Effects of the Addition of Potassium or Sodium, but Not Calcium, to Prepartum Rations on Milk Fever in Dairy Cows[1]

J. P. GOFF[2] and R. L. HORST
USDA, Agricultural Research Service, National Animal Disease Center, Metabolic Diseases and Immunology Research Unit, Ames, IA 50010-0070

ABSTRACT

The effects of prepartum dietary concentrations of K, Na, and Ca on the incidence of periparturient hypocalcemia or milk fever was determined for older (≥4th lactation) Jersey cows. Cows were fed one of six diets differing in K and Ca contents. In addition, the effect of dietary Na (tested only at the high concentration of dietary Ca, and low concentration of dietary K) was examined. Treatments were arranged in an incomplete 2 × 4 factorial design; dietary Ca (0.5 or 1.5%) and dietary strong cations (1.1, 2.1, and 3.1% K or 1.3% Na) were the main effects. Dietary Ca did not significantly affect the incidence of milk fever or the degree of hypocalcemia experienced by the cows. Milk fever occurred in 2 of 20 cows that were fed the prepartum diet containing 1.1% K and 0.12% Na. Increasing dietary K to 2.1 or 3.1% increased the incidence of milk fever to 10 of 20 cows and 11 of 23 cows, respectively. Increasing dietary Na to 1.3% in the diet containing 1.5% Ca induced milk fever in 5 of 8 cows. Addition of strong cations to the prepartum diet increased blood and urine pH and reduced plasma hydroxyproline concentrations, suggesting that bone resorption of Ca is inhibited in cows fed high K or high Na diets as a result of metabolic alkalosis. These data demonstrated that dietary Ca concentration is not a major risk factor for milk fever and that dietary strong cations, especially K, induce metabolic alkalosis in the prepartum dairy cow, which reduces the ability of the cow to maintain Ca homeostasis.

(**Key words**: calcium, milk fever)

Abbreviation key: **PTH** = parathyroid hormone, **1,25(OH)$_2$D** = 1,25-dihydroxyvitamin D.

INTRODUCTION

Milk fever is a metabolic disorder in which Ca homeostatic mechanisms fail to maintain normal plasma Ca concentrations at the onset of lactation. Recent studies (1, 4, 10, 12, 13, 23, 26, 34) have suggested that the response of kidney and bone to parathyroid hormone (**PTH**) is impaired in cows that develop milk fever and that the responsiveness of tissues can be modified by the prepartum diet. The exact dietary factors that predispose cows to milk fever are somewhat controversial. Many prospective and retrospective studies (3, 5, 14, 15, 20, 21, 22, 39, 41) have concluded that prepartum diets that are high in Ca are associated with increased incidence of milk fever. However, there is also evidence that increasing dietary Ca does not cause milk fever and may actually help prevent the disease (9, 19), especially in diets with added anions (2, 8, 30).

The successful use of dietary anions to prevent milk fever has suggested that diets that are high in cations, especially Na and K, increase the susceptibility of cows to milk fever (2, 4, 7, 11, 28). In some remarkably astute experiments, Dishington (7) demonstrated that adding cations (in the form of $NaHCO_3$ or $NaCo_3$) to a basal diet that did not cause milk fever greatly increased the incidence of milk fever. However, high Na diets are not commonly encountered. Forages commonly used in dry cow rations more often contain K. Theoretically, this cation is responsible for the high cation-anion differences in diets that are associated with high morbidity attributable to milk fever. However, to our knowledge, no direct proof exists that K induces milk fever.

The purpose of this experiment was to determine whether the addition of K to a diet that was low in cations and relatively high in anions could induce milk fever in dairy cows. In addition, the effect of dietary Ca across dietary K treatments was determined. We also determined whether the addition of Na to a diet that was low in cations and relatively high in Ca and anions could induce milk fever to try to duplicate the observations of Dishington (7).

Received November 17, 1995.
Accepted April 26, 1996.

[1]Names are necessary to report factually on available data; however, the USDA neither guarantees nor warrants the standard of the product, and the use of the name by the USDA implies no approval of the product to the exclusion of others that may also be suitable.

[2]To whom reprint requests should be addressed.

MATERIALS AND METHODS

Cows

Jersey cows entering ≥4th lactation were assigned to experimental diets; cows were evenly distributed according to age. Cows were housed in free stalls bedded with sand at the National Animal Disease Center (Ames, IA) and were accustomed to being fed rations using the Calan gate feeding system (American Calan, Northwood, NH), permitting accurate determination of feed intake. Feed was placed into the feed bins twice daily, and orts were weighed back once daily. Cows began receiving the experimental diets 3 wk before the expected date of parturition. Blood samples were obtained daily from approximately 2 wk before to 2 wk after calving, and sampling was more frequent when calving seemed imminent. Blood samples were also taken immediately before any treatments for milk fever. Urine samples were obtained by manual stimulation of the vulva of each cow several times before calving to ensure that a sample was obtained from each cow prior to parturition. Only the pH of the urine sample obtained closest to –2 d before calving was used in the data analysis.

