Available online at www.sciencedirect.com
ScienceDirect
The Veterinary Journal 176 (2008) 50–57
The Veterinary Journal
www.elsevier.com/locate/tvjl

The monitoring, prevention, and treatment of milk fever and subclinical hypocalcemia in dairy cows

Jesse P. Goff *

National Animal Disease Center, USDA-Agricultural Research Service, Ames, IA 50010, USA

Accepted 18 December 2007

Abstract

The periparturient cow undergoes a transition from non-lactating to lactating at calving. The animal is tremendously challenged to maintain calcium homeostasis. Those that fail can develop milk fever, a clinical disorder that is life threatening to the cow and predisposes the animal to a variety of other disorders. Guidelines for monitoring the incidence of hypocalcemia and methods for treating milk fever are reviewed. The physiological factors that cause milk fever and strategies for prevention of milk fever are discussed, focusing on the effects diet cation–anion difference can have on tissue sensitivity to parathyroid hormone. Another major risk factor for milk fever is hypomagnesemia, which is observed when animals are fed inadequate amounts of magnesium, or some factor is present in the diet that prevents adequate absorption of magnesium. Moderate hypomagnesemia impairs the ability of the cow to maintain calcium homeostasis and hypocalcemia occurs.
Published by Elsevier Ltd.

Keywords: Milk fever; DCAD; Hypomagnesemia; Hypocalcemia; Anionic salts

Introduction

Inadequate blood calcium (Ca) concentrations can cause a cow to lose the ability to rise to her feet as Ca is necessary for nerve and muscle function. This results in the metabolic disease known as milk fever, although it is more properly termed periparturient hypocalcemia or periparturient paresis, as an elevated body temperature is not typically observed. Milk fever is a particular concern in the newly calved cow, where the sudden demand for calcium at the onset of lactation severely tests the calcium homeostatic capabilities of the animal. Less severe disturbances in blood Ca concentration cause reduced feed intake, poor rumen and intestine motility, poor productivity, and increases susceptibility to other metabolic and infectious disease.

Mechanisms for maintaining normal blood Ca concentration perform efficiently most of the time, but occasionally these homeostatic mechanisms fail and hypocalcemia ensues. Understanding how and why they fail may allow the practitioner to develop strategies to avoid these disorders. Surveys in the USA suggest around 5% of cows will develop milk fever each year and the incidence of subclinical hypocalcemia – blood Ca values between 2 and 1.38 mmol/L (8 and 5.5 mg/dL) during the periparturient period – is around 50% in older cows (Horst et al., 2003). Milk fever and subclinical milk fever should be considered gateway diseases that greatly reduce the chance for full productivity in the ensuing lactation. Hypocalcemia reduces rumen and abomasal motility increasing the risk of abomasal displacement. Hypocalcemia reduces feed intake so that greater body fat mobilization occurs in early lactation. Hypocalcemia reduces all muscle contraction including the teat sphincter muscle responsible for closure of the teat orifice after milking, thus increasing the risk of mastitis. More recently we have demonstrated hypocalcemia directly impairs immune cell response to an activating stimulus (Kimura et al., 2006).

* Tel.: +1 515 663 7547; fax: +1 515 663 7458.
E-mail address: jesseg@westcentral.net

1090-0233/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.tvjl.2007.12.020

Ca homeostasis and monitoring for hypocalcemia

Blood Ca in the adult cow is maintained between 2.1 and 2.5 mmol/L (8.5 and 10 mg/dL). Typically, the nadir in blood Ca concentration occurs between 12 and 24 h after calving and blood samples obtained around this time can reveal the extent of hypocalcemia experienced by a dairy herd. Nearly 25% of heifers will have blood Ca concentration <2 mmol/L (8 mg/dL). About 50% of older cows will fall into this category. In well managed herds following a good anionic salt program or other effective milk fever control measures, the author's experience finds the above values can be cut in half and the number of cows exhibiting clinical milk fever can be reduced to 1% or less.

In order to prevent blood Ca from decreasing at the onset of lactation the cow must replace extracellular Ca lost to milk. She does this by withdrawing Ca from bone and by increasing the efficiency of absorption of dietary Ca. The dairy cow (as are most mammals) is programmed to go into a state of lactational osteoporosis, mobilizing bone Ca to help her achieve normocalcemia in early lactation. This will typically result in loss of 9–13% of her skeletal Ca in the first month of lactation (which is reversible in later lactations) (Ellenberger et al., 1932). Although it might stress her bones, the main objective – to maintain normocalcemia – can be achieved.

