MILK FEVER: HOW TO REDUCE INCIDENCES ON THE FARM?

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Abstract

Adequate blood calcium concentrations are vital to normal function of mammals. Mechanisms for maintaining normal blood calcium function adequately most of the time; however, occasionally they fail and calcium homeostasis is compromised. Milk fever or periparturient hypocalcemia in dairy cattle is a well-documented example of a breakdown in calcium homeostatic mechanisms. This disease occurs at the time of parturition and is unique to adult dairy animals. The disease results from the inability of animals to cope with the sudden demand for calcium in support of colostrum formation. Animals developing the disease become hypocalcemic and require intravenous calcium to survive. The precise metabolic lesions responsible for the onset of milk fever are still being debated. This report will highlight some of the current concepts related to the causes and prevention of milk fever in dairy cattle, as well as contrasting differences in calcium demands that exist between dairy cattle, humans and rats at the onset of lactation.

Introduction

Calcium (Ca) is essential for life in higher animals. It is involved in the normal functioning of a wide variety of tissues and physiologic processes which include bone formation, muscle contraction, nerve transmission, blood clotting and as a second messenger regulating the actions of many hormones. In order for these functions to be carried out properly, blood Ca concentrations must be monitored and regulated within strict limitations. In most mammalian species, plasma Ca concentration is maintained between 9-10 mg/dl through the coordinated efforts of the calcitropic hormones parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D [1,25(OH)2D3]. Any decrease in plasma Ca causes the parathyroid glands to secrete PTH and, within minutes, PTH increases renal reabsorption of Ca from the glomerular filtrate. If the

1 Names are necessary to report factually on available data; however, the USDA neither guarantees nor warrants the standard of the product, and the use of the name USDA implies no approval of the product to the exclusion of others that may also be suitable.
perturbation in plasma Ca is small, plasma Ca returns to normal and PTH secretion returns to baseline concentrations. However, if the demand for Ca is high, PTH remains elevated resulting in an induction of the renal enzyme 1α-hydroxylase which is responsible for producing 1,25(OH)₂D₃ (DeLuca, 1984). The hormone 1,25(OH)₂D₃ is the active form of vitamin D₃. Analogous to other steroid hormones, 1,25(OH)₂D₃ exerts its biological responses at the level of transcription by interacting with its intracellular receptor (VDR) to form a hormone-receptor complex which regulates transcription of 1,25-(OH)₂D₃-sensitive genes (Pike, 1985, Pike et al., 2002).

One of the most important effects of 1,25(OH)₂D₃ is to stimulate active transport of Ca absorption from the intestine. Transcellular transport of Ca involves a three-step process (Bronner, 2003; Wasserman and Fullmer, 1995) including entry of Ca from the intestinal lumen through the Ca channels TRPV5 and TRPV6 (van Abel et al., 2003), translocation of Ca from the brush border to the basolateral membrane by the Ca-binding protein calbindin D9k (Bronner, 1987) and extrusion of Ca through the basolateral membrane by the Ca ATPase PMCA1b (Pannabecker et al., 1995). Each step in this process is under the regulation of 1,25(OH)₂D₃ (Wasserman and Fullmer, 1995).

Calcium can also be absorbed passively by a vitamin D-independent process. Several studies have suggested passive Ca absorption accounts for a major portion of the Ca absorbed when Ca intake is adequate or high (Bronner and Pansu, 1999, Ireland and Fordtran, 1973, Sheikh et al., 1988). However, others have questioned the importance of passive Ca absorption (McCormick, 2002). Indeed, plasma Ca can be normalized in vitamin D deficient rats (Johnson and DeLuca, 2002), vitamin D receptor knockout mice (Li et al., 1998) and 1α-hydroxylase knockout mice (Dardenne et al., 2003) by feeding a diet of 2% Ca and 20% lactose. These animals would otherwise be hypocalcemic if fed normal Ca diets. There are also several studies demonstrating that oral administration of concentrated Ca supplements is an effective means of achieving elevations in serum Ca in normocalcemic and hypocalcemic animals (Goff and Horst, 1993, Goff and Horst, 1994). The elevations occurred with 30 minutes of treatment and resulted in plasma Ca concentrations between 12-16 mg/dl. The authors surmised that these elevations were the result of passive Ca absorption. This approach has been used successfully in treating the metabolic disease, milk fever, and is discussed later.

