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Use of calcitriol to maintain postpartum blood calcium and improve immune function in dairy cows

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ABSTRACT

Our objectives were to determine the effects of an injectable formulation of calcitriol on mineral metabolism and immune function in postpartum Holstein cows that received an acidogenic diet prepartum to minimize hypocalcemia. In experiment 1, cows within 6 h of calving received calcitriol (0, 200, or 300 μg) to determine the dose needed to increase plasma concentrations of Ca; 300 μg was sufficient to sustain Ca for at least 3 d. In experiment 2, multiparous cows were assigned randomly to receive only vehicle (control, n = 25) or 300 μg of calcitriol (n = 25) subcutaneously within the first 6 h after calving. Blood was sampled before treatment and 12 h later, then daily until 15 d in milk (DIM), and analyzed for concentrations of ionized Ca (iCa), total Ca (tCa), total Mg (tMg), and total P (tP), metabolites, and hormones. Urine was sampled in the first 7 DIM and analyzed for concentrations of tCa, tMg, and creatinine. Neutrophil function was evaluated in the first week postpartum. Dry matter intake and production performance were evaluated for the first 36 DIM. Calcitriol administration increased concentrations of calcitriol in plasma within 12 h of application from 51 to 427 pg/mL, which returned to baseline within 5 d. Concentrations of iCa and tCa increased 24 h after treatment with calcitriol. Concentrations of iCa (control = 1.08 vs. calcitriol = 1.20 m*M*), tCa (control = 2.23 vs. calcitriol = 2.33 m*M*), and tP (control = 1.47 vs. calcitriol = 1.81 m*M*) remained elevated in cows treated with calcitriol until 3, 5, and 7 DIM, respectively, whereas concentration of tMg (control = 0.76 vs. calcitriol = 0.67 m*M*) was less in calcitriol cows than control cows until 3 DIM. Concentrations of parathyroid hormone decreased in calcitriol cows compared with control cows (control = 441 vs. calcitriol = 336 pg/mL). Calcitriol tended to increase plasma concentrations of β-hydroxybutyrate and serotonin, but concentrations of glucose, nonesterified fatty acids, and C-telopeptide of type I collagen in plasma did not differ between treatments. Cows treated with calcitriol excreted more urinary tCa (control = 0.5 vs. calcitriol = 2.1 g/d) and tMg (control = 4.5 vs. calcitriol = 5.0 g/d) in the first 7 and 2 DIM, respectively, than control cows. Compared with control, calcitriol improved the proportion of neutrophils with oxidative burst (control = 31.9 vs. calcitriol = 40.6%), mean fluorescence intensity for oxidative burst (control = 90,900 vs. calcitriol = 99,746), and mean fluorescence intensity for phagocytosis (control = 23,887 vs. calcitriol = 28,080). Dry matter intake, yields of milk, and milk components did not differ between treatments. Administration of 300 μg of calcitriol at calving was safe and effective in increasing blood concentration of iCa and plasma concentrations of calcitriol, tCa, and tP for the first 6 d after treatment, and improved measures of innate immune function in early-lactation Holstein cows.
Key words: calcitriol, dairy cow, hypocalcemia, vitamin D

INTRODUCTION

A large proportion of dairy cows undergo a period of hypocalcemia with the onset of colostrogenesis and lactation. The large demands for Ca for colostrum and milk synthesis induce a sudden drop in blood concentrations of ionized (**iCa**) and total Ca (**tCa**), so that some cows develop clinical hypocalcemia, also known as milk fever (DeGaris and Lean, 2008; Goff, 2014). Normal concentrations of tCa in the blood usually range between 2.2 and 2.7 m*M*, but the onset of lactation results in sequestration of Ca in the mammary gland before calving (Visek et al., 1953), followed by loss with colostrum secretion, which can represent 7 to 10 times the estimated amount of tCa present in blood of a cow (Horst et al., 2005) and result in decreased blood tCa to concentrations less than 2.2 m*M*. The inability of the