Bone Ca mobilization is regulated by parathyroid hormone (PTH) which is produced whenever there is a decline in blood Ca. Renal tubular reabsorption of Ca is also enhanced by PTH. However, the total amount of Ca that can be recovered by reducing urinary Ca excretion is relatively small as only small amounts of calcium are typically lost to urine each day. A second hormone, 1,25-dihydroxyvitamin D, is required to stimulate the intestine to efficiently absorb dietary Ca. This hormone is made from vitamin D by the kidney – but only in response to an increase in blood PTH. Put simply, hypocalcemia and milk fever occur when cattle do not extract enough Ca from their bones and diet to replace the Ca lost to milk. Several nutritional factors are involved in the breakdown of Ca homeostasis that results in milk fever.

Factors impairing Ca homeostasis at the cellular level

Metabolic alkalosis

Metabolic alkalosis predisposes cows to milk fever and subclinical hypocalcemia (Craige and Stoll, 1947). Metabolic alkalosis blunts the response of the cow to PTH (Gaynor et al., 1989; Leclerc and Block, 1989; Goff et al., 1991; Phillippo et al., 1994). We now believe the conformation of the PTH receptor is altered during metabolic alkalosis rendering the tissues less sensitive to PTH (Fig. 1). 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 also 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.

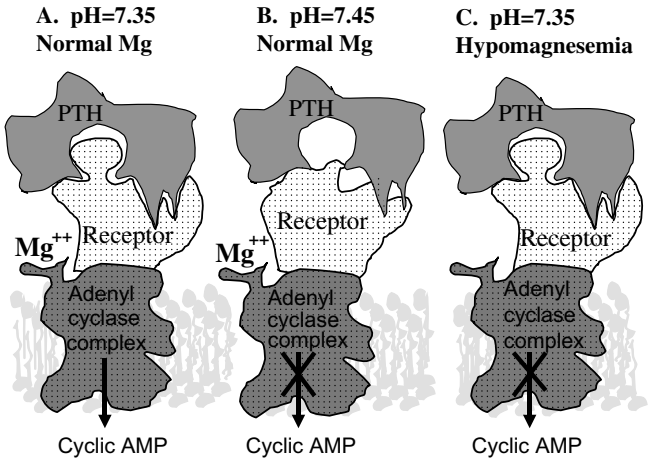

Fig. 1. Current hypothesis on parathyroid hormone (PTH) effects at the surface of target bone and kidney cells under various physiological circumstances. Panel A: Under normal conditions, PTH released in response to hypocalcemia interacts with its receptor, located on the surface of bone and kidney cells, in a lock and key fashion. This stimulates G-proteins and adenylate cyclase (adenylate cyclase complex) resulting in production of cyclic AMP, which acts as a second messenger within the cytosol of target cells. This initiates mechanisms such as bone Ca resorption and renal production of 1,25-dihydroxyvitamin D to restore blood Ca concentration to normal levels. Panel B: Alkalotic conditions induced by high potassium diets induce a change in the shape of the PTH receptor protein so that it is less able to recognize and bind PTH, resulting in failure to activate the cell by producing cyclic AMP. Panel C. Mg is required for full function of the adenylate cyclase complex. Hypomagnesemia reduces ability of PTH stimulated cells to produce cyclic AMP, resulting in failure to activate the cell.

Metabolic alkalosis is largely the result of a diet that supplies more cations (K, Na, Ca, and Mg) than anions (chloride [Cl], sulfate [SO_4], and phosphate [PO_4]) to the blood. In simplest terms, a disparity in electrical charge in body fluids occurs in animals fed these diets because a greater number of positively charged cations enter the blood than negatively charged anions. To restore electroneutrality to this high cation, positively charged blood, a positive charge in the form of a hydrogen ion (H^+) must be lost from the blood compartment. A reduction in H^+ concentration is equivalent to an increase in the pH of the blood (Stewart, 1983). For a more detailed description of how dietary cation–anion balance influences blood pH the reader is referred to recent reviews on this subject (Constable, 1999; Goff, 2000). Adding readily absorbable anions to the diet increases the total negative charges in the blood allowing more H^+ to exist and the blood pH decreases as it is more acidic.

Hypomagnesemia

Cow plasma Mg concentration is normally between 0.75 and 1.0 mmol/L (1.8 and 2.4 mg/dL). Hypomagnesemia

affects Ca metabolism in two ways, firstly by reducing PTH secretion in response to hypocalcemia (Littledike et al., 1983), and secondly by reducing tissue sensitivity to PTH (Rude, 1998).

