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Review

Dietary Cation Anion Balance in the Ruminants I- Effects on Milk Fever

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ABSTRACT

Milk fever is an economically important disease, which not only reduces the productive life of a cow, but also increases the milk production cost. In dry period, calcium (Ca^{+2}) requirements are minimal (10-12 g of Ca^{+2}/day) but just after parturition these requirements increase and plasma Ca^{+2} concentration declined due to Ca^{+2} loss (23 g) in each milking. At parturition, the cow must bring more than 30g Ca^{+2}/day into the Ca^{+2} pool. As a consequence of this sudden change, nearly all cows experience some degree of hypocalcemia, during first day after calving. Plasma Ca^{+2} is controlled by the calcitropic hormones: (parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3), which are produced in response to hypocalcemia and act to increase the entry of Ca^{+2} into the plasma Ca^{+2} pool. Major underlying cause of milk fever is metabolic alkalosis. Incidence of milk fever depends on the abundance of the cations, relative to the anions which is generally referred to as the dietary cation-anion balance (DCAB). Anion addition reduces both blood and urine pH and is associated with reduction in milk fever as opposed to cations, which increase blood and urine pH and increase milk fever incidence. Low DCAB prevents metabolic alkalosis by increasing target tissue responsiveness to PTH, which controls renal 1-α-hydroxylase and resorption of bone Ca^{+2}. Mild metabolic acidosis induction with the addition of anions can increase Ca^{+2} mobilization from bone by releasing Ca^{+2} from bone surfaces, increase osteoclastic bone resorption and synthesis of 1,25-dihydroxyvitamin D_3 in cows. Elemental sulfur (S^{-2}) can be used to raise dietary DCAB, but no evidence exists that elemental S^{-2} (as opposed to sulfate) acidifies the blood. The majority of the S^{-2} fed excretes with the feces because it is highly insoluble and there is risk of S^{-2} toxicity. The high dietary Ca^{+2} increased the risk of milk fever. During prepartum period, low Ca^{+2} diets stimulate PTH and 1,25-dihydroxyvitamin D_3 production which at the time of parturition helps to maintain the Ca^{+2} level but currently it has been noted that high dietary Ca^{+2} is required to enhance the efficacy of anionic diets.

Key Words: Dietary Cation-Anion Balance; Milk Fever; Calcium; Sulfur; Chloride

INTRODUCTION

The transition from the pregnant, non-lactating state, to the non-pregnant lactating state is too often a disastrous experience for the cow. Most of the metabolic diseases of dairy cows like milk fever, ketosis, retained placenta and displaced abomasum occur within the first 2 weeks of lactation. The well being and profitability of the cow could greatly be enhanced by understanding those factors that account for the high disease incidence in parturient cows.

Milk fever is an economically important disease and can reduce the productive life of a dairy cow by 3.4 year (Payne, 1968). The average cost per case has recently been estimated at $334 (Guard, 1996). This value is on the direct cost associated with treating clinical cases and estimated production losses.

Calcium homeostasis. Milk fever is characterized by rapid decline in plasma calcium (Ca^{+2}) concentrations resulting from its expeditious loss to the formation of colostrum. A cow producing 10 liter of colostrum, for example, loses about 23 g of Ca^{+2} in a single milking. This amount is about 9X as much Ca^{+2} as is present in the entire plasma Ca^{+2} pool of the cow. Ca^{+2} lost from the plasma pool must be replaced by increasing intestinal Ca^{+2} absorption, or increasing bone Ca^{+2} resorption, or both. During the dry period, when Ca^{+2} requirements are minimal (fetal and endogenous fecal Ca^{+2} drain are 10-12 g of Ca^{+2}/day), these mechanisms for replenishing plasma Ca^{+2} are relatively inactive (Ramberg *et al.,* 1984). At parturition, however, the cow must bring ≥ 30 g of Ca^{+2}/day into the Ca^{+2} pool. As a consequence of this sudden change in Ca^{+2} requirement, nearly all cows experience some degree of hypocalcemia during 1st day after calving as the intestine and bone adapt to the Ca^{+2} demands of lactation. In some cows, the mammary drain of Ca^{+2} causes extracellular and plasma Ca^{+2} concentrations to decline to levels that disrupt neuromuscular function, resulting in the clinical syndrome of' milk fever. Intravenous Ca^{+2} treatments (usually 8-10 g of Ca^{+2}) are used to keep the cow alive long enough. If left untreated, about 60-70% of the high producing cows die (Hibbs, 1950).