Another function of 1,25(OH)₂D₃ is to stimulate bone Ca resorption. This function is carried out in concert with PTH. Calcium exists within bone in two states. The readily available Ca pool is relatively small and exists in solution in the fluids surrounding the bone cells. This pool is quite labile and serves as a readily mobile Ca reserve analogous to glycogen as a mobile reserve in glucose homeostasis. The Ca within the dense bone matrix is less labile and functions as a slowly mobilized Ca source. The readily-mobilizable Ca in the bone fluids is separated from the extracellular fluids of the body by a syncytium of bone lining cells. Upon stimulation by
PTH and 1,25(OH),D, the bone lining cells rapidly transfer this bone fluid Ca into the extracellular pool (Capen and Marin, 1983). The size of this readily available Ca pool in the adult cow is estimated to be 6 to 10 g Ca (Vagg and Payne, 1970).

**Milk Fever**

The homeostatic mechanisms for maintaining blood Ca perform efficiently most of the time, although occasionally they fail resulting in metabolic disease. For example, the transition from the pregnant, nonlactating state to the nonpregnant, lactating state is often a disastrous experience for some species. In dairy cattle this period of productive life is commonly referred to as the “transition period”. During the transition period there is an abrupt change in demand for Ca and energy needed to support production of Ca-rich colostrum. If animals fail to adapt, they develop hypocalcemia, which is commonly referred to as milk fever (more accurately described as periparturient hypocalcemia). This metabolic disease occurs almost exclusively in ruminants such as dairy cows and dairy goats selected for their ability to produce large quantities of milk. Milk fever generally occurs 12 to 24 hours after giving birth. The hallmark of this disease is severe hypocalcemia, which accounts for most of the clinical signs. Cows exhibiting clinical signs generally have plasma Ca concentrations of <5.5 mg/dl. The clinical signs for milk fever can last for several hours. Initially, the animal appears dull and listless, has cold ears and a dry nose, and exhibits incoordination when walking. As hypocalcemia progresses the cow is unable to stand and the progressively loss of consciousness follows. Heart sounds become nearly inaudible and the heart rate increases to 120 beats per minute. Other signs observed are a reduction or absence of digestive tract contractions, and constipation. The term “milk fever” is a misnomer because animals commonly experience a decrease in body temperature, usually ranging from 96°F to 100°F. Normal body temperature for an adult cow ranges from 101°F to 103°F. Intravenous Ca treatments (usually 8 to 10 g Ca in the form of Ca borogluconate) are used to keep the cow alive long enough for intestinal and bone Ca transport mechanisms to adapt. If left untreated approximately 60 to 70% of the animals will eventually die due to this condition (Hibbs, 1950).

Although there have been numerous theories regarding the cause of milk fever, one fact appears undisputable, i.e., the mammary gland must be present, as was demonstrated in experiments performed in 1949 by Neidermeier et al. and later by Goff et al. (2002). These researchers demonstrated that mastectomy totally eliminated any decline in blood Ca that occurs at parturition. Normally, a cow will produce about 10 liters of colostrum at parturition. This represents a loss of ~23 g of Ca on the first day of production. This is about nine times as much Ca as is present in the entire plasma Ca pool of the cow (Figure 1). Calcium lost from the plasma pool must be replaced by Ca absorption from the intestine and/or Ca resorption from bone. This can be a formidable task for a cow, because during the last two months of gestation when cows are normally not lactating, Ca requirements are minimal (10 to 16 g/d) and limited to fetal growth (3-6 g Ca/day) and endogenous fecal Ca losses
Therefore, mechanisms (increased bone Ca resorption and increased intestinal Ca absorption) needed for replenishing plasma Ca at the onset of lactation are relatively quiescent (Ramberg et al., 1984). The inability to activate these mechanisms in a timely manner when the Ca demand increases at the onset of lactation results in hypocalemia. Most of the preventative measures used by today’s dairy nutritionists and veterinary practitioners target stimulation of intestinal Ca absorption and bone Ca resorption. Some of these approaches will be discussed later.