The integrity of the interaction between PTH and its receptor is vital to Ca homeostasis. Hypomagnesemia, independently of metabolic alkalosis, can also interfere with the ability of PTH to act on its target tissues. When PTH binds its receptor on bone or kidney tissues, it normally initiates activation of adenylate cyclase, resulting in production of the second messenger, cyclic AMP. PTH–receptor interactions should also cause activation of phospholipase C in some tissues, resulting in production of the second messengers diacylglycerol and inositol 1,4,5-triphosphate. Both adenylate cyclase and phospholipase C have a Mg^{++} binding site which must be occupied by a Mg ion for full activity (Rude, 1998). In humans, it is well recognized that hypomagnesemia can cause hypocalcemia and that Mg therapy alone restores the serum Ca concentration to normal; Ca and/or vitamin D therapy are ineffective (Rude, 1998). Field evidence suggests that blood Mg concentrations < 0.65 mmol/L (1.5 mg/dL) in the periparturient cow will increase the susceptibility of cows to hypocalcemia and milk fever (van de Braak et al., 1987).

Maintenance of normal plasma Mg concentration is nearly totally dependent on a constant influx of Mg from the diet. 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 (Martens and Rayssiguier, 1980). 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 (Martens and Gabel, 1986).

The soluble concentration of Mg in rumen fluid is obviously dependent on the magnesium content of the diet. However, Mg solubility declines sharply as rumen pH rises above 6.5 and solubility can be a problem on higher forage diets. Forages also can contain *trans*-aconitic acid. A metabolite of *trans*-aconitic acid, tricarballylate, can complex Mg and is resistant to rumen degradation and may play a role in hypomagnesemic tetany (Cook et al., 1994).

Active transport of Mg across the rumen wall is necessary when diet Mg is not in great supply. Unfortunately, high K concentration in the rumen fluid depolarizes the apical membrane of the rumen epithelium reducing the electromotive potential needed to drive Mg across the rumen wall (Martens and Schweigel, 2000). Thus a ration that might otherwise be adequate in Mg results in a Mg deficient state when diet K is excessive.

A second pathway for absorption of Mg exists that is not affected by K. Unfortunately, this passive transport process only operates at high rumen fluid Mg concentrations, which allow Mg to flow down a concentration gradient into the extracellular fluids of the cow (Martens and Schweigel, 2000). The concentration of Mg in rumen fluid needed to utilize concentration gradient driven absorption of Mg is >4 mmol/L (9.2 mg/dL) – about 4-fold higher than blood Mg concentration (Care et al., 1984; Ram et al., 1998). The minimum level of Mg required in the diet to prevent negative Mg balance in the face of high K levels in ruminants is approximately 3.5 g/kg (0.35%) (Ram et al., 1998). (This would translate into about 150 mmol/L Mg in the diet – but not all of the Mg is soluble and salivary secretions and dietary water dilute the Mg in the rumen liquor considerably.) Thus, Mg content of the close-up dry cow ration and the early lactation ration should be between 3.5 and 4 g/kg (0.35% and 0.4%) as insurance against the possibility that the active transport processes for Mg absorption are impaired.

Assessing Mg status

In the animal receiving adequate dietary Mg, the blood level of Mg is generally maintained at levels that are just above the threshold for renal excretion of Mg. Sampling the blood of several cows within 12 h after calving provides an effective index of Mg status of the periparturient cows. Typically, the effect of PTH secreted to control hypocalcemia on the kidney at calving raises the threshold for renal excretion, thus raising blood Mg concentration if there is Mg to spare from the diet. If serum Mg concentration is not $\geqslant 0.8$ mmol/L (1.8 mg/dL) it suggests inadequate dietary Mg absorption and that hypomagnesemia may be limiting productivity as well as contributing to hypocalcemia in the herd.

Cows with blood Mg between 0.5 and 0.8 mmol/L (1.15 and 1.8 mg/dL) have few obvious clinical symptoms, though they often are slow to eat and are not producing milk up to their potential. Clinical signs of hypomagnesemia, such as recumbency, convulsions, nystagmus, are only observed when blood Mg falls <0.4–0.5 mmol/L (0.9–1.15 mg/dL). Tetany is generally accompanied by severe hypocalcemia, so effective treatment of grass tetany entails treating the cow with both Mg and Ca salts intravenously (IV) – but slowly. Hypomagnesemia is very amenable to prevention by increasing dietary magnesium content and insuring that it is an available form.

