# Update on Transition Strategies to Prevent Hypocalcemia,

# Not Just Milk Fever, in Transition Cows

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Calcium is necessary for proper contraction of muscle. Severe hypocalcemia prevents skeletal muscle contraction to the point that the clinical syndrome known as milk fever occurs. While milk fever is a severe form of hypocalcemia, Reinhardt et al., (2011) found more than half of older cows developed subclinical hypocalcemia (blood Ca below 8.0 mg Ca/dl, but above 5.5 mg Ca/dl) shortly after calving. Cows with sub-clinical hypocalcemia had elevated concentrations of non-esterified fatty acids (NEFA) compared with normocalcemic cows. Martinez et al (2012) demonstrated that sub-clinical hypocalcemia (blood calcium below 8.6 mg/dl) was a major risk factor for metritis and immune dysfunction.

## PREVENTING HYPOCALCEMIA

Ca homeostasis is primarily controlled by the parathyroid glands, which respond to hypocalcemia by secreting parathyroid hormone (PTH). The primary targets the PTH acts on are bone and kidney cells. PTH stimulates bone cells is to take calcium out of bones to support normal blood calcium. PTH acts on the kidney to reduce urine calcium losses which returns Ca to the blood. More importantly, PTH stimulates the kidney to produce a 2$^{nd}$ hormone derived from vitamin D – called 1,25-dihydroxyvitamin D. The 1,25-dihydroxyvitamin circulates in the blood and reaches the cells of the small intestine. Under the influence of 1,25-dihydroxyvitamin D, intestinal cells begin producing proteins that allow them to pump Ca from the diet into the blood stream. This allows efficient use of diet Ca. When the system is working normally, there is a small decline in blood calcium at the onset of lactation and then Ca homeostasis kicks into gear and blood calcium returns to normal in a matter of hours.

WHY DOES CALCIUM HOMEOSTASIS FAIL IN SOME COWS?

Mounting evidence suggests the key to milk fever prevention lies in reducing the degree of metabolic alkalosis experienced by the cow just before calving. Cows fed high potassium diets (High DCAD) are in a state of compensated metabolic alkalosis. We fed late gestation cows a High DCAD, alkalinizing diet or a Low DCAD, acidifying diet and treated the cows with synthetic exogenous PTH. The cows fed the alkalinizing diet had a greatly diminished response to the PTH compared to cows fed the acidifying diet. Their kidneys did not produce as much $1,25(OH)_2D$ and serum Ca did not rise as quickly. It appears the tertiary structure of the PTH receptor is altered during metabolic alkalosis, reducing its affinity for PTH and resulting in a state of pseudohypoparathyroidism (Goff et al., 2014). In highly alkaline cows, despite the fact that bone and kidney cells are exposed to very high concentrations of PTH at the onset of lactation, they respond only poorly to the PTH. Addition of acidifying anions to a diet to counteract cations in the diet of a cow reduces the alkalinity of the blood and restores tissue responsiveness to PTH at the onset of lactation. Hypomagnesemia can also interfere with PTH function. It also affects the ability of tissues to respond to PTH and it can also inhibit PTH secretion (Goff, 2014).

UNDERSTANDING DCAD - DESIRED MINERAL PROFILE OF PRE-PARTUM DIET

The difference between the number of cation and anion particles absorbed from the diet determines the pH of the blood. *The pH of the blood determines whether the tissues will respond properly to PTH stimulation.* The diet cation-anion difference (DCAD) of a diet is commonly described in terms of mEq/kg of just Na, K, Cl, and $SO_4$ (S) as follows:

$$DCAD = (mEq\ Na^+ + mEq\ K^+) - (mEq\ Cl^- + mEq\ S^{--})$$

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. Evaluation of the relative acidifying activity of dietary Cl vs. $SO_4$ demonstrates $SO_4$ is only about 60% as acidifying as Cl (Goff et al., 2004). The DCAD of a diet and its acidifying activity is more accurately described by the following equation: $(Na^+ + K^+) - (Cl^- + 0.6\ S^{--})$. The response to $SO_4$ is actually not linear. At low diet concentrations, $SO_4$ is as effective as Cl as an acidifier. But at higher diet concentrations it appears there is a block of intestinal $SO_4$ absorption making $SO_4$ much less effective than Cl. While DCAD equations provide a theoretical basis for dietary manipulation of acid-base status they are not necessary for formulation of mineral content of prepartum dairy cow rations because, with the exception of K and Cl, the rate of inclusion of the other macrominerals can be set at fixed rates.