Prevention of Milk Fever

Vitamin D and Vitamin D metabolites—In the early 1900’s, scientists showed that vitamin D was important in the absorption of Ca from the intestine (Steenbock and Black, 1924). Until recently, most of the attempts at preventing milk fever were a function of our advancing knowledge of the vitamin D endocrine system. One of the first published reports suggested milk fever could be prevented by the use of large oral doses of vitamin D, during the few weeks prior to parturition (Hibbs and Pounden, 1955). At the time, the hypothesized mechanism of action suggested that vitamin D acted directly on target tissues (bone and intestine) to increase movement of Ca from these areas to the blood stream. However, we now know that the mechanism of action was associated with production of the more active metabolites of vitamin D (Horst and Reinhardt, 1983, Reinhardt and Conrad, 1980). For a period of approximately 30 years there were considerable resources and interest associated with this form of treatment. However, in 1968, Blunt et al. discovered a metabolite of vitamin D, that was more active than vitamin D,. This form of vitamin D, was identified as 25OHD, and was also thought at the time to be the active form. However, we now know that the active, hormonal form of vitamin D, is 1,25(OH),D, which is produced from 25OHD, in the kidney by the enzyme 1α-hydroxylase. Shortly following its discovery, research from several laboratories demonstrated that 1,25(OH),D, was metabolized to other less-active trihydroxylated metabolites, which are thought to be 1,25(OH),D, inactivation products. These include 1,25,26(OH),D, and 1,24,25(OH),D, (Reinhardt et al.; 1982, Reinhardt et al., 1981). As expected, the discovery of 1,25(OH),D, and its metabolites generated considerable interest in their potential use as milk fever preventatives (Gast et al., 1979; Horst et al., 2003; Hove and Kristiansen, 1982; Hove and Kristiansen, 1984). One potential problem using vitamin D, and its metabolites is an inhibitory feedback effect on the kidney 1α-hydroxylase. In studies summarized by Horst et al. (2003) periparturient hypocalcemia was prevented in many of the cows treated with vitamin D, or 1α-hydroxylated vitamin D, metabolites; however, they developed a delayed hypocalcemia and clinical signs of milk fever which became evident 10 to 14 days postpartum. The cows treated with the vitamin D, compounds were unable to produce endogenous 1,25(OH),D, once the exogenous treatments were withdrawn and were, therefore, unable to maintain normocalcemia as lactation progressed. The inability to produce 1,25(OH),D, was thought to be due to inhibition of the kidney 1α-hydroxylase by hypercalcemia associated with the use of the vitamin D, sterols as well as direct feedback.
inhibition caused by high circulating concentration of vitamin D_3 compounds resulting from the pharmacological doses administered. This research fostered the investigation into the next generation of vitamin D_3 compounds that were more active and longer-lasting analogues of the naturally-occurring forms. One of these analogues, 24-F-1,25(OH)_2D_3, surfaced as a potential alternative for use in milk fever prevention (Goff et al., 1988). They incorporated this analogue into a subcutaneous implant which released 24-F-1,25(OH)_2D_3 slowly throughout the peripartum period, avoiding high-circulating concentrations and abrupt withdrawal associated with intramuscular injections. This strategy had the advantage of protecting animals from milk fever and later lactation hypocalcemic episodes. This compound, however, never advanced beyond the experimental investigation stage. An analogue that has been marketed in Israel and used with varying degrees of success is 1αOHD_3 (Sachs et al., 1977). This analogue was originally used as a precursor in the chemical synthesis of 1,25(OH)_2D_3. It also can be activated by the body following 25-hydroxylation in the liver to form 1,25(OH)_2D_3. Use of this analogue, however, suffered similar disadvantages with earlier compounds of inducing hypercalcemia and inhibiting the endogenous synthesis of 1,25(OH)_2D_3.

