INTRODUCTION

Periparturient hypocalcemia or milk fever is a common condition of dairy cows with an annual incidence of 5 to 8%. Feeding rations with low dietary cation-anion difference (DCAD) to dairy cows for at least 2 weeks before calving decreases the incidence of periparturient hypocalcemia. The most likely reason for this effect is that ingestion of a low DCAD diet increases calcium (Ca) flux, which is non-lactating cows is most readily detected as an increase in urinary calcium excretion. An increase in calcium flux allows the periparturient dairy cow to more readily cope with the abrupt and marked increase in calcium demand that occurs at the onset of lactation by shifting calcium from urine to milk. The result is a smaller decrease in serum \([\text{Ca}^{2+}]\) on the first day after calving when compared to cows fed a high DCAD diet during the last weeks of gestation.

The increase in calcium flux in ruminants fed a low DCAD ration is due to an increase in the rate of calcium entry into the exchangeable calcium pool that approximates the rate of calcium exit from the exchangeable calcium pool. Increased calcium entry into the exchangeable pool occurs by 4 main mechanisms: enhanced intestinal absorption, hyperchloremic displacement of calcium from binding sites on albumin, increased bone resorption, and decreased bone accretion. We have shown recently that \([\text{Ca}^{2+}]\) in plasma at \(\text{pH} = 7.40\) increases by 0.007 mmol/L for every 1 mmol/L increase in plasma chloride concentration. It is currently not clear which of the 4 potential mechanisms for increasing calcium entry is the most important; however, the latter 2 mechanisms appear active only in the presence of acidemia (jugular venous blood \(\text{pH} < 7.35\)). Enhanced intestinal absorption and hyperchloremic displacement of albumin bound calcium are probably the most important mechanisms by which ingestion of an acidogenic high chloride diet leads to an increase in the rate of calcium entry into the exchangeable calcium pool.

Our 2018 finding involving 106 Holstein cows that mean plasma calcium concentration was decreased by 9 hours before parturition contrasts with the consensus view that plasma calcium concentration does not decrease until after parturition. Our finding strongly suggests that post-calving oral or subcutaneous calcium may be administered too late to be beneficial.

TREATMENT OF HYPOCALCEMIA

Calcium should be administered by the oral, subcutaneous, or intravenous route, depending on the severity of the clinical signs.
Stage I milk fever (standing, muscle fasciculations, slight nervousness/apprehension): Oral 
CaCl₂ (calcium gels). These are commercially available and preferred to calcium drenches that 
are more likely to be aspirated. Most formulations contain 40-50 g of calcium per dose as a 
CaCl₂ salt; some formulations also have CaSO₄ included. Calcium carbonate formulations should 
not be used because the calcium is poorly available. Oral calcium increases the serum calcium 
concentration within 5 minutes and stays increased for approximately 6 hours. Retreat at 12-24 
hours but don’t exceed 120 g of calcium in a 24-hour period. The cow must be able to swallow, 
otherwise pharyngeal/esophageal necrosis and death may result from oral administration of a 
bolus. The orally administered calcium is absorbed by a dose-dependent passive diffusion 
process across ruminal epithelium and a dose-independent calcium-binding protein mechanism 
in the small intestine that is modulated by Vitamin D.

Subcutaneous administration of calcium solutions has been practiced for many years. To 
facilitate absorption, it is preferable to administer no more than 125 ml at a site, although this 
supposition (and volume) does not appear to have been verified. A 14-gauge needle is placed 
subcutaneously over the lateral thorax, 125 ml is administered, the needle is redirected and 
another 125 ml administered. The process is then repeated on the other side of the cow. 
Subcutaneous administration of calcium gluconate is also effective in recumbent cows despite 
decreased peripheral blood flow. Calcium chloride is not recommended for subcutaneous 
administration because of extensive tissue damage; the addition of dextrose to the 
administered calcium is also not recommended because it increases the tonicity of the solution 
and propensity for bacterial infection and development of abscesses at the site of injection. 
Rectal calcium administration is not recommended because it causes severe mucosal injury and 
tenesmus but does not increase plasma concentrations of calcium.

