to be very depressed. Though inappetance will greatly reduce the amount of K entering extracellular pools some other factor must also be causing depletion of extracellular and intracellular K.

The possibilities causing low plasma K include exaggerated renal excretion of K and excessive uptake of K by cells. The possibilities causing intracellular K depletion include prolonged fasting and exaggerated renal excretion of K.

Excessive aldosterone secretion by the adrenal gland is relatively rare in cattle. However, drugs with glucocorticoid activity are often administered to cattle in early lactation as anti-inflammatory agents or to stimulate gluconeogenesis in cows exhibiting ketosis. If those drugs also have mineralocorticoid activity they will stimulate urinary K secretion. In the inappetant cow the muscles are releasing K to support normokalemia. If this K is being rapidly excreted by the kidney the muscle K pool will be quickly depleted and severe hypokalemia can ensue. Isoflupredone acetate is administered to cows for its glucocorticoid activity but it has enough mineralocorticoid activity to enhance renal K secretion and administration of this steroid has been implicated as a factor causing severe hypokalemia in cows. Usually affected cows have been repeatedly injected with isoflupredone acetate prior to the onset of recumbency (Peek et al. 2003; Sielman et al. 1997).

Insulin causes a very rapid uptake of K by muscle and liver. Administration of exogenous insulin was considered a factor contributing to hypokalemia in several cows developing severe hypokalemia (Peek et al. 2003). Endogenous insulin release occurring after intravenous administration of glucose or oral administration of glucose pre-cursors such as glycerol, propionate, and propylene glycol will also shuttle K from extracellular to intracellular pools, but the effect is unlikely to be as long lived as with exogenous insulin.

Systemic alkalosis will cause K to leave the extracellular fluids and could be a cause of hypokalemia. Ten of fourteen hypokalemic animals described by Sattler et al. (1998) exhibited alkalosis as did eight of ten cases described by Sielman et al. (1997) and 9/17 cases described by Peek et al. (2003). Hypochloremia, with or without alkalosis was also a common feature of many cases. Metabolic alkalosis may have precipitated the hypokalemia, but since hypochloremia is a consistent observation in affected cows it seems more likely that gastrointestinal ileus in the animals
with severe hypokalemia caused sequestration of Cl within the abomasums. This alone will cause a metabolic alkalosis, and acts to drive even more K intracellularly.

3. SUMMARY

Four macrominerals have the distinction of being involved in the “downer cow” syndrome, which is, unfortunately, often associated with parturition in cows. Inadequate blood calcium (Ca), phosphorus (P), magnesium (Mg), or potassium (K) concentrations can cause a cow to lose the ability to rise to her feet as these minerals are necessary for nerve and muscle function. Less severe disturbances in blood concentrations of these minerals can cause reduced feed intake, poor rumen and intestine motility, poor productivity, and increased susceptibility to other metabolic and infectious disease. Mechanisms for maintaining blood Ca, P, Mg and K concentrations perform efficiently most of the time but occasionally these homeostatic mechanisms fail and metabolic diseases such as milk fever occur. Understanding how and why these mechanisms fail may allow the practitioner to develop strategies to avoid these disorders.

4. KEY WORDS

Calcium, milk fever, magnesium, phosphorus, potassium.

5. RESUME

Quatre éléments sont plus particulièrement impliqués dans le syndrome de la vache couchée, qui est malheureusement, souvent consécutif à la parturition. Une concentration sanguine inadaptée en calcium (Ca), phosphore (P), magnésium (Mg) ou potassium (P) peut empêcher la vache de se relever étant donné le rôle de ces éléments dans les fonctions nerveuses et musculaires. Des modifications moins marquées de ces macro-éléments peuvent provoquer une diminution de l’ingestion, une faible motricité ruminale ou intestinale, une baisse de la productivité, et une augmentation de la sensibilité à d’autres maladies métaboliques ou infectieuses. Les mécanismes qui régulent la concentration sanguine en Ca, P, Mg et K sont la plupart du temps, très efficaces, mais occasionnellement ces mécanismes homéostatiques sont déficients et des maladies métaboliques telles que la fièvre de lait apparaissent. Comprendre pourquoi et comment ces mécanismes deviennent déficients, pourra aider le praticien à développer des stratégies afin de prévenir ces désordres.

6. MOTS CLES

Calcium, fièvre de lait, magnésium, phosphore, potassium.

7. ZUSAMMENFASSUNG

Makromineralien sind dafür bekannt beim Festliegen von Rindern beteiligt zu sein, was leider häufig beim Kalben vorkommt. Unzureichende Kalzium (Ca), Phosphor (P), Magnesium (Mg) oder Kalium (K) Konzentrationen führen dazu, dass Rinder nicht mehr aufstehen können, da diese Mineralien essential für Nerven- und Muskelfunktionen sind. Suboptimale Blut-Konzentrationen dieser Mineralien kann zu vermindelter Futteraufnahme, verringriger Pansen- und Darmmotorik, verringerte Leistung und erhöhter Empfindlichkeit gegenüber anderen metabolischen sowie infektiösen Erkrankungen führen. Die Regulation der Blutkonzentrationen für Ca, P, Mg and K funktioniert in der Regel gut, jedoch kann es gelegentlich zum Versagen dieser Homeostase kommen, was zu metabolischen Erkrankungen wie zum Beispiel Milchfieber führt. Detailliertes Wissen über das wie und warum diese Regulationsmechanismen versagen wird es dem Praktiker erlauben Strategien zu entwickeln, um diese Erkrankungen zu verhindern.

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9. RESÚMEN

Son cuatro los macrominerales que destacan por estar envueltos con el llamado “síndrome de la vaca caída” el que se lo asocia con el parto en Ganado vacuno. Inadecuadas concentraciones sanguíneas de calcio (Ca), fosforo (P), magnesio (Mg) o potasio (K) pueden causar en la vaca su habilidad para pararse por sí sola puesto que estos minerales son necesarios para un funcionamiento normal de los nervios y los músculos. También se sabe que cuando las concentraciones de estos minerales en la sangre no son tan severas, existe una disminución del apetito, la motilidad del rúmen y el intestino es por debajo de lo normal, existe una reducción en la capacidad del aparato de la reproducción, y un incremento de la susceptibilidad a enfermedades de orden metabólico e infeccioso. En la mayoría de los casos, los mecanismos fisiológicos que mantienen los niveles sanguíneos de Ca, P, Mg and K se llevan a cabo en forma eficiente, pero en ocasiones, estos mecanismos homeostáticos fallan y enfermedades metabólicas tales como la fiebre de la lactancia ocurren. El entendimiento de cómo y porque estos mecanismos fallan podría ayudar al veterinario para desarrollar estrategias dirigidas a evitar estas anomalías.

10. PALABRAS CLAVES

Fiebre de la lactancia, calcio, fosforo, magnesio, potasio.

11. REFERENCES