**Calcium Gels** — Oral administration of large amounts of Ca salts to force Ca into the blood by passive diffusion can also be used to increase blood Ca concentration during the periparturient period. The Ca salt used has traditionally been CaCl_2 (Dhiman and Sasidharan, 1999; Hallgren, 1965; Jonsson and Pehrson, 1970; Ringarp et al., 1967). When the CaCl_2 was given for several days prior to calving and for 1 to 2 days after calving, it was effective in reducing the incidence of milk fever. More recently, a commercial CaCl_2 paste (54 g of Ca) given at calving and 12 and 24 hours after calving reduced milk fever, and had the added benefit of reducing the incidence of displacement of the abomasum (Oetzel, 1996). Calcium chloride solutions and gel preparations offer a very soluble, very concentrated (36% Ca), and rapidly absorbed source of Ca, making its use in gels and drenches attractive. However, CaCl_2 solutions and gels have several disadvantages. Aqueous solutions of CaCl_2 and some gel products are very caustic and cause ulceration of the mouth and digestive mucosa in some cows (Ward, 1966). All CaCl_2 products cause a reduction in blood pH. To a degree, this is beneficial in the periparturient cow as a major effect of adding anions to prepartal diets is to reduce the alkalinity of the blood (discussed below), increasing the sensitivity of tissues to PTH (Goff et al., 1991). However, excessive oral CaCl_2 can induce severe metabolic acidosis (Goff and Horst, 1993; Goff and Horst, 1994), which can cause inappetence at a time when feed intake is already compromised.

An alternative Ca salt, Ca propionate, can be formed into a thick paste and can raise blood Ca when given to cows (Goff et al., 1996). Although its effects on blood Ca concentrations are not as rapid as with CaCl_2, the activity of Ca propionate may be more sustained (Goff and Horst, 1994). Calcium propionate does not have an acidifying effect on blood pH, and the propionate can serve as a gluconeogenic precursor at a time when the animal is in negative energy balance. Calcium propio-
nate has the disadvantage of being only 21.5% Ca, thus requiring larger volumes of preparation to be given orally.

**Parathyroid Hormone**—In 1925 Dryerre and Greig suggested that the hypocalcemia of milk fever might be the result of insufficient PTH secretion. However, subsequent reports have concluded that PTH secretion in response to hypocalcemia in cows developing milk fever is equal to or greater that that of non-milk fever cows (Capen and Young, 1967; Horst and Reinhardt, 1983; Mayer et al., 1969). Several groups injected cows with crude extracts of PTH and found that older cows were less responsive than younger cows and that PTH did not prevent milk fever (Hibbs et al., 1947; Jackson et al., 1962). Martig and Meyer (1973) observed that the prepartum cow responded to exogenous PTH, but this response was blunted when compared with the response observed in postpartum cows. These findings lead to the current theory that responsiveness of the target tissue to PTH stimulation may be deficient or delayed in the periparturient cow.

Since these early reports, the physiological function of PTH and its interactions with the vitamin D endocrine system have been discovered. Also, there have been great advancements made with regard to the synthesis of large quantities of PTH suitable for use in pharmaceutical studies. Goff et al. (1986, 1989a) reevaluated the use of PTH for milk fever prevention and found that milk fever as well as subclinical hypocalcemia could be prevented with PTH infusions or injections. They observed that intramuscular injections required about 20 times as much PTH to be effective as intravenous infusions. They concluded that development of an implant to provide sustained release of small amounts of PTH might be a practical method of prevention.

