Role of Acid-Base Physiology on the Pathogenesis of Parturient Hypocalcaemia (Milk Fever) – the DCAD Theory in Principal and Practice

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Goff JP, Horst RL: Role of acid-base physiology on the pathogenesis of parturient hypocalcaemia (milk fever) – the DCAD theory in principal and practice. Acta vet. scand. 2003, Suppl. 97, 51-56. – The hypocalcemia associated with the clinical disease known as milk fever is due to a failure of the calcium homeostatic mechanisms in the cow to restore normal blood calcium concentration in a timely manner at the onset of lactation. The defect in calcium homeostasis appears to reside in the sensitivity of bone and kidney tissues to parathyroid hormone (PTH) stimulation. Evidence suggests the acid-base status of the cow dictates the sensitivity of the tissues to PTH stimulation, and that metabolic alkalosis is responsible for blunting tissue PTH responsiveness. Hypomagnesemia can also reduce tissue PTH responsiveness but hypomagnesemia can be corrected in most rations. Excessive dietary potassium is very common and is the most important factor causing metabolic alkalosis in dairy cows. Formulation of rations to reduce metabolic alkalosis and / or induce a compensated metabolic acidosis in the pre-partal cow has proved a useful strategy for prevention of milk fever. The concept of dietary cation-anion difference manipulation and the physiologic effects this can have in the cow are presented, with special emphasis on the Strong Ion Difference theory of acid-base physiology.

acid-base; milk fever; hypocalcemia; dietary cation-anion difference; metabolic alkalosis.

Introduction

Metabolic alkalosis predisposes cows to milk fever and subclinical hypocalcemia (Craig & Stoll 1947). Under most circumstances the metabolic alkalosis is typically induced by the potassium (a cation) in the cow’s ration (Goff & Horst 1997). Unfortunately modern agronomic practices encourage luxury consumption of soil potassium by the forage crops commonly fed to dairy cows. Norwegian scientists (Ender et al. 1971, Dishington 1975), in a series of elegant studies, demonstrated that adding anions to the diet of dairy cows prior to parturition effectively reduced the incidence of milk fever. Numerous studies since that time have demonstrated that dietary cation-anion adjustment helps reduce the degree of hypocalcemia experienced by cows at parturition (Block 1984, Oetzel et al. 1988, Gaynor et al. 1989, Beede 1992).
Alkalosis affects Parathyroid Hormone sensitivity of tissues

Two parathyroid hormone (PTH) dependent functions, bone resorption and renal production of 1,25-dihydroxyvitamin D, are enhanced in cows fed diets with added anions which increases their resistance to milk fever and hypocalcemia (Block 1984, Gaynor et al. 1989, Goff et al. 1991, Wang and Beede 1992, Block 1993). In vitro studies demonstrate that simulating metabolic alkalosis in bone tissue culture systems reduces bone Ca resorption activity in response to PTH as well (Martin et al. 1980, Bushinsky 1996). There is evidence to suggest that under normal conditions, when blood pH is about 7.35, PTH and its receptor, located on the surface of bone and renal tissue cells, interact in a tight "lock and key" fashion allowing the PTH to adequately stimulate the target cell. Unfortunately in cows fed a high cation diet the blood pH may become more alkaline, changing the conformational structure of the PTH receptor so that PTH and its receptor do not interact as efficiently (Krapf et al. 1992, Bushinsky 2001). This reduces the cow's ability to respond to a Ca challenge.

Other actions of DCAD beneficial to Ca homeostasis

Bone acts as a major reservoir of buffer for acid-base control of body fluids. When animals are placed on acidifying diets the blood pH decreases. To counteract the drop in blood pH the bone releases cations (primarily Ca) into the blood to bring blood pH back toward "normal". Because the animals are in positive Ca balance at this time the extra Ca entering the extracellular fluid Ca pool is excreted by the kidneys. Schonewille et al. (1995) have demonstrated that addition of anions to the diet of cows increased urinary Ca excretion from less than 0.1 g Ca / day to 4.3 g Ca / day prior to calving. When hypocalcemia was induced in these cows the animals were able to reduce urine Ca excretion dramatically. These observations suggest that one of the mechanisms by which the anionic diets work is by inducing a low grade Ca release from bone into the extracellular fluid Ca pool (4-5 g/day) prior to parturition. Upon parturition the ensuing lactational drain of Ca is partially replaced by renal tubular resorption of this "bone" Ca. This 4-5 g of Ca resorbed from the urine appears to be a small amount relative to the total Ca lost to lactation. However, it should be kept in mind that the standard treatment for milk fever consists of 8-12 g Ca administered intravenously and this small amount effects a clinical cure in most cases!