Ca^{+2} is present in plasma in three major forms: ionized, protein bound, and complexed. The ionized form is the biologically active one, contributing about 50% of the total plasma Ca^{+2} pool (Ender *et al.*, 1962). Total input of ionic calcium (iCa) into blood Ca^{+2} pool

depends mainly on its absorption from intestine and mobilization from bone, in addition to the dissociation of protein bound Ca^{+2} (Ramberg *et al.*, 1975). Plasma Ca^{+2} is controlled by the co-ordinated efforts of the calcitropic hormones, parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2$ D_3], which are produced in response to milk fever and act to increase the entry of Ca^{+2} into the plasma Ca^{+2} pool. Any decrease in plasma Ca^{+2} causes the parathyroid glands to secrete PTH. Within minutes, PTH increases renal reabsorption of Ca^{+2} from the glomerular filtrate. If the perturbation in plasma Ca^{+2} is small, plasma Ca^{+2} returns to normal and PTH secretion returns to baseline levels. However, if the Ca^{+2} drain from the extracellular pool is large, continued PTH secretion stimulates resorption of the Ca^{+2} that is stored in bone (Horst & Reinhardt, 1983). Bone is the major source of Ca^{+2} during periods of low Ca^{+2} intake. Ca^{+2} exists within bone in two states. A small amount of readily available Ca^{+2} exists in solution in the fluids surrounding the bone cells and within the canaliculi of the bone. The soluble Ca^{+2} in the bone fluids is separated from the extracellular fluids of the body by a syncytium of bone lining cells. Upon stimulation by PTH, the bone lining cells rapidly transfer this bone fluid Ca^{+2} into the extracellular pool (Cappen & Marin, 1983).

PTH also induces the renal enzyme producing the $1,25(OH)_2$ D_3 (Tanaka & DeLuca, 1973). This steroid hormone acts synergistically with PTH to raise plasma Ca^{+2} by stimulating osteoclastic bone resorption and increasing renal tubular reabsorption of Ca^{+2}. However, $1,25(OH)_2D_3$ is most important for its ability to stimulate active transport of dietary Ca^{+2} across the intestinal epithelium. Efficient absorption of Ca^{+2}, when its dietary concentration is low and demand is very high, occurs by active transport across the intestinal epithelial cells. This process requires $1,25(OH)_2D_3$, which stimulates the production of Ca-binding protein that carry Ca^{+2} across the intestinal epithelial cells. Once Ca^{+2} is transported to the basolateral membrane, it is extruded from the cell against a 1000X concentration gradient by Magnesium (Mg^{+2})-dependent Ca-ATPase, which is also increased by $1,25(OH)_2D_3$ (Bronner, 1987).

A small amount of Ca^{+2} exists in solution in the fluids surrounding the bone cells and within the canaliculi of the bone, and is readily exchangeable with the blood (Capen & Marin, 1983). Vagg and Payne (1970) estimated 6-10 g Ca^{+2} as readily exchangeable bone pool of Ca^{+2} in the adult cow (assuming that the total extracellular fluid Ca^{+2} pool consists of about 8-10 g Ca^{+2}). Furthermore, they demonstrated that the amount of readily exchangeable bone fluid Ca^{+2} could be increased to 5-6 g by feeding ammonium chloride to induce metabolic acidosis, which may be sufficient to prevent many cases of milk fever. Anionic diets produced a larger pool of exchangeable Ca^{+2} and did not increase the Ca^{+2} deposition in the body and probably increased Ca^{+2} excretion (Fredeen *et al.*, 1988) and could also produce negative effects when administered in excess by inducing metabolic acidosis (Fredeen *et al.*, 1988), inducing osteoporotic conditions, and decreasing serum calcitriol response to low Ca^{+2} diets (Bushinsky *et al.*, 1985).