Reducing diet cation–anion difference to prevent hypocalcemia

Reducing the number of absorbable dietary cations and/or increasing the number of absorbable dietary anions greatly diminish the incidence of hypocalcemia and milk fever in dairy cows (Ender et al., 1971; Block, 1984). The major cations present in feeds and the charge they carry are Na (+1), K (+1), Ca (+2), and Mg (+2). The major anions and their charges found in feeds are Cl (−1), SO_4 (−2), and phosphate (assumed to be −3). In theory all the cations and anions in a diet are capable of exerting an influence on the electrical charge and hence the pH of the blood. Cations or anions present in the diet will only alter the electrical charge of the blood if they are absorbed

into the blood. Trace elements present in diets are absorbed in such small amounts that they are of negligible consequence to acid–base status. Organic acids such as the volatile fatty acids are generally absorbed in the undissociated form so that they carry both a positive and negative charge into the blood. They also are rapidly metabolized within the liver so they have only a small effect on general acid–base balance under most circumstances.

The difference between the number of cation and anion particles absorbed from the diet determines the general acid–base balance of the body and therefore the pH of the blood. The cation–anion difference of a diet is commonly described in terms of mEq/kg DM (some authors prefer to use mEq/100 g diet DM) of just Na, K, Cl, and SO_4, although it must be kept in mind that Ca, Mg, and P absorbed from the diet will also influence blood pH. The relative merits of the various DCAD equations proposed are addressed elsewhere (DeGaris and Lean, 2008). 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 in this author's opinion because, with the exception of K and Cl, the rate of inclusion of the other macrominerals can be set at fixed rates.

The USA National Research Council (2000) requirement for Na in the diet of a late gestation cow is about 1.2 g/kg (0.12%). A small amount of salt is added to the diet to prevent pica, which often is manifest as a desire to drink urine from the floor. Unlimited access to NaCl is to be avoided in late gestation because it will increase the risk of udder edema, not because it greatly affects acid–base status.

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). It appears from these studies that close-up diet Ca concentration should be maintained between 8.5 and 10 g/kg (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 3.5–4.0 g/kg (0.35–0.4%). This higher dietary Mg concentration allows the cow to take advantage of passive absorption of Mg across the rumen wall.

Dietary P concentration should be fed at a level to meet the NRC requirement for P in the late gestation cow. This is generally about 4 g/kg (0.4%) P for most cows. A diet supplying more than 80 g P/day (Barton, 1978; Kichura et al., 1982) will block renal production of 1,25-dihydroxyvitamin D and will actually cause milk fever.

Dietary S must be kept above 0.22% to ensure adequate substrate for rumen microbial amino acid synthesis. Corn (maize) silage diets are notoriously low in sulfur. Diet S should be kept below 4 g/kg (0.4%) to avoid possible neurological problems associated with S toxicity (Gould et al., 1991).

Now, with the exception of K and Cl, the 'variables' in the various proposed DCAD equations have become more or less '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 10 g/kg or 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 5 g/kg (0.5%) less than the concentration of K in the diet. In other words, if diet K can be reduced to 13 g/kg (1.3%), the Cl concentration of the diet should be increased to 8 g/kg (0.8%). Add Cl at this level and observe urine pH after 3–4 days. This is often a conservative approach and the final concentration of Cl needed to truly acidify the urine may have to be brought up to within 4 or even 3 g/kg (0.4–0.3%) of dietary K. It is important never to start an anion supplement program with higher levels of Cl.

If cows are over-acidified at the onset it becomes very difficult to evaluate urine pH as feed intake will quickly be affected. The dry cow pen should always be worked up to the adequate Cl dose. If dietary K can not be reduced below 20 g/kg (2.0%) the diet Cl would need to be at least 15 g/kg (1.5%) to acidify the cow. This level of Cl in the diet is likely to cause a decrease in dry matter intake independent of over-acidification. 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 higher pH, a portion of the ammonium cation is converted to ammonia, which is highly irritating when smelled by the cow. Prilling the Cl (and SO_4) salts reduces the unpleasant taste of the salts. In our experience hydrochloric acid has proved the most palatable source of anions. Hydrochloric acid can be extremely dangerous to handle when it is procured as a liquid concentrate. Several North American 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 ~7.8). 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 h or more after a ration change. Urine samples should be free of feces and made on midstream collections to avoid alkalinity from vaginal secretions. Anion supplemented diets are generally fed for the last three weeks before calving, though the length of time these diets need to be fed to induce a compensated metabolic acidosis is no more than 4–5 days. When fed longer than 6 weeks the urine pH of cows ready to freshen will have risen as the bone successfully buffers the acidity generated by the diet. In practice this means when anions are fed the entire dry period the urine pH target for the final week before calving must be increased by about 0.5 units. Alternatively one can simply monitor urine pH in those cows that have been on the diet for at least 1 week but not longer than 3 weeks.

