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Diet-induced pseudohypoparathyroidism: A hypocalcemia and milk fever risk factor

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ABSTRACT

Subclinical hypocalcemia may affect half of all multiparous cows, and clinical hypocalcemia or milk fever affects approximately 5% of dairy cows each year. This disorder of calcium homeostasis can be induced by several dietary factors. Recent studies implicate high dietary potassium and high dietary cation-anion difference (DCAD) with increased risk of milk fever. The hypothesis tested in this study was that high-DCAD diets fed to prepartum cows reduce tissue sensitivity to parathyroid hormone (PTH), inducing a pseudohypoparathyroid state that diminishes calcium homeostatic responses. Multiparous Jersey cows were fed low- or high-DCAD diets in late gestation, creating a compensated metabolic alkalosis in the high-DCAD cows and a compensated metabolic acidosis in the low-DCAD cows. They then received synthetic PTH injections at 3-h intervals for 48 h. Parathyroid hormone is expected to cause an increase in plasma calcium by increasing renal production of 1,25-dihydroxyvitamin D and increasing bone calcium resorption. Plasma calcium concentration increased at a significantly lower rate in cows fed the high-DCAD diet. Cows fed the high-DCAD diet also produced significantly less 1,25-dihydroxyvitamin D in response to the PTH injections than cows fed the low-DCAD diet. Serum concentrations of the bone resorption marker carboxyterminal telopeptide of type I collagen were numerically lower in cows fed the high-DCAD diet but this difference was not statistically significant. These data provide direct evidence that high-DCAD diets reduce tissue sensitivity to PTH. The metabolic alkalosis associated with high-DCAD diets likely induces a state of pseudohypoparathyroidism in some dairy cows at the onset of lactation, resulting in hypocalcemia and milk fever.

Key words: milk fever, pseudohypoparathyroid, dietary cation-anion difference

INTRODUCTION

Milk fever is the common name given to a severe, acute hypocalcemic condition occurring in 5 to 6% of all dairy cows within days of calving. Subclinical hypocalcemia, defined as plasma Ca concentration <8 mg/dL, affects about 50% of all multiparous cows and 25% of heifers (Reinhardt et al., 2011). Hypocalcemia occurs because the mammary gland demand for Ca at the onset of milk production draws Ca from the plasma and extracellular fluid Ca pool faster than it can be replaced. As cows develop hypocalcemia, they respond rapidly by increasing secretion of parathyroid hormone (**PTH**). In cows that do not develop subclinical hypocalcemia or the clinical hypocalcemia of milk fever, PTH rapidly activates Ca homeostatic mechanisms such as renal re-absorption of urinary calcium, osteoclastic bone resorption, and increased renal production of the hormonal form of vitamin D, 1,25-dihydroxyvitamin D [**$1,25(OH)_2D$**] to enhance intestinal absorption of dietary Ca (Ramberg et al., 1984). When Ca homeostatic mechanisms are functioning properly, only a small decline in blood Ca occurs. More severe hypocalcemia occurs when these mechanisms are not rapidly or fully initiated. At one time, it was thought that milk fever occurred as a result of failure of the parathyroid gland to recognize and respond to the hypocalcemia developing at the onset of lactation and that excessively high dietary Ca in the prepartum ration caused the parathyroid gland dysfunction (Capen and Young, 1967). However, it was later discovered that cows developing milk fever have very high concentrations of PTH in their blood (Mayer et al., 1969). In a landmark study, Martig and Mayer (1973) were able to demonstrate that the response of late-gestation cows to exogenous PTH (an increase in blood Ca) was diminished compared with the response elicited by PTH in cows in lactation, but they were not able to discern the cause. In severe cases of "relapsing" milk fever (cows relapsing and becoming recumbent again some hours after the

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typical intravenous calcium treatment), it was observed that the secreted PTH in these cows failed to stimulate production of $1,25(OH)_2D$ as quickly as it does in cows with less severe hypocalcemia (cows that require only a single intravenous calcium treatment to effect a recovery), suggesting again that the periparturient cow's tissues could be temporarily refractory to PTH. In that study, the cows were fed a diet with alfalfa hay as the forage, which would be considered a high-DCAD diet (Goff et al., 1989).