**Low Ca Diets**—A seemingly contradictory approach to prevention of milk fever is to limit dietary Ca. Cows fed a very low Ca diet (<20 g/day) prior to calving cannot meet their Ca requirements (~30 g/day) for maintenance and fetal skeletal development from the diet. As a result, these animals are in negative Ca balance. This may lead one to conclude that low dietary Ca would exacerbate hypocalcemia. However, in reality, low dietary Ca can be a very effective means of preventing milk fever. Limiting dietary Ca to below that required for maintenance and reproduction results in stimulating PTH and 1,25(OH)_2D production prior to calving (Green et al., 1981). The elevations in PTH and 1,25(OH)_2D lead to activation of bone osteoclasts enhancing bone Ca resorption mechanisms. Elevations in plasma PTH and 1,25(OH)_2D also result in more efficient Ca absorption from the intestine and activation of renal tubules to reabsorb urinary Ca. Thus, at the onset of lactation, these Ca homeostatic mechanisms are active, preventing a severe decline in plasma Ca concentration in the cow (Boda and Cole, 1954; Goings et al., 1974; Green et al., 1981; Jorgensen, 1974; Kichura et al., 1982). After giving birth, the cow is normally switched to a high Ca diet, and therefore can use both bone and dietary Ca to maintain normocalcemia. Most commonly used ruminant feedstuffs contain concentrations of Ca that prevent formulation of diets low enough (<20 g/d) to be used in a practical setting.
Therefore, this approach has not received wide acceptance in the U.S. Recent studies have shown, however, that it is possible to create a pseudo Ca-deficient diet by supplementing rations with Ca binders (Thilsing-Hansen et al., 2002; Wilson, 2003). These binding agents offer an intriguing alternative to relying on low Ca feedstuffs and work well when dietary Ca is limited to <50g/day. However, they do not bind Ca specifically and have the potential to compromise the in vivo status of other macro and trace elements.

Dietary Cation Anion Difference (DCAD)—One of the most significant and yet least understood findings in the use of dietary modifications to control milk fever was the observation made by Ender et al. (1971). They discovered that feeding inorganic acids (a mixture of sulfuric and hydrochloric acids) to cows prepartum resulted in a significant reduction of milk fever incidence. They proposed that the milk fever incidence depended on the amount of the dietary cations sodium (Na) and potassium (K) relative to the anions chloride (Cl) and sulfate (SO₄). Their concept is currently referred to as the dietary cation anion difference or DCAD. Some remarkably astute experiments conducted later by Dishington. He provide some clarity and support for this concept. Dishington (Dishington, 1975) demonstrated that adding cations (in the form of Na bicarbonate or Na carbonate) greatly increased the incidence of milk fever. The effects of the high dietary Na content could be offset by the addition of a mixture of CaCl₂, Al₂(SO₄)₃, and MgSO₄ salts. Diets that are high in Na are, however, not commonly encountered on present-day dairy farms. Rather, the cation that is present in high amounts in the forages and other feedstuffs commonly fed to dairy cattle is K, which suggests that the high dietary K, rather than Na, content may be more important in predisposing cows to milk fever. Goff and Horst (1997) demonstrated in a recent report that this was indeed the case. In their experiments, the incidence of milk fever was increased simply by increasing prepartum dietary K concentration from 1.1 to 3.1%. Addition of Na also induced milk fever, corroborating the observations of Dishington (Dishington, 1975). As shown by Goff and Horst (1997), a major physiologic effect of the additional dietary K and/or Na was an increase in alkalinity of the blood and urine. Since ruminants normally consume forage and other feedstuffs high in K, they are normally in a state of mild metabolic alkalosis.