What is DCAB and how it Works? The incidence of milk fever depended on the abundance of the cations (Sodium [Na^+] & Poptassium [K^+]) relative to the anions (Chloride [Cl^-]& Sulfate [SO_4^{2-}]). This concept is now generally referred to as the dietary cation-anion balance (DCAB) and is expressed using various equations. Two of the most important equations most widely used were reviewed by Horst *et al.* (1997) includes:

DCAB (mEq/kg) = (mEq of Na^+/kg + mEq of K^+/kg) - (mEq of Cl^-/kg + mEq of SO_4^{-2})……..……Eq. I

DCAB (mEq/kg) = (0.38 mEq of Ca^{+2}/kg + 0.3 mEq of Mg^{+2}/kg + mEq of Na^+/kg + mEq of K^+/kg) - (mEq of Cl^-/kg + 0.6 mEq of SO_4^{-2}/kg)……...……..Eq. II

Supplementation of various mineral salts namely $CaCl_2.2H_2O$, $MgSO_4.7H_2O$ and $Al_2(SO_4)_3.18H_2O$ has been used to manipulate DCAB.

The CAD concept is based on the theory of strong ion difference, as described by Stewart (1983). This theory suggests that a net influx of any mineral cation or anion into the body results in a perturbation in the acid-base status of the animal. The extent of the perturbation depends on the quantity of the ion entering the system. Therefore, the difference in the number of cation and anion equivalents in a diet available for absorption determines the metabolic acid-base status of the cow. Cows become acidotic, if absorbable anions predominate, but they become alkalotic if absorbable cations predominate. Addition of anionic salts to a ration, therefore, results in a reduction in pH of blood and urine and is associated with a reduction in milk fever (Gaynor *et al.,* 1989; Goff *et al.,* 1991); addition of Na^+ or K^+ to rations increases blood and urine pH and is associated with an increase in milk fever incidence (Goff & Horst, 1997). A useful method for determining whether an animal is responding to added dietary anions is to monitor urinary pH. Urinary pH between 5.5 and 6.2 is associated with effective administration of anions (Gaynor *et al.,* 1989; Goff & Horst, 1997). If urinary pH is <5.5, dietary anions should be reduced to avoid severe metabolic acidosis (Horst *et al.,* 1997).

Reduced DCAB increased Ca^{+2} absorption from the intestine due to intestinal pH (Lomba *et al.*, 1978), particularly in older cows (Hove, 1986); increased rate of bone mobilization (Block, 1984) in response to the activation of the parathyroid gland (Lomba *et al.*, 1978), probably both mechanisms are involved (Fredeen *et al.*, 1988; Takagi & Block, 1991); and reabsorption from renal tubules. Reducing DCAB has also been shown to lower blood pH in dairy cattle (Tucker *et al.*, 1988a), hence enhancing bone mobilization in order to provide systemic buffering capacity (Guyton, 1986), with the consequential but potentially important release of bone Ca^{+2}. This idea was supported by Block (1984), who reported that feeding diet low in DCAB during the dry period completely prevented milk fever. Active transport of Ca^{+2} across the intestine is mediated by 1,25-$(OH)_2D_3$ (Bronner, 1987). Inadequate production of 1,25-$(OH)_2D_3$ could contribute to development of milk fever. Plasma concentrations of 1,25-$(OH)_2D_3$ were correlated inversely with plasma Ca^{+2} concentration and related directly to plasma PTH concentration. Goff *et al.* (1991) suggested that delayed or insufficient production of 1,25-$(OH)_2D_3$ may be a common cause of milk fever in dairy cows, fed cationic diets. A reduction in DCAB increased the production of 1,25-$(OH)_2D_3$/unit of PTH and thus reversed the tissue resistance to PTH that developed at the end of pregnancy and at the onset of lactation (Goff *et al.*, 1991).

The exact mechanism of how dietary anions work is still unresolved. However, previous work (Gaynor *et al.,* 1989; Goff *et al.,* 1991) suggested that inducing a mild metabolic acidosis by the addition of Cl^- or SO_4^{2-} to prepartum diets increased tissue responsiveness to PTH. This conclusion was based on the observation that addition of anions to the diet increased Ca^{+2} mobilization from bone by releasing Ca^{+2} from amorphous Ca-phosphates and Ca-carbonates on bone surfaces (Bushinsky *et al.*, 1985) increased osteoclastic bone resorption (Mundy & Raisz, 1981) and synthesis of 1,25-$(OH)_2D_3$ cows (Abu Damir *et al.,* 1994). These physiologic processes are controlled by PTH. Plasma hydroxyproline as an indicator of bone resorption was also increased in cows fed acidogenic diets during periparturient period (Block, 1984; Lecrelec & Block, 1989). Thus Block (1988) hypothesized that feeding DCAB caused an increase in availability of Ca^{+2} from the bones either directly or indirectly through the action of calcitropic hormones, namely PTH and 1,25-$(OH)_2D_3$.