Stages II & III (II = sternal recumbency, hypothermia, cold extremities, rumen hypomotility to 
atony; III = same but lateral recumbency to comatose): Intravenous calcium (as calcium 
gluconate 23%). Gluconate or borogluconate calcium salts are preferred to chloride salts 
because they are much less irritating to tissues. The approximate dose is 2.2 g calcium / 100 kg 
body weight, with cardiac monitoring by auscultation during administration. Typical commercial 
formulations contain 10.7 g of calcium in 500 ml. Some large cows need two 500 ml bottles, but 
studies indicate 6-9 g of calcium is usually sufficient for treatment. You could administer 
solutions that contain magnesium if concurrent hypomagnesia is suspected (which is unusual in 
dairy cows as they are usually hypermagnesemic in the periparturient period).

The normal cardiac response to calcium administration is an increase in the strength of cardiac 
contraction and a slowing of the heart rate. Intravenous administration is continued until the 
first arrhythmia is detected (a bradyarrhythmia such as a prolonged pause); the rate of IV 
administration is then slowed until a second arrhythmia is detected, at which time intravenous 
administration is discontinued and the remainder of the solution placed subcutaneously over 
the lateral thorax. This treatment method titrates the calcium dose required for each animal. 
Auscultation of the heart is an absolute requirement during treatment; visual monitoring of the 
jugular pulse at the base of the neck does not allow the early detection of bradyarrhythmias, 
making it more likely that the cow will receive a toxic and possibly lethal dose of calcium.
The maximum safe rate of calcium administration in cattle is 0.07 mEq of Ca\(^{2+}\)/kg body weight/minute, which is equivalent to 0.065 ml 23% calcium borogluconate/kg body weight/minute. For a 500 kg normocalcemic dairy cow, this corresponds to a maximum safe rate of administration of 33 ml/minute. Typical rates of administration through a 14 gauge needle are 50 ml/minute; this rate of administration is safe for cows with hypocalcemia, provided that cardiac auscultation is performed during administration.

The relapse rate to a single intravenous treatment of hypocalcemia in down cattle is reported to range from 24% to 53%, and consequently improved treatment modalities have been investigated. These include slow calcium administration over several hours (impractical for treatment in the field), administering a higher IV dose of calcium (which increases the risk of fatal cardiac arrhythmias), intravenous and oral administration of calcium, and co-administration of oral monosodium phosphate solution.

**CONTROL OF HYPOCALCEMIA**

We hypothesize that combined antepartum and postpartum calcium treatment of multiparous cows is more beneficial than postpartum calcium treatment alone for controlling hypocalcemia. Support for this hypothesis is provided by the results of studies demonstrating that combined antepartum and postpartum calcium administration decreased the incidence of parturient paresis and left displaced abomasum in dairy cattle. The accurate prediction of parturition within 6 to 12 h remains a major challenge in implementing antepartum calcium administration.

We found in our 2018 a negative linear relationship between plasma [Ca] in the 24 h period after parturition and age, as well as between plasma [Ca] and milk production at 28 days in milk. We hypothesize that high parity and high production dairy cows should be administered calcium more frequently and at a higher total dose in the periparturient period as part of a prevention program for periparturient hypocalcemia and subclinical hypocalcemia.

**Ingestion of an acidogenic diet (low dietary cation-anion difference)**

Ingestion of an acidogenic ration increases calcium exit from the exchangeable calcium pool by decreasing renal tubular calcium reabsorption of filtered calcium, manifest as hypercalciuria. Low luminal pH in the second half of the distal convoluted tubule and connecting tubule decreases the number of epithelial Ca channels termed TRPV5 (transient receptor potential vanilloid member 5); the TRPV5 channel was previously termed EcaC, ECaC1, and CaT2 and is considered to be the primary gatekeeper of active calcium reabsorption in the distal region of the urinary. Low luminal pH also decreases the pore size of the TRPV5 channel, resulting in decreased calcium uptake from the tubular lumen into the epithelial cell. The low luminal pH-induced decrease in TRPV5 number and activity result in decreased calcium absorption in the distal convoluted tubule and connecting tubule, thereby directly resulting in hypercalciuria. If this mechanism is active in cattle similar to rabbits, then low luminal pH (due to a decreased
urinary strong ion difference and manifest as low urine pH) and not decreased blood pH is the
major drive for hypercalciuria in cattle ingesting a low DCAD ration. If this assumption is true,
then the logical goal of milk fever prevention programs should be to decrease urine pH (and
urine strong ion difference) without changing blood pH.