Several meta-analyses have been done concerning risk factors for milk fever. Oetzel (1991), working with a limited number of studies at the time, concluded that dietary S content and DCAD using the equation utilizing milliequivalents of (Na + K) − (Cl + S) most accurately reflected the risk of a diet causing milk fever. That analysis indicated that the milk fever incidence was highest when diet Ca was 1.16% and that dietary Ca well above or well below 1.16% had a preventative effect against milk fever. A few years later, Charbonneau et al. (2006) concluded that the DCAD equation utilizing milliequivalents of (Na + K) − (Cl + 0.6 S) was the best predictor of clinical milk fever risk, reducing the importance of dietary S and determining that an important aspect of DCAD manipulation was an alteration of acid-base status. Lean et al. (2006) concluded that the DCAD equation utilizing milliequivalents of (Na + K) − (Cl + S) accurately reflected the risk of a diet causing milk fever and that the risk of milk fever was greatest with diets that had 1.1 to 1.3% Ca. Their analysis pointed out a pivotal role for inadequate diet Mg as a very strong milk fever risk factor. Their models also demonstrated that excessive diet phosphorus was another milk fever risk factor.

Decreasing the DCAD, defined as the difference in the number of milliequivalents of cations (primarily K and Na) and anions (primarily Cl and S) in the diet, improves Ca homeostasis at the onset of lactation (Ender et al., 1971). Ender et al. (1971), Dishington (1975), and Block (1984) demonstrated that adding acidogenic chloride and sulfate anions to the cows' diet in the final weeks of gestation could prevent milk fever. Goff and Horst (1997) demonstrated that high dietary K increased the risk of a cow developing milk fever. The high dietary K content induced metabolic alkalosis in the cows. They noted that the risk of developing severe hypocalcemia at the onset of lactation was greatest in those cows in a state of metabolic alkalosis. Similar results were observed when Na was added to the prepartum diet. The mechanism by which addition of anions to a diet to counteract cations in the diet of a cow enhances Ca homeostasis is not well understood. Leclerc and Block (1989), Goff et al. (1991), and Phillippo et al. (1994) provided indirect evidence that physiological functions stimulated by PTH, such as bone resorption and production of $1,25(OH)_2D$, were enhanced in cows fed diets with added anions. Unfortunately, differences in milk production, sequestration of Ca in the mammary gland before calving, inappetence on the day of calving and feed intake after calving, and other metabolic stressors (negative energy, protein imbalance) occur on the first day of lactation. This causes difficulty when trying to discern how and why tissues might become refractory to PTH stimulation in experiments conducted around the time of calving. In this study, we tested the hypothesis that metabolic alkalosis induced by diet can induce resistance of target tissues to PTH stimulation in a late-gestation cow model. Using this model, we were able to isolate the effect of high-DCAD diet separately from other risk factors, such as excessive dietary phosphorus and inadequate diet Mg.

MATERIALS AND METHODS

Animals

All procedures used on the cows in this study were approved by the US Department of Agriculture-Agricultural Research Service National Animal Disease Center's Institutional Animal Care and Use Committee. Jersey cows entering their third or greater lactation and in their last 2 mo of gestation, weighing from 490 to 545 kg, participated in this study. They were fed either a low-DCAD (n = 8) or a high-DCAD (n = 8) diet for 2 wk (Table 1) to induce a state of metabolic acidosis or alkalosis before they were treated with PTH (Figure 1). The actual number of days before calving when the PTH treatment was begun averaged 28 d, with a range from 6 d before calving to 41 d before calving. The trial was performed in 4 separate experimental periods using 4 cows with approximately the same expected calving dates (2 cows on each diet treatment) in each experimental period. The diets were formulated by mixing either reagent-grade 36% hydrochloric acid (HCl) or potassium carbonate (K_2CO_3) into a basal corn silage–grass hay ration to achieve DCAD of −181 and +188 mEq/kg of DM for the low- and high-DCAD diets, respectively. Cows were housed individually in box stalls and limit fed 8.0 kg of diet/d (DM basis) to ensure complete intake of added anions or cations during the course of the trial. Orts were less than 0.75 kg of DM/d in all cows and consisted primarily of corn cobs and some larger hay fibers.

The diets were also formulated to avoid other dietary factors identified as factors that increase the risk of hypocalcemia, allowing isolation of the effects of DCAD. The diets were 0.76% Ca, well below the levels the meta-analyses cited above have implicated as most likely to