Impaired responsiveness to PTH is found in some instances, which is similar to the condition described for a milk fever subtype (Goff *et al.,* 1989). For cows suffering from this condition, production of $1,25(OH)_2D_3$ is non-existent or low. This syndrome has occurred in cows that suffered recurrence of milk fever (requiring infusions of Ca^{+2} on more than a single occasion). Plasma $1,25(OH)_2D_3$ concentrations did not increase as the cows became hypocalcemic, which is in contrast to the typical response, in which the cow has elevated $1,25(OH)_2D_3$ (Horst *et al.,* 1977; Goff *et al.,* 1989). After 24-48 hours of severe hypocalcemia, these relapsing cows eventually began to produce $1,25(OH)_2D_3$ and recovered. Plasma PTH concentrations were as high in these cows with relapsing milk fever as in cows that did not relapse. Because PTH should have stimulated renal production of $1,25(OH)_2D_3$, the data again suggested that kidneys of cows that have milk fever are temporarily refractory to PTH stimulation. Although still indirect, these data support the hypothesis that receptors for PTH on the surface of the bone and kidney cells responsible for recognizing PTH, are less able to function at high blood pH. Without a functional receptor, PTH cannot work on the tissues and Ca^{+2} homeostasis is compromised.

Collectively, these data suggest that a major underlying cause of milk fever is metabolic alkalosis which causes an inability of cow tissues to respond adequately to PTH. This lack of response in turn reduces the ability of the cow to draw on bone Ca^{+2} stores and production of $1,25(OH)_2D_3$ which is needed for active transport of Ca^{+2} within the intestine. The presumption is that metabolic alkalosis somehow disrupts the integrity of PTH receptors on target tissues (Beck & Webster, 1976). Low DCAB diets prevent metabolic alkalosis, increasing target tissue responsiveness to PTH, which controls renal 1-α-hydroxylase and resorption of bone Ca^{+2}. Increased responsiveness permits the cow to adapt successfully to the Ca^{+2} stress associated with the onset of lactation.

Nutritional risk factors for milk fever. It has been established that Sulfur (S^{-2}) and DCAB are important nutritional risk factors for milk fever (Oetzel, 1991). A number of studies confirmed (Block, 1984; Oetzel *et al.*, 1988; Gaynor *et al.*, 1989; Goff *et al.*, 1991) that increasing anions of diets by addition of Cl^- and SO_4^{-2} can greatly reduce the severity and duration of the hypocalcemia associated with parturition in dairy cows. The most significant, yet least understood findings on 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 significantly reduced the incidence of milk fever. Block (1984) revived interest in DCAB showing that cows fed anionic salts had reduced incidence of milk fever. Subsequently, numerous publications (Oetzel *et al.,* 1988; Gaynor *et al.,* 1989; Beede *et al.,* 1991; Goff *et al.,* 1991; Beede, 1992) have validated the DCAB concept

and demonstrated the utility of adding anions to prepartum diets for prevention of milk fever postpartum. These research suggest that a DCAB of 50 mEq/kg of diet to –100 mEq/kg of diet is optimal for the prevention of milk fever.

Blood acid-base status. Equation I is convenient and relatively accurate predictor of the effect of diet on blood acid-base status. A limitation for this equation is that it ignores the contribution of other dietary cations and anions such as Ca^{+2}, Mg^{+2}, and PO_4^{-3} which might have an effect on acid-base balance. It also assigns the same acidification potency to each mEq of Cl^- and SO_4^{-2} diet. Whereas, Tucker *et al.* (1991b) found that when dietary calcium chloride ($CaCl_2$) replaced dietary limestone, Cl^- is absorbed to a greater extent than is SO_4^{-2}; blood H^+ increased, whereas blood HCO_3^- decreases linearly, however this trend was reversed postpartum, making Cl^- a more potent acidifier of the blood.