Concerns have been raised about the safety of feeding low DCAD diets in that acidogenic
rations can decrease dry matter intake in late gestation and lactation, thereby exacerbating the
metabolic effects of negative energy balance in early lactation. The reduction in dry matter
intake only occurs when blood pH is decreased below the reference range; once again this
emphasizes the goal of feeding low DCAD diets is to decrease urine pH and urine strong ion
difference without changing blood pH. Assuming that increased calcium flux is the most
important method for decreasing the incidence and severity of hypocalcemia at calving, and
assuming that urine [Ca^{2+}] provides a clinically useful insight into calcium flux in the
periparturient cow, it appears that measurement of urine [Ca^{2+}] may provide the best method
for evaluating the risk of periparturient hypocalcemia and the effectiveness of feeding a DCAD
ration. However, more research is needed to clarify the role that calcium intake has on urine
[Ca^{2+}], and the optimal calcium intake for cattle being fed low DCAD diets. Our recent studies
have demonstrated a linear negative association between urine [Ca^{2+}] and urine pH; this finding
suggests that measurement of urine pH may provide a practical on farm method for evaluating
calcium flux in cows before parturition.

The most accurate insight into acid-base homeostasis in healthy cattle is obtained by measuring
urine net acid excretion (NAE) or net base excretion (NBE). However, when urine pH is between
6.3 and 7.6, urine pH provides an inexpensive and clinically useful insight into acid-base
homeostasis in cattle. This is because the change in urine pH over this pH range accurately
reflects the change in NAE or NBE. Optimum target values for urine pH to decrease the
incidence of milk fever in dairy herds have not been identified and recommendations for
optimal urine pH values vary widely. We have recently developed a general electroneutrality
equation for bovine urine such that urine pH = 6.12 + log_{10}(NBE + [NH_4^+] - [Cl^-] - [SO_4^{2-}]) = 6.12 + log_{10}([K^+] +
[Na^+] + [Mg^{2+}] + [Ca^{2+}] + [NH_4^+] - [Cl^-] - [SO_4^{2-}]). This equation indicates that an increase in urine
[Ca^{2+}] without a change in urine strong anion concentration will alkalinize urine; the
observation that urine [Ca^{2+}] increases as urine pH decreases in all species studied to date is
consistent with our working hypothesis that a low luminal pH in the distal urinary tract drives
the increase in urine [Ca^{2+}] and therefore the increase in the rate of calcium loss from the
exchangeable calcium pool. A recent meta-analysis suggested that decreasing urine pH from 7.0
to 6.0 or lower led to a modest decrease in the incidence of milk fever but markedly increased
the risk of decreased dry matter intake in the prepartum period. The goal of milk-fever
prevention strategies should therefore be to increase calcium flux by challenging but not
overwhelming acid-base and calcium homeostasis. The influence of calcium intake on flux
needs to be clarified; it is currently believed that an acute increase in calcium intake increases
calcium flux by increasing the moles of calcium absorbed but a sustained increase in calcium
intake decreases calcium flux and absorption via changes in Vitamin D activity and other
homeostatic systems.
Measurement of urine pH

Urine pH provides an important screening test for cows that are being fed an acidogenic diet (low cation-anion diet). Moreover, urine pH can be used to identify cows that are increased risk of milk fever. Urine can be typically obtained at random from 67-80% of dairy cows (higher percentage if the cow has been lying down). If the pH >8.25 in the 48 hour period before calving then the cows is at increased risk of developing milk fever (Se = 1.00; Sp = 0.81). The major challenge remains an accurate prediction of parturition. We have an ongoing research project related to this topic.