Feeding a Ca deficient diet to stimulate PTH secretion pre-calving to prevent hypocalcemia

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. 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). This works even in the face of metabolic alkalosis as metabolic alkalosis reduces but does not totally eliminate tissue PTH sensitivity. Prolonged exposure to high PTH levels induced by the low Ca diet overcomes the reduced tissue sensitivity to PTH.

The 2000 NRC lists the Ca requirement of the cow in terms of absorbable Ca, since the availability of Ca in diets varies. The absorbable Ca requirement (National Research Council, 2000) of the late gestation cow is from 14 g/day in Jerseys to about 22 g in large Holsteins. A truly low Ca diet must supply considerably less absorbable Ca than required by the cow if it is to be capable of stimulating PTH secretion. For example, a 600 kg cow consuming 13 kg DM must be fed a diet that is <1.5 g/kg (0.15%) absorbable Ca if it is to provide <20 g available Ca/day. Low Ca diets are more practical under grazing situations. In these cases the total dry matter intake of pasture may be just 6–7 kg DM/day and the grasses being grazed can be <4 g/kg (0.4%) Ca, which would provide <28 g total Ca and somewhere around 9–10 g absorbable Ca/day (Sanchez, 2003). It is important to note that after calving the animal must be switched to a high Ca diet.

Recently, two methods have been developed to reduce the amount of dietary Ca available for absorption. The first method involves incorporation of zeolite (an alumino-silicate such as clinoptilolite) into the ration. This 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 (varies from 0.25 to 1 kg/day for 2 weeks before calving) and zeolite may have negative effects on P (and possibly trace mineral) absorption which may not be overcome with extra P in the diet (Thilsing-Hansen et al., 2002; Katsoulos et al., 2005; Pallesen et al., 2007). However, by chemically modifying the zeolite it is theoretically possible to increase the affinity and the specificity of the zeolite for Ca, which may allow its 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 methods have been successfully used in cattle fed diets containing 30–50 g Ca/day. They irreversibly bind enough dietary Ca to cause the reaction typically seen when the diet provides <15 g absorbable Ca/day.

Vitamin D supplementation

A reasonable practice is to supplement the dry cow with 20–30,000 IU vitamin D/day in the diet. Earlier literature often recommended feeding or injecting massive doses (up to 10 million units of vitamin D) 10–14 days prior to calving to prevent milk fever. These vitamin D doses pharmacologically increased intestinal Ca absorption, and sometimes prevented milk fever. Unfortunately, the dose of vitamin D that effectively prevented milk fever was very close to the dose causing irreversible metastatic calcification of soft tissues. Lower doses (500,000–1 million units of vitamin D) actually induced milk fever in some cows because the high levels of 25-OH D and 1,25-dihydroxyvitamin D resulting from treatment suppressed PTH secretion and renal synthesis of endogenous 1,25-dihydroxyvitamin. These animals become hypocalcemic once the exogenous source of vitamin D that had maintained elevated intestinal Ca absorption rates was cleared from the body. In some cases the ability to begin endogenous production of 1,25-dihydroxyvitamin D was suppressed for a week after calving resulting in milk fever 1–2 weeks after calving (Littledike and Horst, 1980).

Treatment with 1,25-dihydroxyvitamin D and its analogues can be more effective and much safer than using vitamin D but problems associated with timing of administration remain. The problem of suppression of renal 1,25-dihydroxyvitamin D production can be minimized by slow withdrawal of the exogenous hormone over a period of days after calving (Goff and Horst, 1990).

Treatment of milk fever

Acute hypocalcemia can also occur under many conditions involving infections, such as mastitis or metritis, especially if endotoxins are elaborated. As a rule the blood Ca concentration is <2 mmol/L (8 mg/dL), but >1.5 mmol/L (6 mg/dL). It is due to redistribution of Ca within organs

and will not be discussed further other than to be a reminder that not all hypocalcemic cows have the syndrome known as milk fever.