The NRC (2001) requirement for Na in the diet of a late gestation cow is about 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. Exceeding the requirement for Na using 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). Beede et al. (2001) fed 0.47, 0.98, 1.52, and 1.95 % Ca diets to cows in late gestation being fed a high Cl diet to prevent milk fever. Cows fed 1.5% Ca diets had slightly reduced feed intake when compared to control cows while those fed the 1.95% Ca diet had significantly lower feed intake. Dietary Ca did not influence the degree of hypocalcemia experienced at calving or milk production in the subsequent lactation. It appears from this study that a close-up diet Ca concentration of 1% is optimal. This is similar to the level the cow will receive in the lactating diet and though higher diet Ca may contribute some extra Ca to the blood via the paracellular route of intestinal Ca absorption, higher dietary Ca could negatively impact feed intake, and it is adding to the alkalosis of the cow.

Dietary Magnesium can only be absorbed from the rumen in cows. Two mechanisms exist to transport Mg across the rumen wall. The first mechanism is effective even when diet Mg concentration is low. Unfortunately, Potassium can inhibit this magnesium transporter in the rumen wall. A second Mg transporter also exists, but it only works at higher diet Mg concentrations. To ensure adequate concentrations of Mg in the blood of the periparturient cow the dietary Mg concentration should be 0.35-0.4%. This level of Mg ensures the second Mg transporter in the rumen will be able to work even in the face of the inhibitory effects of dietary potassium. This is particularly important in the pre-partum diet and the early lactation diet. Further, hypomagnesemia is the primary cause of mid-lactation milk fever in cows. The details behind this rationale will be discussed in detail in the section on Mg.

Dietary P concentration should meet but not exceed the NRC requirement for P in the late gestation cow. This is generally about 0.3% P for most cows. A diet supplying more than 80 g P/day greatly increases the risk of milk fever. Keeping dietary phosphorus below 50 g / day seems to be safe, though lower levels (as low as 0.21% P or 34 g P /day) may actually improve Ca homeostasis (Peterson, et al., 2005). *Low P in the prepartum diet does not contribute to the hypophosphatemic downer cow condition*, which is sometimes observed as a sequelae of milk fever.

Dietary S must be kept above 0.22% (to ensure adequate substrate for rumen microbial amino acid synthesis) but below 0.4%. Sulfur toxicity is not common in dairy cows but feedlot steers can develop neurological problems associated with S toxicity when diets exceed 0.4% S. Ca sulfate and Mg sulfate are good sources of sulfur that may also supply any needed Ca and Mg, though their palatability is poor at high levels.

Now, with the exception of K and Cl, the “variables” in the various proposed DCAD equations have become “fixed”. The key to milk fever prevention (Holstein cows) is to keep K as close to the NRC requirement of the dry cow as possible (about 1.0% diet K). The key to reduction of subclinical hypocalcemia, not just milk fever prevention, is to add $Cl^-$ anions 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 should first be set at 0.5% less than the concentration of K in the diet. In other words, if diet K can be reduced to 1.3%, the Cl concentration of the diet should be increased to 0.8%. This will adequately acidify about 20% of herds in this author's experience. Ultimately in many herds the amount of chloride added will have to be brought to within 0.3% of the diet potassium for proper acidification. A conservative approach should be taken when formulating the diet of close-up cows – going immediately to the higher chloride diet will cause over acidification of 20% of herds, which can reduce feed intake creating many other metabolic disease challenges. Move to the higher dose of chloride only if urine acidification (described as a monitoring tool below) is not achieved at the lower chloride level. There is also a limit on how much anion can be added to a diet without affecting feed intake. In this author's experience, when diet potassium exceeds 1.4% it is difficult to add enough chloride to the diet using the traditional chloride salts (Ca, ammonium, and magnesium chloride) to acidify the cow and maintain adequate dry matter intake. With some of the more palatable commercial anion supplements it is possible to acidify the diets and maintain feed intake when diet potassium is as high as 1.8%. If dietary K can only be reduced to 2.0% the diet Cl would need to be at least 1.5% to acidify the cow. Raising Cl to this level in the diet is likely to cause a decrease in dry matter intake. Chloride and sulfate sources differ in their palatability and since achieving low dietary K can be difficult it is prudent to use a palatable source of Cl or sulfate when formulating the diet. Ammonium chloride (or ammonium sulfate) can be particularly unpalatable when included in rations with a high pH. At the higher pH of high forage and straw (i.e. lower corn silage) rations where pH of the diet exceeds 5.5, the ammonium cation is converted to ammonia, which is highly irritating when smelled by the cow. In this author's experience hydrochloric acid has proved the most palatable source of anions as well as the strongest acidifying agent. Hydrochloric acid can be extremely dangerous to handle when it is procured as a liquid concentrate. Several companies now manufacture anion supplements comprised of hydrochloric acid adsorbed onto feed particles, which are safe to handle and palatable.