Factors affecting renal production of 1,25-dihydroxyvitamin D

Horst et al. (1977) demonstrated that production of 1,25-dihydroxyvitamin D was similar in both milk fever and non-milk fever cows. In fact peak plasma 1,25-dihydroxyvitamin D concentration was higher in milk fever cows than in non-milk fever cows. However, in reviewing plasma 1,25-dihydroxyvitamin D concentration profiles in cows that had not developed milk fever and those that developed a severe recurring milk fever with relapses to intravenous Ca treatment, it became clear that 1,25-dihydroxyvitamin D production was delayed and inadequate to increase intestinal Ca absorption in time to prevent hypocalcemia (Goff et al. 1989). Full recovery from milk fever only occurred after the cow began synthesizing 1,25-dihydroxyvitamin D.

Diets high in cations reduce renal synthesis of 1,25-dihydroxyvitamin D at the time of parturition in dairy cows (Gaynor et al. 1989, Goff et al. 1991, Phillips et al. 1994). The evidence suggests metabolic alkalosis reduces the sensitivity of the renal tissue to PTH so that the renal tissue fails to upregulate the 25-hydroxvitamin D, 1alpha -hydroxylase enzyme needed to produce the hormone.

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Dietary Cation-Anion Difference and Acid-Base Status

Stewart (1983) proposed the Strong Ion Difference Theory of acid-base physiology. There are two basic tenets of this theory. 1. The number of moles of positively charged particles (cations) in any given solution (including body fluids) must equal the number of moles of negatively charged particles (anions) in the solution. 2. The product of the concentration of hydrogen ions and hydroxyl ions is always equal to the dissociation constant of water, which is approximately $1 \times 10^{-14}$.

1. $\# \text{Moles cations} = \# \text{Moles anions}$
2. $[H^+] \times [OH^-] = 1 \times 10^{-14}$

Both equations must be satisfied simultaneously. Since pH is the negative log of the concentration of hydrogen ions this essentially means that the pH of a solution is dependent on the difference between the number of negatively and positively charged particles in the solution. If positively charged particles are added to a solution such as the plasma the number of $H^+$ cations will decrease and the number of $OH^-$ anions will increase to maintain the electroneutrality of the solution (the solution becomes more alkaline). Conversely, adding anions to a solution causes an increase in $H^+$ and a decline in $OH^-$ to maintain electroneutrality, and the pH decreases (the solution becomes more acidic).

The primary cations and anions in the blood are:

a. Bicarbonate anions [HCO$_3^-$].

The blood HCO$_3^-$ concentration is essentially determined by the concentration of CO$_2$ in the blood as predicted by the Henderson-Hasselbach equation, $pH = pKa \ (6.1) + \log \frac{\text{HCO}_3^-}{\text{H}_2\text{CO}_3}$. Blood CO$_2$ concentration is under the control of the respiratory system and allows minute by minute fine tuning of blood pH. When respiratory function is depressed, CO$_2$ concentrations increase, increasing the concentration of HCO$_3^-$ anion causing blood pH to decline. Conversely, when respiratory rate is elevated (as occurs in heat stress) blood CO$_2$ declines, blood [HCO$_3^-$] declines and pH increases.

b. The concentration of non-metabolizable anions and cations.

The difference between the total number of non-metabolizable cations and anions in the blood is referred to as the Strong Ion Difference. Strong Ions enter the blood from the digestive tract making the cation-anion difference of the diet the ultimate determinant of blood Strong Ion Difference. Once absorbed the concentration of Strong Ions in the blood is regulated by the kidneys. Adjustment of the Strong Ion Difference of the blood is slower than respiratory control of blood pH but is capable of inducing much greater changes in blood pH.

In theory all the cations and anions in the diet are capable of exerting an influence on the Strong Ion Difference of the blood. The major cations present in feeds and the charge they carry are sodium (+1), potassium (+1), Ca (+2), and Mg (+2). The major anions and their charges found in feeds are chloride (-1), sulfate (-2), and phosphate (assumed to be -3 by this author; others use the number 1.8 to reflect blood phosphate buffer rather than the dietary form of phosphate). Cations or anions present in the diet will only alter the Strong Ion Difference of the blood if they are absorbed into the blood. The trace elements present 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 blood pH under most circumstances. However in the
case of lactic acidosis the lactate anion can build-up in the blood of the affected animal and cause severe metabolic acidosis.

The difference between the number of cation and anion particles absorbed from the diet determines the pH of the blood. The cation-anion difference of a diet is commonly described in terms of mEq/kg of just sodium, potassium, chloride, and sulfate as follows:

Dietary Cation-Anion Difference (DCAD) = (Na\(^+\) + K\(^+\)) - (Cl\(^-\) + S\(^-\)).