Treatment of milk fever and 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 'crush syndrome' effect on the down side appendages in as little as 4 h. This causes ischemia of the muscles and nerves and is followed by necrosis of these tissues resulting in the downer cow syndrome. The fastest way to restore normal plasma Ca concentration is to administer an IV injection of Ca salts (commonly Ca borogluconate). In general, commercial preparations for IV use supply from 8.5–11.5 g Ca/500 mL. They may also contain sources of Mg, P (often as ineffective phosphite) and glucose (dextrose). The most effective IV Ca dose is about 2 g Ca/100 kg BW. A good rule of thumb is to administer the Ca at a rate of 1 g/min. If administered too rapidly, fatal arrhythmia of the heart and cessation during systole can occur. Intravenous Ca treatments elevate blood Ca above normal for about 4 h.

Calcium salts can also be injected subcutaneously (SC), but absorption is variable since blood flow to the periphery is often compromised. The amount of Ca that can be injected into a single SC site should be limited to 1–1.5 g Ca (50–75 mL of most commercial preparations). Ca preparations designed for intramuscular administration are also available (Ca levulinate or Ca lactate). Most of these preparations must be limited to 0.5–1.0 g Ca/injection site to avoid tissue necrosis. To get an effective dose of Ca into the clinically hypocalcemic animal might therefore require 6–10 injections into widely separated spots. This can greatly impact meat quality in the site of injection and have therefore fallen out of favor. Oral Ca treatments are not recommended as treatments for clinical milk fever cases, though they can be effective aids in prevention of milk fever.

Oral calcium treatments at calving to prevent hypocalcemia

Calcium administered to the fresh cow may arguably be called a treatment rather than a preventative measure for hypocalcemia. 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 orally it is possible to force Ca across the intestinal tract by means of passive diffusion between, not across, intestinal epithelial cells. Best results are obtained with doses of Ca between 50 and 125 g Ca/dose.

Calcium chloride has been used but can be caustic. Large or repeated doses of calcium chloride can induce an uncompensated metabolic acidosis in the cow, especially if the cow is already being fed an acidogenic diet (Goff and Horst, 1993). Calcium propionate is less injurious to tissues and is not acidogenic. It has the added benefit of supplying propionate, a gluconeogenic precursor (Pehrson et al., 1998). For best control of hypocalcemia a dose is given at calving and again 24 h later. Larger or more frequent dosing can be toxic. Toxic doses of Ca can be delivered orally – about 250 g Ca in a soluble form will kill some cows. 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).

Conclusions

Prevention of hypocalcemia, not just milk fever, should be a major goal of dairy farms. Hypocalcemia is essentially caused by metabolic alkalosis in the cow induced by high potassium diets. The higher blood pH interferes with the action of parathyroid hormone on its target tissues – bone and kidney. As a result bone calcium is not resorbed and 1,25-dihydroxyvitamin D is not produced and the cow cannot restore blood Ca to normal levels. A second cause of hypocalcemia is hypomagnesemia. Magnesium is a necessary co-factor to allow parathyroid hormone to stimulate cyclic AMP production in target tissues. Once again the inability of bone and kidney to respond to parathyroid hormone results in hypocalcemia. To prevent hypocalcemia it is necessary to reduce diet cations – in particular potassium and to increase diet anions – particularly chloride and to a lesser extent sulfate. This will induce a compensated metabolic acidosis in the cow restoring the ability of parathyroid hormone to regulate blood calcium levels. By raising diet Mg to 0.4% with a very available Mg source it is generally possible to avoid development of hypomagnesemia at calving and thus rule out hypomagnesemia as a cause of periparturient hypocalcemia. In some cases diet potassium is so high and unavoidable that another tactic for prevention of hypocalcemia may be considered. If total absorbed diet calcium is substantially less than required by the cow it is possible to stimulate the secretion of parathyroid hormone before calving which can stimulate bone Ca resorption and intestinal Ca absorption mechanisms prior to calving to prevent milk fever, even in the face of metabolic alkalosis. Options for clinical treatment of milk fever should include IV treatment with calcium solutions (2 g Ca/100 kg BW) with consideration given to oral Ca gels or pastes to help prevent relapses to milk fever.

Conflicts of interest statement

At the time this paper was written and submitted for publication the author (Jesse P. Goff), was an employee of the United States Department of Agriculture and had no financial or personal relationship with other people or organisations that could inappropriately influence or bias the paper entitled *The monitoring, prevention, and treatment of milk fever and subclinical hypocalcemia*. Currently the author is Director of Research and Development of West Central Farmer's Cooperative, a company that produces

and markets an anion supplement based on research done by the author.

References

Barton, B.A., 1978. Studies of vitamin D, calcium, and phosphorus metabolism of the dairy cow. Master's thesis dissertation. University of Wisconsin, Madison, WI, USA.