Diets

A basal ration with low Ca and K concentrations was formulated based primarily on corn silage, beet pulp, distillers grains, and soybean meal (Table 1). A diet that was low in Ca and K with a cation-anion difference [(Na + K) – (Cl + S)] of approximately –100 meq/kg of diet was achieved by adding $NH_4H_2PO_4$, $MgSO_4$, and NH_4Cl to the basal ration. A diet that was high in Ca and low in K with a cation-anion difference of approximately –50 meq/kg of diet was achieved by adding $CaHPO_4$, $CaSO_4$, $MgSO_4$, NH_4Cl, $CaCl_2$, and $CaCO_3$ to the basal ration. The K content and cation-anion difference of the low and high Ca diets were increased by adding $KHCO_3$ to the diets. The diets were formulated to be isocaloric and isonitrogenous and also were formulated to be similar in Na, S, P, and Cl content. Samples of the diets were obtained periodically for mineral, fiber, energy, and protein analyses (Northeast DHIA Laboratory, Ithaca, NY). Cows were offered 7.3 kg of DM of each diet daily. Low Ca diets (0.5% Ca) supplied approximately 36 g of Ca and 48 g of P daily, and high Ca diets (1.5% Ca) supplied approximately 109 g of Ca and 47 g of P daily. The low, medium, and high K

TABLE 1. Formulation of diets and results of mineral analysis.

	0.5% Ca			1.5% Ca			
	1.1% K	2.1% K	3.1% K	1.1% K	2.1% K	3.1% K	1.3% Na
Ingredient, g/100 g							
Corn silage	40.6	38.9	38.0	39.7	38.4	36.8	37.3
Soybean meal (44% protein)	13.6	13.0	12.7	13.2	12.7	12.2	12.4
Distillers grain (without solubles)	10.9	10.4	10.2	10.6	10.0	9.8	9.9
Beet pulp (without molasses)	24.8	23.8	23.2	24.0	23.1	22.2	22.4
Alfalfa hay	5.4	5.2	5.0	5.2	5.0	4.8	4.9
Vitamin mix[1]	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Trace mineral salt	0.26	0.26	0.26	0.26	0.26	0.26	0.26
$CaHPO_4$	. . .	. . .	. . .	2.66	2.66	2.66	2.66
$CaSO_4$	. . .	. . .	. . .	0.76	0.76	0.76	0.76
$CaCO_3$	. . .	. . .	. . .	1.71	1.71	1.71	1.71
$CaCl_2$	. . .	. . .	. . .	0.28	0.28	0.28	0.28
NH_4Cl	0.5	0.5	0.5	0.27	0.27	0.27	0.27
$MgSO_4$	0.90	0.90	0.90	0.25	0.25	0.25	0.25
$NH_4H_2PO_4$	2.13	2.13	2.13	. . .	. . .	. . .	. . .
Urea	. . .	. . .	. . .	0.58	0.58	0.58	0.58
$KHCO_3$	. . .	3.08	6.16	. . .	3.08	6.16	. . .
$NaHCO_3$	. . .	. . .	. . .	. . .	. . .	. . .	5.47
Chemical analysis[2]							
Ca	0.52	0.50	0.54	1.38	1.61	1.51	1.46
P	0.63	0.67	0.66	0.61	0.65	0.61	0.61
Na	0.11	0.16	0.11	0.14	0.13	0.14	1.30
K	1.19	2.10	3.09	1.14	2.22	3.22	1.09
Mg	0.33	0.35	0.36	0.28	0.24	0.26	0.26
Cl	0.60	0.57	0.60	0.62	0.57	0.64	0.65
S	0.45	0.36	0.42	0.37	0.42	0.39	0.36
Cation-anion difference, meq/kg (Na + K) – (Cl + S)	–98	222	408	–54	202	461	436

[1]Contained 125,000 IU of retinyl palmitate, 25,000 IU of vitamin D_3, 2125 IU of α-tocopherol acetate, and 1.1 mg of Se.

[2]Means for all diets: crude protein, 17.1%; ADF, 23.8%; NDF, 40.8%; NE_L, 1.54 Mcal/kg.

diets contained approximately 1.17, 2.16, and 3.16% K, respectively (Table 1). A diet that was high in Na and Ca but low in K was formulated by adding $NaHCO_3$ to the diet that was high in Ca and low in K. The high Na diet was approximately 1.30% Na (Table 1). Within 16 h after calving, each cow was placed on the high Ca, high K diet for the duration of the experiment.