An alternate Equation II takes into account differences in availability of each of the major dietary cations or anions based on the average efficiency of absorption for each in cattle (NRC, 1989). From this equation, an equivalent of Cl^- causes a greater change in blood pH than an equivalent of SO_4^{-2} (Tucker *et al.,* 1991a). The efficiency of SO_4^{-2} absorption in late-gestation may be closer to 20%, making SO_4^{-2} even, less active an acidifying agent (Horst *et al.,* 1997). Also, this equation is very good as predicting why a salt such as $CaCl_2$ is an effective acidifying agent but NaCl has little or no effect on acid-base perturbations. Dietary supplementation of Cl^- with a relatively poorly absorbed Ca has been demonstrated to yield metabolic acidosis (Tucker *et al.*, 1988b) with a concomitant release of buffers and Ca^{+2} from the bone. Absorption of dietary Cl^- is associated with increased systemic generation of acid (Tucker *et al.*, 1988b) and subsequent bone Ca^{+2} mobilization; this may be the mechanism that allows heifers to access endogenous Ca^{+2} more readily than mature cows.

$CaCl_2$ in addition to improving Ca^{+2} status, has a diuertic effect (Merck, 1983) that might prove useful to prevent udder edema. Tucker *et al.* (1991b) suggested that feeding 1% $CaCl_2$ for 3 week pre-partum should provide prophylaxis for milk fever without seriously affecting systemic acid-base status. The acidifying properties of a salt depend on the preferential absorption of the anion over the cation that makes up the salt. For instance, NaCl is a neutral salt Both Na^+ and Cl^- are efficiently absorbed. Every Cl^- atom absorbed is accompanied by Na^+. $CaCl_2$ is an acidifying salt because Cl^- is absorbed efficiently (>90%), but Ca^{+2} is absorbed less efficiently (<40%) (NRC, 1989). Thus, more equivalents of Cl^- will be absorbed than Ca^{+2}. More H^+ will be absorbed to maintain electroneutrality, and the animal will become acidotic. With the increase in Cl^- absorption, blood HCO_3^- normally decreased (Guyton, 1986) causing a reduction in blood pH. Blood HCO_3^- was affected most dramatically by the 1.5% $CaCl_2$ diet (Tucker *et al.*, 1991b). The reduction in blood HCO_3^- with $CaC1_2$ supplementation likely is attributable to the acidogenic nature of Cl^-.

Urine H^+ increased with increasing dietary $CaCl_2$, apparently in response to the acidogenic properties of $CaCl_2$. These results confirmed the effectiveness of $CaCl_2$ as a urinary acidifying agent (Tucker *et al.*, 1991b) and were consistent with those of Tucker *et al.* (1988b). Acidosis increased the flow of Ca^{+2} through the readily exchangeable Ca^{+2} pool (Takagi & Block, 1988). The absence of sustained metabolic acidosis after removal of $CaCl_2$ from the diet indicates that the metabolic acidosis was quickly corrected and that feeding $CaCl_2$ to dry cows should have no adverse effect on systemic acid-base status once lactation begins (Tucker *et al.*, 1991b).

The increased urinary Ca^{+2} excretion that accompanies a low DCAB might be attributed to increased intestinal absorption of Ca^{+2} (Takagi & Block, 1988), increased mobilization of Ca^{+2} from bone (Fredeen *et al.*, 1988), an acidosis induced reduction in renal Ca^{+2} resorption (Rose, 1984; Takagi & Block. 1988) or to a combination of these factors. Feeding a low DCAB paradoxically increases urinary Ca^{+2} excretion and provides protection against milk fever. The mechanism of action appears to increase Ca^{+2} availability to the cow for metabolic functions, which is reflected in the greater clearance of Ca^{+2} via the kidneys.

Prevention of milk fever requires that the blood pH should be reduced to prevent metabolic alkalosis. Using Equation II, blood pH can be reduced by adding anions or by reducing the number of cations in the diet. Commonly used sources of anions include the Cl^- and SO_4^{-2} salts of Ca^{+2}, ammonium and Mg^{+2}. The phosphate salts have not been used generally because they are only weakly acidifying; phosphate is absorbed with only slightly greater efficiency than the corresponding cation. Also, at high concentrations, blood phosphate can increase to concentrations that depress renal synthesis of $1,25\text{-}(OH)_2D_3$ (Tanaka & DeLuca, 1973), resulting in milk fever (Kichura *et al.,* 1982). Elemental S is being used in the field as an inexpensive means of raising dietary S^{-2} to influence DCAB (Horst *et al.,* 1997), yet no evidence exists that elemental S^{-2} (as opposed to SO_4^{2-}) acidifies the blood. In all likelihood, the majority of the S^{-2} fed excreted with the feces because it is highly insoluble.