Beede, D.K., Pilbean, T.E., Puffenbarger, S.M., Tempelman, R.J., 2001. Peripartum responses of Holstein cows and heifers fed graded concentrations of calcium (calcium carbonate) and anion (chloride) three weeks before calving. Journal of Dairy Science 84, 83.

Block, E., 1984. Manipulating dietary anions and cations for prepartum dairy cows to reduce incidence of milk fever. Journal of Dairy Science 67, 2939.

Care, A.D., Brown, R.C., Farrar, A.R., Pickard, D.W., 1984. Magnesium absorption from the digestive tract of sheep. Quarterly Journal of Experimental Physiology 69, 577–587.

Constable, P.D., 1999. Clinical assessment of acid–base status. Strong ion difference theory. Veterinary Clinics of North America: Food Animal Practice 15, 447–471.

Cook, G.M., Wells, J.E., Russell, J.B., 1994. Ability of *Acidaminococcus fermentans* to oxidize *trans*-aconitate and decrease the accumulation of tricarballylate, a toxic end product of ruminal fermentation. Applied and Environmental Microbiology 60, 2533–2537.

Craige, A.H., Stoll, I.V., 1947. Milk fever (parturient paresis) as a manifestation of alkalosis. American Journal of Veterinary Research 8, 168.

DeGaris, D.J., Lean, J.J., 2008. Milk fever in dairy cows – a review of pathophysiology and control principles. The Veterinary Journal, this issue.

Ellenberger, H.B., Newlander, J.A., Jones, C.H., 1932. Calcium and phosphorus requirements of dairy cows. II. Weekly balances through lactation and gestation periods. Vermont Agricultural Experiment Station, Bulletin 342, June 1932.

Ender, F., Dishington, I.W., Helgebostad, A., 1971. Calcium balance studies in dairy cows under experimental induction and prevention of hypocalcaemic paresis puerperalis. The solution of the aetiology and the prevention of milk fever by dietary mean. Zeitschrift für Tierphysiologie, Tierernährung und Futtermittelkunde 28, 233.

Gaynor, P.J., Mueller, F.J., Miller, J.K., Ramsey, N., Goff, J.P., Horst, R.L., 1989. Parturient hypocalcemia in jersey cows fed alfalfa haylage-based diets with different cation to anion ratios. Journal of Dairy Science 72, 2525–2531.

Goff, J.P., 2000. Pathophysiology of calcium and phosphorus disorders. Veterinary Clinics of North America: Food Animal Practice 16, 319–337, vii.

Goff, J.P., Horst, R.L., 1990. Effect of subcutaneously released 24F-1,25-dihydroxyvitamin D3 on incidence of parturient paresis in dairy cows. Journal of Dairy Science 73, 406–412.

Goff, J.P., Horst, R.L., 1993. Oral administration of calcium salts for treatment of hypocalcemia in cattle. Journal of Dairy Science 76, 101–108.

Goff, J.P., Horst, R.L., 1997. Effects of the addition of potassium or sodium, but not calcium, to prepartum ratios on milk fever in dairy cows. Journal of Dairy Science 80, 176–186.

Goff, J.P., Horst, R.L., Mueller, F.J., Miller, J.K., Kiess, G.A., Dowlen, H.H., 1991. Addition of chloride to a prepartal diet high in cations increases 1,25-dihydroxyvitamin D response to hypocalcemia preventing milk fever. Journal of Dairy Science 74, 3863–3871.

Gould, D.H., McAllister, M.M., Savage, J.C., Hamar, D.W., 1991. High sulfide concentrations in rumen fluid associated with nutritionally induced polioencephalomalacia in calves. American Journal of Veterinary Research 52, 1164–1169.

Green, H.B., Horst, R.L., Beitz, D.C., Littledike, E.T., 1981. Vitamin D metabolites in plasma of cows fed a prepartum low-calcium diet for prevention of parturient hypocalcemia. Journal of Dairy Science 64, 217–226.

Horst, R.L., Goff, J.P., McCluskey, B.J., 2003. Prevalence of subclinical hypocalcemia in US dairy operations. Journal of Dairy Science 86 (Suppl. 1), 247.

Jardon, P., 1995. Using urine pH to monitor anionic salt programs. Compendium on Continuing Education for the Practicing Veterinarian 17, 860.

Katsoulos, P.D., Roubies, N., Panousis, N., Arsenos, G., Christaki, E., Karatzias, H., 2005. Effects of long-term dietary supplementation with clinoptilolite on incidence of parturient paresis and serum concentrations of total calcium, phosphate, magnesium, potassium and sodium in dairy cows. American Journal of Veterinary Research 66, 2081–2085.