The alkalinizing effect of K and other dietary cations and the underpinnings of the DCAD concept can be explained by the strong ion difference theory described by Stewart (1983). Highly dissociated nonmetabolizable ions are referred to as strong ions. Examples of strong ions would be Na⁺, K⁺, Ca²⁺, Mg²⁺, Cl⁻, SO₄⁻, and PO₄⁻. The difference between the strong cations and strong anions in the blood is referred to as the strong ion difference. Strong ions enter the blood from the digestive tract making the strong ion difference of the diet the ultimate determinant of blood strong ion difference. According to Stewart’s theory (Stewart, 1983), the difference in the number of equivalents of cations and anions in a diet available for absorption determines the metabolic acid-base status of the animal. Animals become acidotic if
anions predominate, whereas they become alkalotic if cations predominate. As stated earlier, in most ruminant diets K contributes so many absorbable cations to the blood that most cows are in a state of mild metabolic alkalosis. Most human diets, on the other hand, are high in protein, PO₄, and SO₄ causing them to be in a mild acidic state. Various inorganic salts added to the diet can affect the acid-base balance of the animal. For example, CaCl₂ and MgCl₂ are acidic salts because the cations (Ca and Mg) are absorbed with less efficiency than the Cl. Because more equivalents of Cl are being absorbed than Ca or Mg, there is an imbalance in favor of anions, which according to Stewart (Stewart, 1983) creates an acidic environment. In the case of NaCl or KCl, the Na and K are absorbed with about the same efficiency as the Cl resulting in no net difference in cations and anions being absorbed. The in vivo experimental evidence also supports this concept (Gaynor et al., 1989; Goff and Horst, 1997; Goff et al., 1991; Goff et al., 2004).

The cation-anion difference of a diet is commonly described in terms of milliequivalents per kilogram (meq/kg) of diet. The value is calculated using the following equation:

\[ DCAD = (0.15 \text{Ca}^{2+} + 0.15 \text{Mg}^{2+} + \text{Na}^+ + \text{K}^+) - (\text{Cl}^- + 0.6 \text{SO}_4^{2-} + 0.6 \text{PO}_4^{3-}). \]

In this equation Na, K, and Cl are considered to be absorbed with 100% efficiency, whereas Ca and Mg, SO₄ and PO₄ are absorbed with lower efficiency. Also from this equation, an equivalent of Cl would be predicted to cause a greater reduction in blood pH than an equivalent of SO₄, which is consistent with the experimental evidence (Goff et al., 2004; Tucker et al., 1991). Commonly used sources of anions include the Cl and SO₄ salts of Ca, NH₄, and Mg. In each of these cases, the cation is absorbed with lower efficiency than the corresponding anion therefore, they are good candidates for achieving metabolic acidosis. Phosphate salts have not been commonly used as they are only weakly acidifying, because PO₄ is absorbed with only slightly greater efficiency than the corresponding cation. Also, high dietary PO₄ results in elevated blood PO₄, which can depress renal synthesis of 1,25(OH)₂D₃ (Tanaka and DeLuca, 1973) and result in increased incidence of milk fever (Kichura et al., 1982).

The exact mechanism of how feeding dietary anions and subsequent metabolic acidosis works to prevent milk fever is still unresolved. There is an abundance of evidence in humans and other mammals showing that metabolic acidosis can create a negative Ca balance by increased urinary Ca loss secondary to decreased renal tubular reabsorption of Ca (Bushinsky et al., 1982; Lemann et al., 1967; Schonewille et al., 1999; Wang and Beede, 1992). In cows fed diets high in anions (acidic diets), the urinary Ca is elevated to ~6-7 g/day compared to <1 g/day of urinary Ca in cows fed a diet high in cations (alkaline diets) (van Mosel et al., 1993). The argument has been made that the Ca lost in the urine as a result of metabolic acidosis may be recovered under the influence of PTH and therefore act as a reservoir of Ca during
periods of Ca stress (Schonewille et al., 1999). There is also evidence that intestinal Ca absorption may be increased in response to metabolic acidosis (Braithwaite, 1972; Schonewille et al., 1994). However, others suggest intestinal Ca absorption remains unchanged (Bleich et al., 1979; Vagg and Payne, 1970). Regardless, there is agreement that the plasma Ca concentration is maintained at the onset of lactation predominantly by increased bone Ca resorption. This concept is supported by in vitro (Bushinsky and Nilsson, 1995) and in vivo (Vagg and Payne, 1970) studies. In addition, Vagg and Payne (1970) suggested that inducing metabolic acidosis can increase the rapidly exchangeable pool of Ca from 6-9 g to 12-14 g. In contrast to the effects of acidosis, metabolic alkalosis induces an influx into bone (Bushinsky, 1996). Bone dissolution and the accompanying loss of bone Ca and PO4 during an acidic episode, therefore, undoubtedly plays a major role in preventing hypocalcemia as well as maintaining normal blood pH. During acidosis, Ca leaves bone in an attempt to increase the cation content of blood, reducing the blood acidity.