Urine appears to be the optimal fluid to monitor calcium and acid-base status in dairy cattle; however, it remains to be determined whether laboratory measurement of urinary calcium concentration is more accurate and cost-effective than cow-side measurement of urine pH or laboratory determination of urinary strong ion difference and NBE when evaluating the effectiveness of milk-fever control programs. Measurement of urinary strong ion difference, NAE or NBE is more time consuming and expensive than measurement of urinary pH and has been difficult to perform on the farm.

Subcutaneous calcium borogluconate immediately before calving

Subcutaneous administration of calcium solutions has been practiced for many years. To facilitate absorption, it is preferable to administer no more than 125 ml at a site, although this supposition (and volume) do not appear to have been verified. A 14-gauge needle is placed subcutaneously over the lateral thorax, 125 ml is administered, the needle is redirected and another 125 ml administered. The process is then repeated on the other side of the cow. Calcium chloride is not recommended for subcutaneous administration because of extensive tissue damage; the addition of dextrose to the administered calcium is also not recommended because it increases the tonicity of the solution and propensity for bacterial infection and development of abscesses.

The major difficulty with SC calcium is an accurate prediction of the day and time of calving. Possible SC calcium advantages (based on 500 to 1000 ml of 23% Ca-borogluconate) include a rapid increase in serum [Ca], duration of action 8-12 hours, and the ease and safety of administration. A typical preventive treatment to a dairy cow at risk of periparturient hypocalcemia is 500 ml of 23% calcium borogluconate, this provides 10.7 g of calcium. Although the calculated calcium deficit in a recumbent periparturient dairy cow is 4 g calcium, we should provide additional calcium to overcome the continued loss of calcium in milk. A field study comparing the effectiveness of different IV doses of calcium for treating periparturient milk fever determined that 9 g of calcium was superior to 6 g. A good rule of thumb for administering 23% calcium borogluconate solutions (2.14 g calcium/100 ml) to cows to prevent periparturient hypocalcemia is therefore to administer 1 ml/kg body weight.

Oral calcium chloride immediately before calving
Oral CaCl₂ (calcium gels) have been used in Europe since 1962. These are commercially available and are preferred to calcium drenches, which are more likely to be aspirated. Most formulations contain 50-70 g calcium per dose. Retreat at 12-24 hours, and don’t exceed 120 g in a 24-hour period. Oral calcium salts are effective at increasing plasma calcium concentration; orally administered calcium is absorbed by a dose-dependent passive diffusion process across ruminal epithelium and a dose-independent calcium-binding protein mechanism in the small intestine that is modulated by Vitamin D. Passive diffusion across the ruminal epithelium occurs when the ruminal calcium concentration >1.5 mmol/L but is substantial when the calcium concentration in rumen fluid is greater than 6 mmol/L, which is approximately 2-3 times the normal value in plasma (normal range 2.2-2.6 mmol/l). Rapid correction of hypocalcemia by oral calcium administration must utilize passive ruminal diffusion, as small intestinal absorption is too slow to be of clinical value.

Two calcium formulations are currently recommended for oral administration to ruminants; CaCl₂ and calcium propionate, but most commercially available products contain 50 g of CaCl₂. Calcium chloride has the advantage of low cost and low volume (because of its high solubility), but CaCl₂ can severely damage the pharynx and esophagus in ruminants with reduced swallowing ability, can lead to necrosis of the forestomach and abomasum when administered in high doses, and can lead to aspiration pneumonia when administered as a drench. Calcium propionate has the advantages that it is less irritating while providing a gluconeogenic substrate (propionate), but the disadvantages of higher volumes and cost. Oral calcium solutions should only be administered to cattle that have normal swallowing ability, precluding their administration to animals with advanced clinical signs of hypocalcemia. Higher plasma calcium concentrations are obtained more quickly when calcium solutions are drenched after administration of vasopressin to induce esophageal groove closure, or when the calcium solution is administered as a drench instead of ororuminal intubation.

References of potential interest

5. Constable PD, Stampfli HR. Hyperchloremia directly increases ionized calcium concentration in bovine plasma: an additional and novel mechanism by which high