## MONITORING URINE PH

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. If you think of acidifying the urine as a chemistry experiment, the titration curve of the urine has an equivalence (or halfway) point at pH 6.8. This is because phosphate is the predominant buffer in the urine. Urine pH on high cation diets is generally above 8.2. Limiting dietary cations will reduce urine pH only a small amount (down to 7.8-8.2). As anions are added to the diet the urine pH drops slowly as the phosphate buffer is consumed. Once the equivalence point of 6.8 is reached it only takes a small increase in diet anion to decrease urine pH down to 6.0 or so. For optimal control of subclinical hypocalcemia the average pH of the urine of Holstein cows should be between 6.0 and 6.6 during the last week of gestation, which essentially requires addition of anions to the ration. In Jersey cows



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the average urine pH of the close-up cows has to be reduced to between 5.8 and 6.3 for most effective control of hypocalcemia. If the average urine pH is between 5.0 and 5.5, excessive anions have been added and there is the danger they have induced an uncompensated metabolic acidosis and the cows will suffer a decline in dry matter intake, even if a palatable anion supplement is used. The gain in blood Ca around the time of calving in cows fed to have a urine pH of 5.7 vs 6.3 is very small – but the risk of developing uncompensated metabolic acidosis is greatly increased.

When low (below 5.7) and high (above 7.5) urine pH samples are seen in a group of close-up cows be aware that it can signal one of three things. 1. Cows are sorting the diet. 2. You have an overcrowded close-up pen. 3. You have too much anion in the diet and are seeing cows get overly acidified and go off feed until they alkalinize themselves- then they binge eat again and get overly acidified. Be aware that cows moved into the maternity pens for more than a few hrs before calving may decide the nice long straw utilized to bed the calving area is pretty tasty and this can be high in potassium and undue the low DCAD diet.

PARTIAL DCAD DIETS

There are farms that feel urine pH testing is too much work and want to settle for sub-optimal control of hypocalcemia. This author cringes when I see the same farms willing to spend several dollars to run blood BHBA several times on fresh cows, but fail to want to spend 10 cents and a little time to grab urine from close-up cows. One goal with urine pH testing is to tell you when you are at risk of over-acidification. One can avoid this by feeding less than optimal amounts of an anion supplement. The question becomes- Is there any benefit to adding some anions to the diet – even if you do not intend to get urine pH all the way down to ~ 6.3? Our research suggest cows do get some improvement of blood Ca with a partial "Low" DCAD diet – but only if it succeeds in bringing urine pH below 7.5. With many diets this will be the case when chloride is added to be within 0.6 to 0.5 % of diet K. ie % K- % Cl = 0.6 to 0.5%. You will still see milk fever cows – but far fewer in number and more responsive to a single bottle of Ca intravenously and unless forages change dramatically in potassium content, you should have very little risk of over-acidification of the cows

HYPOMAGNESEMIA

Insufficient dietary Mg supply or availability leads to hypomagnesemia. Hypomagnesemia is a major risk factor for milk fever. Hypomagnesemia affects Ca metabolism by reducing tissue sensitivity to PTH and by reducing PTH secretion in response to hypocalcemia. Adding Mg to diets before and after calving should eliminate hypomagnesemia as a contributor to hypocalcemia. Unfortunately issues with bioavailability of magnesium sources have arisen.