Although physical-chemical reactions are important in explaining bone Ca loss during metabolic acidosis, modifications in tissue responsiveness to hormonal stimuli can also play a role. Initial research conducted by our laboratory (Gaynor et al., 1989; Goff et al., 1991) and others (Abu Damir et al., 1994; Phillippo et al., 1994) provided indirect evidence that metabolic alkalosis decreases tissue responsiveness to PTH. More recently, Goff and Horst (2004) treated pregnant cows in their last trimester with PTH. The treated cows were provided either a low DCAD (acidic) or high DCAD (alkalotic) diet. They demonstrated that in response to the PTH treatment, cows receiving the acidic diets had higher plasma 1,25(OH)2D3 and plasma Ca than animals fed the alkaline diet. Similar results have been reported in experiments conducted with rats (Gafter et al., 1980). The studies of Goff and Horst (2004), therefore, provided the first direct evidence in cows that alkaliotc diets cause a pseudohypoparathyroid state in which tissues become less responsive to PTH. Acidic diets reverse the pseudohypoparathyroid state and prevent milk fever. This impaired responsiveness to PTH is similar to that observed in studies involving a milk fever subtype (Goff et al., 1989b). In cows suffering from this condition (~20% of the milk fever cows), increased production of 1,25(OH)2D3 was nonexistent or delayed. This syndrome was seen in cows that suffered relapses of milk fever (requiring intravenous Ca on more than a single occasion) and likely represents an exaggeration of the general breakdown in calcium homeostasis observed in many cows at parturition. In these relapsing milk fever cows, plasma 1,25(OH)2D3 concentrations did not increase as the animals became hypocalcemic. This response is in contrast to the typical milk fever case in which elevated 1,25(OH)2D3 is typically observed in response to hypocalcemia (Horst et al., 1977). These relapsing cows only recovered once they began to produce 1,25(OH)2D3. Plasma PTH concentrations were as high or higher in these relapsing milk fever cows as in non-relapsing milk fever cows. Since PTH should have stimulated renal 1,25(OH)2D3 production, the data again suggest that kidneys of milk fever cows are temporarily refractory to PTH stimulation, which is likely due to a disruption in PTH target tissue receptors. Without a functional receptor, PTH cannot
activate tissues and Ca homeostasis is compromised. Further support of this hypothesis can be seen in studies utilizing rats and dogs (Beck and Webster, 1976), which indicate that bone and perhaps renal tissues are refractory to the effects of exogenously administered PTH in the alkaline state, and that the stimulatory effects of PTH are enhanced during metabolic acidosis.

Collectively, these data suggest that the underlying cause of milk fever is metabolic alkalosis, which causes an inability of cow tissues to respond adequately to PTH. As summarized in Figure 2, metabolic alkalosis causes reduced ability to draw on bone Ca stores and poor production of 1,25(OH)₂D₃, which is needed for active transport of calcium from the intestine. Low DCAD diets prevent metabolic alkalosis, restoring target tissue responsiveness to PTH and allowing for stimulation of renal 1α-hydroxylase and bone Ca resorption. This permits the cow to successfully adapt to the Ca stress associated with the onset of lactation.