Dietary Manipulation of Acid-Base Status

Removing dietary cations. Addition of anions to the

diet to reduce DCAB is limited because of palatability problems of the anionic salt sources (Oetzel & Barmore, 1993). If the DCAB is >250 mEq/kg, it will be particularly difficult to add enough anionic salts to lower the DCAB to the recommended level of -100mEq/kg of diet without experiencing palatability problems. However, as suggested by the Equation II, blood pH (and, therefore, incidence of milk fever) can also be reduced by removing cations from the diet. However, caution must be taken not to reduce the dietary cation below the requirement (NRC, 1989) of the cow, particularly Na and Mg, which can be low in some natural feedstuffs. Goff and Horst (1997) have recently provided the first direct evidence that cows fed a diet low in K^+ or Na^+ have less milk fever than those fed diets high in K^+ or Na^+. This study demonstrated the utility of reducing the cation content of a diet to prevent milk fever, rather than relying solely on the addition of anions. The cation present in the highest amounts in commonly fed ruminant diets is K^+ derived from the forages fed to the cows. Alfalfa, for example, is commonly fed to dairy cows as a highly palatable source of fibre that is also high in protein. However, the K^+ concentration of alfalfa can reach very high concentrations; based on the DCAB concept, the use of alfalfa in the transition diet of the dry cow would be limited. Alfalfa harvested at the late-vegetative and bloom stages supplied 2.75 and 1.75% K^+, respectively (Baker & Reid, 1977). Immature forage is higher in forage quality than more mature forage and is recommended for high producing dairy cows. Utilization of mature alfalfa might reduce the dietary K^+ of the dry cow, but the higher neutral detergent fibre content of the more mature plant is likely to inhibit feed intake during the transition period (Buxton & Mertens, 1995).

Low calcium diets. Ca^{+2} is a strong cation. From Equation II, addition of Ca^{+2} to the diet would seem to increase the blood pH, which would predispose cows to milk fever. Many workers (Jorgensen, 1974; Green *et al.,* 1981; Kichura *et al.,* 1982) concluded that prepartum diets high in Ca^{+2} were associated with increased incidence of milk fever. However, evidence also exists that increasing dietary Ca^{+2} does not cause milk fever and may actually help prevent milk fever (Green *et al.,* 1981), especially in diets with added anions (Oetzel *et al.,* 1988; Beede *et al.,* 1991).

Cows fed a diet that is very low in Ca^{+2} (10-20 g) prior to calving cannot meet Ca^{+2} requirements for maintenance or fetal skeletal development (30g/day). As a result, these cows are in negative Ca^{+2} balance, which results in stimulating PTH and $1,25(OH)_2D_3$ production prior to calving (Green *et al.,* 1981). This process also activates bone osteoclasts, stimulating bone Ca^{+2} resorption and activates renal tubules to resorb urinary Ca^{+2}. Thus, at the onset of lactation, these Ca^{+2} homeostatic mechanisms are active, preventing a severe decline of plasma Ca^{+2} concentration in the cow (Green *et al.,* 1981; Kichura *et al.,* 1982). Careful review of the research reveals that the dietary Ca^{+2} was restricted to <20 g/day to obtain significant stimulation of the parathyroid glands (Green *et al.,* 1981). When $CaCO_3$ was added to low Ca^{+2} diets to raise dietary Ca^{+2} (80 to 120 g/day), which was well above the requirement (30 g/day) of the cow, the incidence of milk fever greatly increased. Based on these experimental observations, it was routinely recommended that dietary Ca^{+2} be kept as low as possible in the pre-partum diet. Although dietary Ca^{+2} could generally be limited only to about 50 g/day and this was often a successful means of preventing milk fever (Jorgenson, 1974). To achieve a diet with <50 g of Ca^{+2}/day required that high Ca^{+2} forages such as alfalfa be removed from the ration and replaced with low Ca^{+2} forages such as corn silage or grass hays. This strategy also greatly reduced DCAB (Reinhardt *et al.,* 1988), because alfalfa contains 2.5-4% K^+ whereas K^+ contents of corn silage is generally <1.7%.

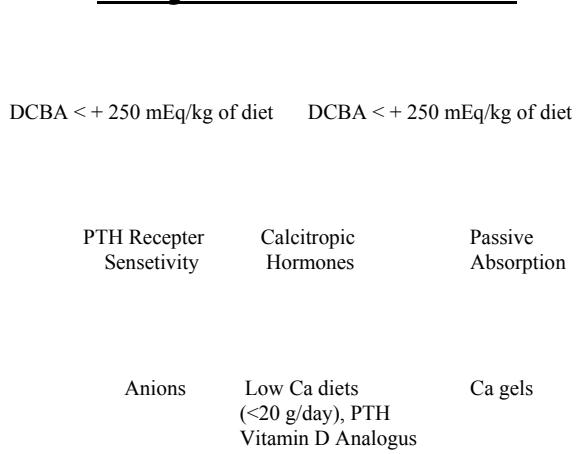
A controlled experiment testing the merits or demerits of Ca^{+2} supplementation in cows fed diets supplying 0.5 and 1.5% Ca^{+2} and DCAB -100, +200 and +400 mEq/kg of diet, was carried out (Goff & Horst, 1997). The low Ca^{+2} diet supplied 36 g of Ca^{+2}/day (above the requirement) and the high Ca^{+2} diet supplied 110 g of Ca^{+2}/day. There was no significant effect of dietary Ca^{+2} on the, incidence of milk fever in these cows.

$CaCl_2$ is a hygroscopic Ca^{+2} salt that has been administered therapeutically as a diuretic and urine acidifying agent (Tucker *et al.*, 1991b). $CaCl_2$ lowered intestinal pH (Bland, 1963) which is required to prevent milk fever. It could be incorporated easily into the concentrate of the dry cow for 2 to 3 wk prepartum in practice. To prevent the occurrence of milk fever when high Ca^{+2} diets are fed to dry cows, DCAB apparently must be reduced below –3 mEq/100g of dietary DM.

The cows fed diets containing Ca^{+2} as a mixture of the Cl^-, SO_4^{-2} and phosphate salts did not show any change in blood and urine pH (Goff and Horst, 1997), however the risk of milk fever enhanced in cows fed diets containing $CaCO_3$. Ca is generally added to the dry cow diet in the form of $CaCO_3$ and which can increase the risk of this problem (Green *et al.,* 1981). Equation II predicts that $CaCO_3$ added to the prepartum ration in large amounts will raise blood pH in the same manner as do mono-valently charged cations Na^+ and K^+. In a diet that is marginally high in DCAB, the addition of $CaCO_3$ could increase blood pH to the point that cows would develop metabolic alkalosis and milk fever.

Role of phosphorus in the etiology of milk fever. Phosphorus (P) plays an important role in the etiology of parturient hypocalcemia. Ca^{+2} and P are chemically bound in bone; mobilization of Ca^{+2} from the bone in response to a low DCAB would be expected to increase availability of P as well (Tucker *et al.*, 1991b). They further stated that urinary P concentration was not affected by plasma P concentration; however, similar to urinary Ca^{+2}, urinary P was positively associated with increased H^+ in both blood and urine. Romo *et al.* (1991) stated that the low Ca^{+2} high P anionic ration did not prevent parturient hypocalcemia, probably because of the high P level depleted its exchangeable pool of Ca^{+2} due to a low Ca^{+2} diet and high urinary excretion of Ca^{+2} and P caused by the high dietary P. P restriction is a potent activator of calcitriol biosynthesis, independent of blood Ca^{+2} levels and parathyroid gland regulation (Barton *et al.*, 1987). High P diets probably reduced calcitriol biosynthesis and thus active intestinal absorption, which together with the anionic diets affects the renal excretion and produced hypocalcemia.

Fig. 1. Strategies of milk fever prevention with dietary cation-anion balance (Adopted from Horst *et al.,* 1997**)**



Ca:P ratio has also been shown to influence milk fever. Decreasing Ca:P ratio from 2.3:1 to 1:1 increased incidence of parturient hypocalcemia (Gardner & Park, 1973). Romo *et al.* (1991) observed the Ca:P ratio of the treatment affected with milk fever was 1.1:1; however, cows fed a similar ratio but cationic diets showed no milk fever. Success in preventing milk fever using anionic diets has been reported primarily when high Ca^{+2} low P diets were used (Oetzel *et al.*, 1988).

Strategies for preventing milk fever. Several options exist to control the milk fever (Fig. 1). If DCAB is <250 mEq/kg of diet, then sources of anions (Cl^- & SO_4^{2-}) can be safely added to the diet with minimal effects on DMI. The best sources of anions are $CaCl_2$, $CaSO_4$ and $MgSO_4$. If after all attempts to reduce the DCAB to as low as possible, DCAB is still >250 mEq/kg of diet than other dietary options include feeding a low Ca^{+2} diet (<20 g/day) and administering Ca-gels at calving time. Other options are the administration of vitamin D analogues (e.g. 24-F-1,25-dihydroxyvitamin D_3) and PTH (Horst *et al.,* 1997).

Cows that develop milk fever have higher plasma cortisol concentrations than cows that do not develop milk fever (Horst & Jorgensen, 1982; Goff *et al.,* 1989); these higher concentrations may excerbate the immuno-suppression ordinarily present at calving. Hypocalcemia also results in loss of muscle tone in the uterus and in the teat sphincter that combined with the immuno-suppressive effects of the excess cortisol, might account for the increased incidence of retained placenta, uterine prolapse and mastitis in cows.

Changes in blood pH most likely were responsible for changes in blood iCa concentrations. This was supported by Moore (1970) who demonstrated instantaneous and completely reversible changes in iCa concentration in response to change in pH. The blood concentration of iCa increased in a linear fashion with decreasing pH. He further suggested that effects of pH on iCa concentration may be due to competition between Ca^{+2} and H^+ for binding sites of serum proteins. The increased dissociation of protein bound Ca^{+2} in mildly acidotic cows may contribute to the maintenance of blood Ca^{+2} concentration when the demand for iCa is increased suddenly. Increased iCa from anionic diets blocks the PTH mediated rise in calcitriol, which decreases active intestinal Ca absorption (Bushinsky *et al.*, 1989). Romo *et al.* (1991) noted low incidence of milk fever in cows fed high Ca^{+2} diets and this may because the DCAB in the cationic treatments fell within the critical range (50 to –100 mEq/kg of diet) suggested by Block (1984), and beyond which incidence increases.

Normal plasma Mg^{+2} concentrations range from 0.85-1.20 mmol/liter. Acidosis increased Mg^{+2} excretion in ruminants (Freedeen *et al.*, 1988). Dishington (1975) even observed hypomagnesemia in some cows fed acidogenic diets. High Ca^{+2} intake may decrease Mg^{+2} absorption (Verdaris & Evans, 1976). Urinary excretion of Ca^{+2} and Mg^{+2} are interrelated. Increased excretion of Ca^{+2} was accompanied by increased excretion of Mg^{+2} and vice versa (Mendel & Bennedict, 1909). In goats, diet induced metabolic acidosis increased urinary excretion of both Ca^{+2} and Mg^{+2} (Fredeen *et al.*, 1988). There may be competition between the 2 elements for a common transport system within the intestine and renal tubules (Alcock & MacIntyre, 1962). However,

association between hypercalciuria and hypermagnesuria might be disrupted by acidosis (Stacy & Wilson, 1970) or Mg^{+2} status. Mg^{+2} deficiency reduced Ca^{+2} mobilization from bones (Conteras *et al.*, 1982). Only Mg^{+2} deficiency would impair release of PTH and response of bone and intestine to PTH and 1,25-$(OH)_2$ vitamin D_3 (McManus & Heaton, 1969).

Milk fever and other diseases. Cows contracting milk fever also are susceptible to other secondary problems which significantly increase production cost. For example, Curtis *et al.* (1983) showed that cows recovering from milk fever had an 8X greater incidence of ketosis and mastitis than cows that had never milk fever. Also, the incidences of dystocia, retained placenta, displaced abomasum and uterine prolapse are greatly increased as a result of milk fever.

CONCLUSIONS

Methods to control the milk fever include the DCAB (<250 mEq/kg of diet) with sources of anions (Cl^- and SO_4^{-2}); feeding a low Ca^{+2} diet (<20 g/day) and administering Ca-gels at calving time. Other options include the administration of vitamin D analogues (e.g. 24-F-1,25-dihydroxyvitamin D_3). Anionic diets fed pre-partum reduce the incidence of milk fever by stimulating PTH and 1,25-$(OH)_2D_3$ which increase intestinal Ca^{+2} absorption, bone Ca^{+2} resorption and renal tubular reabsorption of Ca^{+2}. It has been suggested that a DCAB of 50 mEq/kg of diet to –100 mEq/kg of diet is optimal for the prevention of milk fever. Cows recovering from milk fever have an 8 times greater incidence of ketosis and mastitis. Also, the incidences of dystocia, retained placenta, displacement of the abomasum and uterine prolapse are greatly increased as a result of milk fever.

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