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cow to quickly reestablish concentrations of iCa and tCa in blood, because of inadequate intestinal absorption, bone resorption, or urinary reabsorption is responsible for the development hypocalcemia in the first days of lactation. Reinhardt et al. (2011) used cutoff values for serum concentrations of tCa of 1.4 to 2.0 m*M* to detect cows with subclinical hypocalcemia, and concentrations below 1.4 m*M* as an indication of clinical hypocalcemia. Using those cutoff values, the authors reported prevalences of 1% clinical hypocalcemia and 25% subclinical hypocalcemia for primiparous cows, and 7% clinical hypocalcemia and 47% subclinical hypocalcemia for multiparous cows in the first 48 h of calving. More recent experiments with cows fed prepartum acidogenic diets also showed a high incidence of subclinical hypocalcemia postpartum of 65 to 69% (Martinez et al., 2012, 2016). In those experiments, blood was sampled daily, and the threshold for subclinical hypocalcemia was 2.125 m*M,* which likely explains the higher values than observed by Reinhardt et al. (2011) despite the acidogenic diets. Cows that develop subclinical and clinical hypocalcemia have subsequent impaired health and reproduction. They are more susceptible to other periparturient disorders such as dystocia and ketosis (Curtis et al., 1983), displaced abomasum (Massey et al., 1993), uterine prolapse (Risco et al., 1984), retained placenta (Melendez et al., 2004), and metritis (Martinez et al., 2012). Thus, susceptibility to periparturient diseases, particularly those affecting the reproductive tract, increases in dairy cows that are unable to maintain blood concentrations of Ca in early lactation. In fact, it has been reported that both clinical hypocalcemia (Kimura et al., 2006) and subclinical hypocalcemia (Martinez et al., 2014) depress immune function and predispose cows to diseases.

Dietary and therapeutic strategies are available to minimize the risk of hypocalcemia in dairy cattle (DeGaris and Lean, 2008; Goff, 2014; Oetzel and Muller, 2012). One of the most common methods of preventing hypocalcemia is manipulation of the prepartum dietary mineral content by altering the DCAD of the ration. Diets with a negative DCAD induce a compensated metabolic acidosis that promotes increases in iCa and tCa concentrations in the blood of cows immediately after calving (DeGaris and Lean, 2008; Goff, 2014). Still, in spite of such preventative measures, at least 47% of multiparous cows experience subclinical hypocalcemia in the first 48 h after calving (Reinhardt et al., 2011). As cows develop subclinical hypocalcemia and the concentration of blood iCa drops, the parathyroid gland rapidly increases secretion of parathyroid hormone (**PTH**), which activates renal reabsorption of urinary Ca and osteoclastic bone resorption, and increases renal production of the active form of vitamin D_3, calcitriol. Calcitriol enhances intestinal Ca absorption (Pansu et al., 1983), bone resorption (Kitazawa et al., 2003), and urinary Ca and P reabsorption (Hoenderop et al., 2001). Several authors have investigated the use of vitamin D_3 metabolites to prevent the development of clinical hypocalcemia in dairy cows (Jorgensen et al., 1978; Gast et al., 1979; Allsop and Pauli, 1985). Goff et al. (1988) administered a calcitriol analog intramuscularly to prepartum cows at greater risk of developing clinical hypocalcemia, starting 7 d before the expected day of calving and repeating every 7 d until calving. The incidence of clinical hypocalcemia decreased from 85% in untreated controls to 43 and 29% in cows that received 100 and 150 μg of 24-F-1,25-dihydroxyvitamin D_3; however, the repeated treatments prepartum impaired endogenous calcitriol synthesis postpartum in treated cows and eventually resulted in clinical hypocalcemia. Hove and Kristiansen (1982) administered 500 μg of calcitriol orally to 15 cows that were predisposed to clinical hypocalcemia and then grouped them according to the day the treatment was administered relative to calving: within 24 h of calving, 1 to 3 d before calving, or 4 to 5 d before calving. A group of 8 cows remained as untreated controls. Administration of calcitriol 1 to 3 d before calving increased blood Ca and P compared with all other groups. An issue with such strategies prepartum is predicting the day of calving so that vitamin D_3 metabolites are administered at the proper time. Another option is to use calcitriol immediately after calving in an attempt to prevent any further decline in blood Ca that might occur postpartum.

We hypothesized that an injectable formulation of calcitriol administered in the first hours after parturition would sustain blood concentrations of iCa and tCa and improve measures of immune function in early-lactation cows. The objectives of the present experiment were to determine the effect of an injectable formulation of calcitriol on Ca homeostasis, measures of immune function, energy metabolism, and productive performance in early-lactation dairy cows.

MATERIALS AND METHODS

Two experiments were conducted at the University of Florida Dairy Unit to characterize the responses to administration of calcitriol in early-lactation multiparous Holstein cows. The experiments were approved by the University of Florida Institutional Animal Care and Use Committee, protocol number 201408679.

Calcitriol Formulation

A stock solution of calcitriol was prepared by dissolving 10 mg of crystalline powder calcitriol (Cayman