Current dietary recommendations—Current strategies for milk fever prevention suggest a dietary Ca of 1-1.2% and dietary P and Mg of 0.4%. Dietary S should be above 0.25% (to ensure adequate substrate for rumen microbial amino acid synthesis), but below 0.4% (to avoid possible neurological problems associated with sulfur toxicity). The key to milk fever prevention is to keep Na and K as close to the requirement of the cow as you can (0.1% for Na and 1.0% for K). It is more difficult to control milk fever without the addition of anions if dietary K is greater than 1.0%. Although reducing the dietary K results in a reduction in the incidence of milk fever, subclinical hypocalcemia can still occur. The incidence of subclinical hypocalcemia (and milk fever) can be reduced with the addition of anions, particularly Cl, to the ration. Dietary Cl above 1.0% may lead to reduced feed intake. The preferred source of Cl is HCl since there is no countering cation to offset the effects of the Cl addition. However, on-the-farm handling of liquid HCl can be difficult and is not recommended. There are commercially available dry Cl supplements, which use HCl as a source of Cl. Other sources such as MgCl₂ and CaCl₂ are also available and can be incorporated in ration. These inorganic salts can, however, be less palatable and result in intake reduction.

The amount of Cl needed can be estimated using the DCAD equations. Using the physiological DCAD equation described above [DCAD = (0.15 Ca⁺⁺ + 0.15 Mg⁺⁺ + Na⁺ + K⁺) - (Cl⁻ + 0.6 SO₄⁻ + 0.6 PO₄⁻)], the target DCAD for a prepartum diet is about -38 mEq/kg. However, since Ca and Mg are absorbed at a very low rate and PO₄ is not considered a viable anionic source, some nutritionists use the equation (Na⁺ + K⁺) - (Cl⁻ + 0.6 S⁻) with a target DCAD of about -+61 mEq/kg. Others use the equation (Na⁺ + K⁺) - (Cl⁻ + S⁻) with a target DCAD of -50 mEq/kg.

Although the DCAD equations described above can provide a guideline for dietary formulation, urine pH of the cows will be the better gauge of the appropriate diet DCAD. 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 and milk fever, 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 group should be 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. In cows offered feed twice/day the timing of the urine collection does not seem critical. In cows fed fresh feed just once/day the diurnal variation in urine pH can be a full pH unit. The best estimate of acid-base status appears to be from samples obtained 6-9 hrs after fresh feed was offered.

![Diagram of Calcium Homeostasis](image)

**Figure 1.** Calcium homeostasis in the periparturient cow. The extracellular pool of calcium is maintained by inputs from the bone and intestine which for the most part are under the control of parathyroid hormone (PTH) and 1,25(OH)2D3. The output of calcium at the onset of lactation occurs mostly as a result of colostrum formation and to a lesser extent endogenous fecal loss and urinary calcium loss. In normal or mildly hypocalcemic animals, the input of calcium is equal to the output of calcium. In animals developing hypocalcemia (milk fever), the output of calcium exceeds the inputs. The symbols in parentheses represent the biological response of the target tissues to the hormones.
Figure 2. Etiology of milk fever in dairy cattle. The onset of lactation results in a transient hypocalcemia stimulating an elevation in plasma parathyroid hormone (PTH). If the dietary cation anion difference (DCAD) is low, creating a mild acidosis, the PTH is effective at stimulating the production of 1,25(OH)₂D₃ resulting in increased intestinal calcium absorption, increased bone calcium resorption and no or mild hypocalcemia. If DCAD is high, creating a mild metabolic alkalosis, tissues are less sensitive to the PTH signal resulting in lower production of 1,25(OH)₂D₃, decreased intestinal calcium absorption, decreased bone calcium resorption and increased incidence of milk fever (severe hypocalcemia).

References


Steenbock, H. and A. Black. 1924. Fat soluble vitamins. XVII. The induction of growth promoting and calcifying properties in a ration exposed to ultraviolet light. J. Biol. Chem. 61:405-.