This equation is useful, although it must be kept in mind that Ca, Mg, and P absorbed from the diet will also influence blood pH. We have evaluated the relative acidifying activity of various anionic salts by feeding them to dry cows and evaluating their ability to reduce blood and urine pH (which we use in the field to reflect the changes in blood pH). These data lead us to believe the DCAD of a diet and its acidifying activity is more accurately described by the following equation: \((0.15 \text{ Ca}^{2+} + 0.15 \text{ Mg}^{2+} + \text{ Na}^{+} + \text{ K}^{+}) - (\text{Cl}^{-} + 0.6 \text{ S}^{-} + 0.5 \text{ P}^{-})\). This equation suggests that the major dietary factors determining blood and urine pH are Na, K and Cl. It also suggests that sulfate is less acidifying than chloride, in general agreement with the findings of Oetzel et al. (1991). Tucker et al. (1991) also felt that sulfate was about 60% as acidifying as chloride. The particular coefficient is less important than the concept that chloride may be the better choice of acidifying agent. A complete equation should probably also include ammonium as this cation seems to contribute to the cation content of the blood as well (Constable 1999).

Most nutritionists using the equation \(((\text{Na}^{+} + \text{ K}^{+}) - (\text{Cl}^{-} + \text{ S}^{-}))\) have a target DCAD for milk fever prevention of about -50 mEq/kg. Using the more physiologically relevant equation, \((0.15 \text{ Ca}^{2+} + 0.15 \text{ Mg}^{2+} + \text{ Na}^{+} + \text{ K}^{+}) - (\text{Cl}^{-} + 0.60 \text{ S}^{-} + 0.5 \text{ P}^{-})\), the target DCAD should be about +150 mEq/kg. Several of the variables in the above formulas are somewhat fixed. A strategy this author uses is to set dietary Ca at 1-1.2% and dietary P and Mg at 0.4%, and keep dietary sulfur 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 (Gould et al. 1991). As already discussed the integrity of the interaction between PTH and its receptor is vital to Ca homeostasis. Hypomagnesemia is also capable of interfering with the ability of PTH to act on its target tissues. When PTH binds its receptor this normally initiates activation of adenylate cyclase, resulting in production of the second messenger cyclic AMP, or phospholipase C, resulting in production of the second messengers diacylglycerol and inositol 1,4,5-triphosphate. Both adenylate cyclase and phospholipase C require Mg for full activity. In man, 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). The key to milk fever prevention is to keep sodium and potassium as close to the requirement of the cow as you can (0.1% for Na and 1.0% for potassium). The key to reduction of subclinical hypocalcemia is to then add chloride to the ration to counteract the effects of even low levels of potassium on blood alkalinity. These are simply guidelines and are based on the setting of certain parameters at constant values as outlined above. Urine pH of the cows will be the better gauge of the appropriate diet DCAD than any formula (Gaynor et al. 1989, 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 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 cows has to be reduced to between 5.8 and 6.3 for effective control of hypocalcemia. If the average urine pH is between 5.0 and 5.5, excessive anions have induced an uncompensated metabolic acidosis and the cows will suffer a decline in dry matter intake. Urine pH can be checked 48 or more hrs after a ration change. Urine samples should be free of feces and made on midstream collections to avoid alkalinity from vaginal secretions. 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.

c. The concentration of proteins.
Proteins tend to be negatively charged and are considered as anions. Their concentration in blood is generally dependent on liver function. Blood protein levels are fairly constant unless there are large changes in liver function or plasma volume (Constable 1998).

Summary
While several methods can be used to prevent milk fever in dairy cattle the emerging cause of milk fever seems to be metabolic alkalosis caused by high dietary cation intake. Metabolic alkalosis appears to disrupt interaction of parathyroid hormone with its receptor on bone and kidney tissue. Hypomagnesemia and vitamin D deficiency can also be factors but these are readily corrected in most cases by addition of these nutrients to the ration. The Strong Ion Difference theory of acid-base physiology offers an explanation of how diet can influence blood acid-base physiology.

References


Goff JP, Horst RL, Mueller FJ, Miller JK, Kiess GA, Dowlen HH: Addition of chloride to a prepartal diet high in cations increases 1,25-dihydroxyvita-


Schonewille JT, Klooster Ath van't, Beynen AC: Urinary calcium losses in cows fed on a high-chloride ration are reduced when plasma calcium is stressed. Proc. Ninth International Conference on Production Diseases in Farm Animals, Berlin, Germany. 1995, 46.