Magnesium oxide is included in dairy rations for two reasons: to maintain adequate levels of Mg in the blood and as a rumen fluid alkalinizer. Mg sulfate.7 $H_2O$ and Mg chloride.2 $H_2O$ are very soluble, very available sources of Mg. They are acidifying salts of magnesium and are often included in close-up diets as part of a low DCAD diet. Many anion supplements on the market



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include Mg in the sulfate or chloride form and easily meet the dry cow requirements for magnesium. Once the cow begins consuming the lactation diet, the magnesium supplement often switches over to magnesium oxide. MgO takes up little room in the ration, costs less, and is more palatable than some other sources of Mg. It can help alkalinize rumen fluid so it is more appropriately used in lactation diets in conjunction with sodium bicarbonate and other rumen buffers. The feed industry utilizes MgO which is about 54-56% Mg (>58% Mg MgO often indicates the ore was overly heated in the calcining process and the Mg will be poorly available). Unfortunately, there is tremendous variability in MgO quality. For ruminants, MgO should be ground to a fine dust. A quick test can estimate the relative availability of MgO sources. Place 3 g of a MgO source in a container and slowly add 40 ml 5% acetic acid (white vinegar). Cap container and shake well for 15 seconds and let sit. Shake again at the 15 minute mark and let sit. Check the pH at 30 minutes. Vinegar alone is pH 2.6-2.8. The best MgO sources will bring the pH up over 8.2; the worst to just 3.8. pH is a log scale so this represents >10,000 fold difference in the number of hydrogen ions buffered. Remember in lactating rations, MgO is relied upon to combat rumen acidosis- and we are not getting that action from these insoluble MgO sources. In an experiment with four cows with rumen fistulas, the solubility of MgO in vitro (tested in various ways) was found to parallel their solubility in the rumen and their urinary excretion (Schonewille, 1998).

ORAL CALCIUM TREATMENTS AT CALVING

Ca administered to the fresh cow may arguably be called a treatment rather than a preventative measure for hypocalcemia. Contrasts between the effects observed with intravenous, subcutaneous, and oral Ca treatments have been described elsewhere (Goff, 1999). Routine intravenous Ca treatment of older cows at calving may not be a sound practice as it delays Ca homeostasis causing hypocalcemia on day 2 or 3 of lactation (Blanc et al., 2014).

Briefly, the concept behind oral supplementation is that the cow's ability to utilize active transport of Ca across intestinal cells is inadequate to help her maintain normal blood Ca concentrations. By dosing the animal with large amounts of very soluble Ca it is possible to force Ca across the intestinal tract by means of passive diffusion of Ca between intestinal epithelial cells. Best results are obtained with doses of Ca between 50 and 80 g Ca / dose. Ca chloride has been used but can be very caustic when in a drench or gel form. Ca propionate is less injurious to tissues and has the added benefit of supplying propionate, a gluconeogenic precursor. Ca carbonate and calcium sulfate are not soluble enough to induce a rapid rise in blood Ca. For best control of hypocalcemia a dose is given at calving and again 12- 24 hrs later. Toxic doses of Ca can be delivered orally – a single dose of 250 g Ca in a soluble form will kill some cows. The benefit of adding oral Ca drenches/gels in addition to a properly formulated low DCAD program is becoming easier to justify as recent studies link even moderate hypocalcemia with decreased health and performance of the cow (Martinez et al., 2012; Chamberlin et al., 2013). It has been estimated that about 4 g Ca entered the blood of cows given 50 g Ca as $CaCl_2$ in a drench in the first hrs following treatment (Goff and Horst, 1993).

The oral Ca boluses on the market have received great use in the last few years. They are more convenient to give than drenches and pastes and cause lower risk of aspiration pneumonia. The bulk of Ca in these products comes from calcium chloride. The boluses often are coated with fat so that they can slide down the esophagus and do not expose the esophagus to the caustic calcium chloride. They typically only contain 35-44 g Ca – which causes only a very small rise in blood Ca concentration (0.2 to 0.8 mg Ca/dl). They are acidifying and can prolong the action of a low DCAD diet for a short while after the cow is switched to the lactation diet at calving. This may be their major benefit. On their own they are not typically able to acidify the cow to prevent milk ever the way the low DCAD diets do. But they can keep the cow acidified another 12-24 hrs after calving as she moves onto the lactation diet, which may help promote Ca homeostasis.

Author Disclosures

Prior to joining the faculty at Iowa State University, Goff was Director of Research at West Central Farmer's Co-operative. In this capacity he developed anion supplements for prevention of hypocalcemia in cows and Goff continues to consult for this company. Goff also holds a patent using calcium propionate paste to prevent hypocalcemia.

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