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 (Ender et al. 1971, Dishington 1975, Block 1984, Oetzel et al. 1988, Lean et al. 2006, Golf 2008). The most likely reason for this effect is that ingestion of a low DCAD diet increases calcium (Ca) flux, which in non-lactating cows is most readily detected as an increase in urinary calcium excretion (Fredeen et al. 1988, Schoneville et al. 1994, Constable 1999). 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 [Ca²⁺] 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 (Vagg and Payne 1970; Fredeen et al. 1988). Increased calcium entry into the exchangeable pool occurs by 4 main mechanisms: enhanced intestinal absorption (Lomba et al. 1978, Schoneville et al. 1994, Roche et al. 2007), hyperchloremic displacement of calcium from binding sites on albumin, increased bone resorption (Block 1984), and decreased bone accretion (van Mosel et al. 1994). We have shown recently that [Ca²⁺] in plasma at pH=7.40 increases by 0.007 mEq/L for every 1 mEq/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, increased bone resorption and decreased bone accretion appear active only in the presence of acidemia (jugular venous blood 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.

Acidemia-induced decreases in parathyroid hormone (PTH) receptor sensitivity, presumably through a morphologic alteration of the receptor with altered environmental pH, has been hypothesized to play a role in the mechanism by which ingestion of an acidogenic diet decreases the incidence and severity of periparturient hypocalcemia (Goff 2008). However, a PTH effect on mobilization of bone calcium is unlikely to play an important role in increasing calcium flux in late gestation cows because the mobilization effect has been identified only in animals with profound chronic acidemia (blood pH < 7.25), whereas ingestion of acidogenic diets rarely decreases blood pH below 7.35 in dairy cattle (Hu and Murphy 2004, Charbonneau et al. 2006). More importantly, the findings of numerous studies have indicated that ingestion of acidogenic diets can decrease the incidence of periparturient hypocalcemia in dairy cattle without a concomitant change in blood pH (Grünberg et al. 2010).

Ingestion of an acidogenic ration increases calcium exit from the exchangeable calcium pool by decreasing renal tubular calcium reabsorption of filtered calcium (Lemann et al. 1985, Fredeen et al. 1988, Constable 2007), 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) (Lambers et al. 2006); the TRPV5 channel was previously termed EcaC1, and CaT2 and is considered to be the primary gatekeeper of active calcium reabsorption in the distal region of the urinary tract (van de Graaf et al. 2007). 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 (van de Graaf et al. 2007). 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 (Charbonneau et al. 2006, Constable et al. 2009) and lactation (Hu and Murphy 2004), 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 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 [Ca²⁺] provides a clinically useful insight into calcium flux in the periparturient cow, it appears that measurement of urine [Ca²⁺] 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 [Ca²⁺], and the optimal calcium intake for cattle being fed low DCAD diets. The linear negative association between urine [Ca²⁺] and urine pH (Constable et al. 2009, Grünberg et al. 2010) 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 urinary 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 (Constable et al., 2009). 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 (Constable et al. 2009). We have
recently developed a general electroneutrality equation for bovine urine (Constable et al 2009), such that urine pH = 6.12 + log10(NBE + [NH4+]) = 6.12 + log10([K+] + [Na+] + [Mg2+] + [Ca2+] + [HCO3-] - [Cl-] - [SO42-]). This equation indicates that an increase in urine [Ca2+] without a change in urine strong anion concentration will alkalinize urine; the observation that urine [Ca2+] 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 [Ca2+] 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 (Charbonneau et al 2006). 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.

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. However, the general electroneutrality equation for urine indicates that in alkaline urine (particularly when pH > 8.0), urine strong ion difference = urine [HCO3-] because [NH4+] = 0 mEq/L, and therefore NBE = [HCO3-] (Constable et al 2009). Accordingly, measurement of total CO2 by use of an automatic analyzer in an anaerobically collected and stored urine sample (no loss of Pco2 from urine) may provide a simple but clinically useful method for determining NBE in alkaline urine samples from cattle. This supposition needs to be verified.

Key words: DCAD, dairy cow, hypocalcemia.

References:


