Oral Administration of Calcium Salts for Treatment of Hypocalcemia in Cattle

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ABSTRACT

Milk fever is usually treated by i.v. administration of 8 to 10 g of Ca. Oral Ca salts have been suggested as an alternate treatment for milk fever. In our studies, plasma Ca concentration changes effected by various oral Ca preparations were compared. Solutions were administered by oral drenching of cows, and blood was obtained hourly. Calcium chloride increased plasma Ca better than Ca propionate, which increased plasma Ca better than Ca carbonate. A CaCl₂ gel formulation increased plasma Ca better than Ca carbonate, but not as well as did Ca propionate. Concentrated solutions of Ca as CaCl₂ increased plasma Ca better than diluted solutions. Rumen bypass of Ca salts increased plasma Ca concentration more than when Ca salts were placed into the rumen. Oral administration of 50 g of Ca as CaCl₂ raised plasma Ca concentrations to the same extent as 4 g of Ca as CaCl₂ given i.v. We also examined effects of oral Ca salts on plasma Ca concentrations of hypocalcemic periparturient cows and found that oral Ca treatment could treat mild cases of hypocalcemia. We also caution that CaCl₂ use must be limited because excessive amounts cause severe metabolic acidosis.

(Key words: calcium, milk fever, hypocalcemia, parturient paresis)

INTRODUCTION

Milk fever (parturient paresis) is a hypocalcemic disorder associated with the onset of lactation in dairy cows. The hypocalcemia occurs because Ca leaves the extracellular fluid pool to enter the mammary gland faster than it can be replaced by intestinal Ca absorption or bone Ca resorption. Milk fever can be prevented by measures that increase the rate of entry of Ca into the extracellular fluid compartment from intestine, bone, or both. Such measures include reduction of the Ca content (8, 14) or the cation content of the prepartal diet (2, 5, 15), administration of parathyroid hormone (6), and administration of vitamin D metabolites (1, 4, 11). Oral administration of Ca salts prior to and at parturition has also been suggested (10, 13, 18) to prevent milk fever in dairy cattle. Hallgren (10), Ringarp et al. (18), and Jonsson and Pehrson (13) utilized CaCl₂ in aqueous and gel forms with varying success. The recent availability of commercial oral Ca supplements as an aid in the treatment of milk fever has renewed interest in the use of oral Ca salts to prevent milk fever. These studies were conducted to determine 1) whether the absorption of orally administered Ca differs among forms of Ca, using plasma Ca concentration as an indicator of absorption; 2) whether rumen bypass is advantageous; and 3) how oral Ca treatment compares with the standard treatment of Ca administered i.v. in restoration of normal blood Ca concentrations.

MATERIALS AND METHODS

Eight adult (4- to 9-yr-old) nonpregnant, nonlactating Jersey cows were used to discern the relative potency of various Ca salt preparations, whether concentrated or diluted solutions were better, and whether rumen bypass could augment the ability of oral Ca salts to increase plasma Ca concentrations. The Ca salts were obtained from Sigma Chemical Co. (St. Louis, MO) and were >99% pure. The CaCl₂, Ca propionate, and Ca carbonate used in these studies were 36, 21.5, and 40% Ca, respectively. Thus, 138.8 g of CaCl₂ provided 50 g
of elemental Ca. In all of these experiments, 10-ml heparinized blood samples were obtained from the jugular vein before treatment and at .5, 1, 2, 3, 4, 5, and 6 h after treatment. Plasma Ca concentration was determined by atomic absorption spectrophotometry (17).

In the first set of experiments, eight cows received 50 g of Ca as Ca carbonate, Ca propionate, or CaCl₂ in 1 L of water by drenching (force-feeding). This amount was not enough water to solubilize the Ca carbonate, which was administered as a slurry. A fourth treatment consisted of 53 g of Ca as CaCl₂ in a gel form of approximately 300-ml volume (Balance®, Diamond Labs, Des Moines, IA). All eight cows received each treatment in a switchback design experiment. The four treatments were conducted with a 2-d interval between treatments.

In a second trial, conducted 3 d later, the effect of concentration (volume) of the CaCl₂ solution was assessed. The eight cows were given 50 g of Ca as CaCl₂ diluted in a minimal amount of water (250 ml) by drenching. Plasma was obtained at .5, 1, 2, 3, 4, 5, and 6 h after treatment for Ca determination.

To assess the effect that rumen bypass might have on oral Ca absorption, eight nonpregnant, nonlactating Jersey cows were given 50 g of Ca as CaCl₂ in 250 ml of water by three methods in a switchback design experiment: 1) placement of the Ca into the rumen by stomach tube, 2) by oral drenching 5 min after receiving 36 IU of lysine vasopressin (Sigma) i.v. to elicit the esophageal groove reflex (19), or 3) by oral drenching 5 min after receiving 3 ml of saline i.v. Plasma samples were obtained .5, 1, 2, 3, 4, 5, and 6 h after treatment for determination of Ca concentrations. These three treatments were conducted with a 2-d interval between treatments.

Lactose has been utilized to enhance pericellular absorption of Ca. Eight cows received a mixture of 50 g of Ca as CaCl₂ and 75 g of lactose dissolved in 250 ml of distilled water by oral drenching. Blood concentrations of Ca achieved by this treatment were compared with those achieved by CaCl₂ alone in 250 ml of water, as determined earlier.

After 3 mo without treatment, four of the cows received 100 g of Ca (276 g of CaCl₂ in 500 ml of water) by oral drenching. Plasma samples were obtained .5, 1, 2, 3, 4, 5, and 6 h after treatment for Ca determination. Urine grab samples were obtained from the cows before treatment and at 6 and 24 h after treatment to assess urinary pH changes.

Nonpregnant, nonlactating Jersey cows were also used in an experiment to determine plasma Ca changes after i.v. treatment with an 11.1% CaCl₂ solution. Four cows received 2 g of Ca, four cows received 4 g of Ca, and all eight cows received 6 g of Ca i.v. as 50, 100, or 150 ml of CaCl₂ solution supplying 2 g of Ca/50 ml. The solution was infused into the jugular vein at a rate of ~20 ml/min. Blood samples were taken from the contralateral jugular vein at 1 min and at .5, 1, 2, 3, 4, 5, and 6 h after cessation of infusion for plasma Ca determination.

The Cl in CaCl₂ acts as a strong anion, capable of acidifying the blood. An estimate of the maximal tolerable dose of CaCl₂ may be extrapolated from observations made in three severely hypocalcemic Jersey cows in our herd that were given oral CaCl₂ solutions to treat the hypocalcemia. Two cows received two doses of 75 g of Ca as CaCl₂ 12 h apart. Onecow(4,6),(996,991)(4,6),(996,991) received two 100-g Ca doses as CaCl₂ 12 h apart. All three cows were monitored for adverse reactions and response to treatment.

Statistical Analysis

Student’s t test (20) was utilized to test the hypothesis that plasma Ca or urine pH at each time after treatment differed from the value obtained prior to treatment and to test the hypothesis that plasma Ca concentration differed across treatments at each time. When the pretreatment plasma Ca concentrations across groups differed, the data were normalized as a fraction of the pretreatment Ca concentration and analyzed. For comparison of Ca treatments i.v. and orally administered, the relative increase in plasma Ca concentration induced by treatment was considered to be proportional to the area under the curve delineated by the line graph of plasma Ca versus hours after treatment. We determined the area under the curve by graphing average plasma Ca concentrations versus hours after treatment for each treatment on the same scale, drawing a baseline equivalent to average pretreatment plasma Ca concentration, cutting the paper along the outline of the graph, and...
weighing the paper on a balance. The area under the curve is expressed arbitrarily in milligrams.

RESULTS

When 50 g of Ca as 128.8 g of CaCl₂ were administered in 1 L of water, plasma Ca concentrations were significantly (P < .05) increased above pretreatment concentrations within 30 min of treatment and remained elevated for the next 3 h. The Ca propionate increased plasma Ca concentrations less than did CaCl₂, although the increase with Ca propionate was sustained longer. The CaCl₂ gel tended to increase plasma Ca, but the variability in response of the cows prevented the increase from reaching significance. The Ca carbonate was ineffective in raising plasma Ca concentrations within the 6-h time frame of this study (Figure 1).

The concentration of the CaCl₂ solution used for treatment influenced the ability of the 50-g Ca dose to increase plasma Ca concentrations. Administration of the 50 g of Ca (138.8 g of CaCl₂) in 250 ml, rather than in 1000 ml, of water significantly (P < .05) increased the ability of the treatment to raise blood Ca concentrations (Figure 2, A and B).

A comparison of the effect of drenching alone, drenching after administration of vasopressin, and stomach tube administration of 50 g of Ca as CaCl₂ on plasma Ca concentrations is presented in Figure 3, A and B. Drenching after administration of vasopressin to stimulate the esophageal groove reflex resulted in significantly higher (P < .05) plasma Ca concentrations than did drenching without vasopressin. Administration of the Ca into the rumen via stomach tube was least effective in increasing plasma Ca concentrations.

Addition of lactose to the 50 g of Ca as CaCl₂ solution had no enhancing effect on plasma Ca concentrations achieved by drenching (data not shown).

Increasing the dose of Ca from 50 to 100 g resulted in a significant (P < .05) increase in plasma Ca concentrations during the experiment (Figure 4). Urine pH of cows treated with 100 g of Ca as CaCl₂ was 7.98 prior to treatment. Within 6 h of treatment, urine pH was significantly (P < .05) reduced to 6.89, and, by
Figure 3. Plasma Ca concentrations in cows after administration of 50 g of Ca as CaCl₂ in 250 ml of water by stomach tube (●), oral drenching (●), and oral drenching after treatment with vasopressin (○), presented as actual mean and fraction of pretreatment concentrations. a) Treatment with vasopressin significantly increased plasma Ca concentrations from those from drenching without vasopressin \((P < .10)\); b) treatment with vasopressin significantly increased plasma Ca concentrations from those from drenching without vasopressin \((P < .05)\).

24 h after treatment, it had declined to 6.48.

Plasma Ca concentration profiles of cows receiving 2, 4, or 6 g of Ca i.v. as CaCl₂ are presented in Figure 5. The Ca treatment administered i.v. caused a rapid rise in plasma Ca concentrations. Thirty minutes after treatment, plasma Ca concentrations were 10.25, 11.90, and 14.27 mg/dl in cows treated with 2, 4, and 6 g of Ca, respectively. Plasma Ca concentrations declined slowly thereafter. Six hours after treatment, plasma Ca concentrations were 8.99, 9.21, and 12.07 mg/dl in cows treated with 2, 4, and 6 g of Ca, respectively.

Pieces of paper representative of the areas under the curve for mean plasma Ca concentrations versus time of cows treated i.v. and orally with CaCl₂ preparations were weighed, and the results are presented in milligrams. For cows treated i.v. with 2, 4, or 6 g of Ca, the areas under the curve were 92, 253, and 430 mg, respectively. In cows treated orally with 50 or 100 g of Ca as CaCl₂, the areas under the curve were 236 and 802 mg, respectively.

Figure 6, A and B, presents plasma Ca concentration profiles from two hypocalcemic cows treated at parturition with 75 g of Ca as CaCl₂ in 375 ml of water. In both cases, the plasma Ca concentrations at treatment were similar (5.0 mg/dl). Both cows were treated more than once. Plasma Ca concentration in the cow in Figure 6A increased by 2.1 mg/dl within 2 h of treatment. The cow was retreated at 11 and 32 h after parturition. Each treatment was followed by a transient increase in plasma Ca concentration. However, the third treatment effected a much greater increase in plasma Ca concentration. Plasma Ca concentration rose above 8 mg/dl in this cow approximately 4 h after the third dose of Ca.

Plasma Ca concentration in the cow in Figure 6B was increased by 5 mg/dl within 1 h of treatment. Plasma Ca declined slowly thereafter. A second 75-g dose of Ca was administered orally 28 h after parturition, when plasma Ca had declined to 4.1 mg/dl. Plasma Ca concentration again increased, although to a lesser extent, and the cow recovered from hypocalcemia over the next 3 d.

Figure 6C presents the plasma Ca concentration profile of a hypocalcemic cow (Ca = 5.0 mg/dl) treated with 100 g of Ca as CaCl₂ in 500 ml of water at calving and again as 12 h after calving. Each 100-g dose of Ca was effective in raising plasma Ca by >2.0 mg/dl.
CALCIUM SALTS FOR MILK FEVER

Figure 5. Plasma Ca concentration profiles of cows after administration of 2 (○), 4 (□), or 6 (△) g of Ca as CaCl₂ administered i.v.

However, 3 h after the second treatment, the cow exhibited signs of severe metabolic acidosis. The cow was breathing rapidly and deeply, the urine pH was 5.1, and the cow became reluctant to move. Therapy for metabolic acidosis was initiated at this point. The cow was treated with an i.v. solution of saline and sodium bicarbonate, which reduced the severity of the symptoms of metabolic acidosis. A second treatment with sodium bicarbonate administered 7 h later was required to relieve the symptoms of metabolic acidosis. The cow's milk production and appetite slowly returned to normal over the next 2 wk.

DISCUSSION

Plasma Ca concentrations decline in most dairy cattle around parturition as Ca leaves the extracellular Ca pool to enter the mammary gland. On the day of parturition, dairy cows commonly produce 10 L or more of colostrum, containing 23 g of Ca or more, which is approximately six times as much Ca as the extracellular Ca pool contains. The extent of the decline in plasma Ca is dependent on the difference between the amount of Ca that leaves the extracellular pool (colostrum production) and the amount of Ca that can be mobilized from bone and absorbed from the intestine to replenish the extracellular Ca pool. Bone Ca resorption and intestinal Ca absorption are regulated by the calcitropic hormones, parathyroid hormone, and 1,25-dihydroxyvitamin D. Most cows rapidly adapt to the loss of Ca associated with the onset of lactation by increasing bone Ca release and intestinal Ca absorption. These cows suffer only a minor decrease in plasma Ca concentrations during d 1 of lactation. In some cows, the Ca homeostatic mechanisms are slow to adapt. Factors known to affect the cow's ability to adapt include age, breed, and prepatal dietary Ca and anion-cation balance (7). If extracellular Ca cannot be replenished rapidly enough, severe hypocalcemia may ensue, resulting in milk fever.

Approximately 80% of cows suffering from milk fever can be successfully treated by i.v. administration of 8 to 10 g of Ca, which implies that the Ca homeostatic mechanisms successfully replenished all but 8 to 10 g of the
Ca lost to milk production in these cows. We next considered whether oral administration of Ca can increase intestinal Ca absorption by the 8 to 10 g of Ca required to prevent 80% of all milk fever cases.

Intestinal Ca absorption occurs by two mechanisms: active transport across intestinal epithelial cells and passive transport of Ca between intestinal epithelial cells. Transport across cells is dependent on stimulation by 1,25-dihydroxyvitamin D. Treating cows with 1,25-dihydroxyvitamin D or inducing endogenous production of 1,25-dihydroxyvitamin D by placing cows on a low Ca diet before parturition can enhance active transport of Ca and prevent milk fever (7, 9). Passive transport of Ca between epithelial cells is dependent on diffusion down a concentration gradient. Because extracellular fluid ionized Ca concentration is approximately 1 mM, passive diffusion of Ca from the lumen of the gut to the extracellular fluids could occur when the lumenal ionized Ca concentration exceeds 1 mM (3).

The structure of the tight junctions between epithelial cells present a lipophilic barrier against movement of ions and fluids across the pericellular space, which raises the lumen concentration requirement for passive Ca transport slightly. Presumably, oral Ca treatment increases luminal Ca concentration above 1 mM, favoring passive transport of Ca into the extracellular fluids and plasma. Holler et al. (12) demonstrated that net absorption of Ca can occur in the rumen when the Ca concentration is >1.5 mM.

The CaCl₂ proved to be more readily absorbable, using increased plasma Ca concentrations as an index of absorption, than Ca propionate, which, in turn, proved to be more absorbable than Ca carbonate. This difference corresponds well to the relative solubilities of these three Ca salts in water. The reduced response to the CaCl₂ in gel form may stem from a reduced ability to bypass the rumen and from rapid dilution within the rumen. The gel form may limit the solubility of the Ca. The more soluble the Ca, the more likely it is that ionized Ca concentration above epithelial mucosal surfaces will exceed 1.5 mM. A concentrated solution of CaCl₂ and a solution that bypassed the rumen, where it would avoid dilution, would also increase Ca concentrations in the lumen above absorptive epithelium. The highly osmotic CaCl₂ salt solution likely stimulated the esophageal groove reflex, permitting rumen bypass of a portion of the drench. Administration of vasopressin further enhanced the rumen bypass of the drench by pharmacological stimulation of the esophageal groove reflex, as suggested by Scholz (19). The placement of CaCl₂ directly into the rumen via stomach tube still resulted in a rapid increase in plasma Ca, peaking within 30 min, which implies that Ca was passively absorbed from the rumen. Absorption of Ca from the rumen is likely limited, because the solution would be rapidly diluted below a concentration capable of sustaining passive Ca transport.

Calcium propionate was reasonably effective in raising plasma Ca concentrations. The Ca propionate has three attributes that make its use appealing: propionate is gluconeogenic; it has a less objectionable taste; and, because it is not a strong anion, it is less likely to cause metabolic acidosis in the cows. The disadvantage of Ca propionate is the volume of water (≥800 ml) required to solubilize 50 g of Ca as Ca propionate. A paste or gel formulation that incorporates Ca propionate as the source of Ca may have major advantages.

Lactose, which normally increases passive absorption of Ca, failed to have any effect in these studies. Pansu et al. (16) demonstrated that lactose and other hyperosmotic solutions enhance passive Ca absorption by causing the epithelial tissues to expand, widening the tight junctions and increasing their permeability to Ca. The CaCl₂ solutions used in our experiments were already hyperosmotic, which likely precluded an effect from lactose.

Oral administration of 100 g of Ca orally is equivalent to between 8 and 10 g of Ca administered i.v. Based on analysis of the areas under the curve delineated by the graphs of plasma Ca versus hour after treatment, oral administration of 50 g of Ca as CaCl₂ in 250 ml of water and i.v. administration of 4 g of Ca as CaCl₂ were nearly equipotent in their ability to raise plasma Ca concentration in the cows.

Plasma pH is highly dependent on the dietary balance between the cations, Na and K, and the anions, Cl and S (21). Treatment with CaCl₂ upsets this balance. The Cl₂ is readily absorbed from the diet, whereas the Ca is poorly absorbed. The unbalanced, negatively
charged anions cause the pH of the plasma to decrease. The kidneys attempt to compensate for this metabolic acidosis by excreting an acid urine. Vagg and Payne (22) found that cows fed >3 equivalents of chloride (as ammonium chloride) for 7 to 10 d became severely acidotic. We observed severe metabolic acidosis in a cow given 200 g of Ca as CaCl2 within 24 h. The CaCl2 given to this cow provided approximately 3.75 equivalents of chloride during 24 h. They also likely became acidotic, but the kidneys could successfully compensate for the additional anion load. Slight acidosis (reduction of the metabolic alkalosis of most dairy cows that are fed forage) may even be favorable to Ca homeostasis in dairy cows, because it enhances release of Ca from bone (22) and enhances production of 1,25-dihydroxyvitamin D (5).

CONCLUSIONS

The Ca treatments administered i.v. support plasma Ca concentration in hypocalcemic cows until the Ca homeostatic mechanisms of the cow can be activated. In cows with small Ca deficits (<4 g of Ca), oral Ca treatment with 50 g of Ca could be used in the place of Ca treatment administered i.v. Repeated doses may be given; each dose presumably supplies the equivalent of 4 g of Ca to the blood. Severely hypocalcemic cows, such as the Jerseys in this study, or cows that are relapsing from milk fever (cows requiring two or more i.v. Ca treatments) are likely to be in a deficit of 10 to 20 g of Ca. It is unlikely that oral Ca treatment could successfully prevent all milk fever cases; however, oral Ca treatment may be very effective in preventing relapses. We think that the total amount of CaCl2 administered in 24 h should not exceed 288 g (120 g of Ca) to avoid inducing severe metabolic acidosis. Although our research indicates that oral solutions of CaCl2 may be more effective than CaCl2 gels, the risk of aspiration pneumonia precludes their use. The CaCl2 gels are a useful compromise. Development of a Ca propionate gel or mixture of Ca propionate with CaCl2 may permit more Ca to be administered without risk of metabolic acidosis.

With an effective dry cow nutrition program, oral CaCl2 gels could prevent clinical and subclinical hypocalcemia in most dairy cows.

ACKNOWLEDGMENTS

The authors thank Norman Tjelmeland, Creig Caruth, and John Moore for their diligent care of the cows used in these experiments. These studies would not have been possible without the expert technical assistance of R. Joseph Wendling, Derrel Hoy, and Cynthia Hauber. The authors also thank Kathleen Kelderman for preparation of the manuscript.

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