Kichura, T.S., Horst, R.L., Beitz, D.C., Littledike, E.T., 1982. Relationships between prepartal dietary calcium and phosphorus, vitamin D metabolism and parturient paresis in dairy cows. The Journal of Nutrition 112, 480–487.

Kimura, K., Reinhardt, T.A., Goff, J.P., 2006. Parturition and hypocalcemia blunts calcium signals in immune cells of dairy cattle. Journal of Dairy Science 89, 2588–2595.

Leclerc, H., Block, E., 1989. Effects of reducing dietary cation–anion balance for prepartum dairy cows with specific reference to hypocalcemic parturient paresis. Canadian Journal of Animal Science 69, 411–417.

Littledike, E.T., Horst, R.L., 1980. Problems with vitamin D injections for prevention of milk fever: toxicity of large doses and increased incidence of small doses. Journal of Dairy Science 63, 89.

Littledike, E.T., Stuedemann, J.A., Wilkinson, S.R., Horst, R.L., 1983. Grass tetany syndrome. In: Fontenot, J.P., Bunce, G.E., Webb, Jr., K.E., Allen, V. (Eds.), Proceedings of John Lee Pratt International Symposium on the Role of Magnesium in Animal Nutrition. Virginia Polytechnic Institute and State University, Blacksburg, Virginia, VA, USA, pp.173.

Martens, H., Gabel, G., 1986. [Pathogenesis and prevention of grass tetany from the physiologic viewpoint]. Deutsche tierärztliche Wochenschrift 93, 170.

Martens, H., Rayssiguier, Y., 1980. Magnesium metabolism and hypomagnesemia. In: Ruckebusch, Y., Thivend, P. (Eds.), Digestive Physiology and Metabolism in Ruminants. MTP Press Ltd, Lancaster, England, pp. 447–466.

Martens, H., Schweigel, M., 2000. Pathophysiology of grass tetany and other hypomagnesemias. Implications for clinical management. Veterinary Clinics of North America: Food Animal Practice 16, 339–368.

Melendez, P., Donovan, A., Risco, C.A., Hall, M.B., Littell, R., Goff, J., 2002. Metabolic responses of transition Holstein cows fed anionic salts and supplemented at calving with calcium and energy. Journal of Dairy Science 85, 1085–1092.

National Research Council, 2000. Nutrient Requirements of Dairy Cattle, National Academy Press, Washington, DC, USA.

Pallesen, A., Pallesen, F., Jorgensen, R.J., Thilsing, T., 2007. Effect of pre-calving zeolite, magnesium and phosphorus supplementation on periparturient serum mineral concentrations. The Veterinary Journal, June 26. doi:10.1016/j.tvjl.2007.01.007.

Pehrson, B., Svensson, C., Jonsson, M., 1998. A comparative study of the effectiveness of calcium propionate and calcium chloride for the prevention of parturient paresis in dairy cows. Journal of Dairy Science 81, 2011–2016.

Phillippo, M., Reid, G.W., Nevison, I.M., 1994. Parturient hypocalcaemia in dairy cows: effects of dietary acidity on plasma minerals and calciotrophic hormones. Research in Veterinary Science 56, 303–309.

Ram, L., Schonewille, J.T., Martens, H., van't Klooster, A.T., Beynen, A.C., 1998. Magnesium absorption by wethers fed potassium bicarbonate in combination with different dietary magnesium concentrations. Journal of Dairy Science 81, 2485–2492.

Rude, R.K., 1998. Magnesium deficiency: a cause of heterogeneous disease in humans. Journal of Bone and Mineral Research 13, 749–758.

Sanchez, J.M., 2003. Personal Communication. University of Costa Rica, San Jose, Costa Rica.

Stewart, P.A., 1983. Modern quantitative acid–base chemistry. Canadian Journal of Physiology and Pharmacology 61, 1444–1461.

Thilsing-Hansen, T., Jorgensen, R.J., Enemark, J.M., Larsen, T., 2002. The effect of zeolite A supplementation in the dry period on periparturient calcium, phosphorus and magnesium homeostasis. Journal of Dairy Science 85, 1855–1862.

van de Braak, A.E., van't Klooster, A.T., Malestein, A., 1987. Influence of a deficient supply of magnesium during the dry period on the rate of calcium mobilisation by dairy cows at parturition. Research in Veterinary Science 42, 101–108.

Wilson, G.F., 2003. Development of a novel concept (Calcigard) for activation of calcium absorption capacity and prevention of milk fever. Acta Veterinaria Scandinavica. Supplementum 97, 77–82.