Plasma Analysis

Plasma concentrations of Ca, K, Na, and Mg were determined by atomic absorption spectrophotometry (33). Plasma P (31), NEFA (18), and hydroxyproline (6) were determined colorimetrically. Plasma PTH was determined by immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA), which had been previously validated for cows (13). Plasma 1,25-dihydroxyvitamin D [**1,25(OH)$_2$D**] concentration was determined by radioreceptor assay (35). Blood gases and pH were determined on whole heparinized samples of jugular venous blood maintained at 4°C until analyzed (within 1 h of obtaining the sample). Urine pH determinations (Corning 150 pH meter; Costar-Corning, Corning, NY) were made within 1 h of urine collection.

Clinical Disease Criteria

A cow was considered to have milk fever if she was recumbent and if her plasma Ca concentration was <5.5 mg/100 ml. Milk fever and subsequent relapses, if any, were treated with the i.v. administration of 10.5 g of Ca as Ca borogluconate (Norcalciphos; Phoenix Scientific, Inc., St. Joseph, MO). A cow was classified as having subclinical hypocalcemia if plasma Ca concentration fell to <7.5 mg/100 ml at any time during the experiment.

Statistical Analysis

Dietary effects on the incidence of milk fever and subclinical hypocalcemia were assessed by chi-square analysis. Effects of dietary Ca, K, and interactions of dietary Ca and K on plasma constituents were analyzed by repeated measures two-way analysis of variance or two-way analysis of variance if only one determination was used in the analysis (i.e., blood gases, blood pH, and urine pH). Effects of dietary Na were analyzed by repeated measures analysis of variance by comparing data derived from cows fed the diet that was high in Ca and Na and low in K with data derived from cows fed the diet that was high in Ca but low in Na and K. When analysis of variance suggested a significant treatment effect, means were compared with Fischer's least significant difference test.

RESULTS

The incidence of milk fever and the number of i.v. Ca treatments applied to the cows in each dietary treatment block are presented in Table 2. There was no significant effect of dietary Ca across the dietary K treatments on the incidence of milk fever; 12 of 31 cows fed the low Ca diets and 11 of 32 cows fed the high Ca diets developed milk fever. Across dietary Ca treatments, only 2 of 20 cows fed the 1.1% K diets developed milk fever. Addition of $KHCO_3$ significantly increased the incidence of milk fever ($P < 0.001$), but, surprisingly, the incidence of milk fever in cows fed the 2.1% K diet (10 of 20 cows) was similar to the incidence in cows fed the 3.1% K diet (11 of 23 cows). The incidence of milk fever in cows fed the diet that was high in Ca and K was only 3 of 13 cows, but 8 of 10 cows fed the diet that was low in Ca and high in K developed milk fever, showing a significant effect of

TABLE 2. Incidence of milk fever, subclinical hypocalcemia [plasma Ca <7.5 mg/100 ml], and number of i.v. Ca treatments (trt) administered within each dietary treatment block.

	Dietary K			Effect of dietary Ca
	1.1%	2.1%	3.1%	
0.5% Dietary Ca				
Milk fever, no. of cases/no. of cows	0/10	4/11	8/10	12/31
Hypocalcemia, no. of cases/no. of cows	9/10	11/11	10/10	30/31
Ca trt, no. of trt/no. of milk fever cases	0/0	9/4	16/8	25/12
1.5% Dietary Ca				
Milk fever, no. of cases/no. of cows	2/10	6/9	3/13	11/32
Hypocalcemia, no. of cases/no. of cows	9/10	9/9	12/13	30/32
Ca trt, no. of trt/no. of milk fever cases	2/2	9/6	4/3	15/11
Effect of dietary K				
Milk fever, no. of cases/no. of cows	2/20	10/20	11/23	
Hypocalcemia, no. of cases/no. of cows	18/20	20/20	22/23	
Ca trt, no. of trt/no. of milk fever cases	2/20	18/10	20/11	

dietary Ca at the highest K concentration ($P < 0.001$). The number of i.v. Ca treatments required to treat paretic recumbent cows (initial treatment and relapses) may be an indication of the severity of milk fever experienced in each dietary treatment group. Although dietary Ca (across dietary K treatments) did not influence the number of cows with milk fever, the number of treatments for paretic recumbent cows was greater ($P < 0.001$) for those cows fed the low Ca diet. As with milk fever, the number of treatments for paretic recumbent cows was increased by the addition of K to the diet, but there was no significant difference between the 2.1 and 3.1% K diets in the severity of milk fever observed. Nearly all cows fed all diets could be classified as subclinically hypocalcemic (plasma Ca <7.5 mg/100 ml) at some time within the first 24 h after calving.

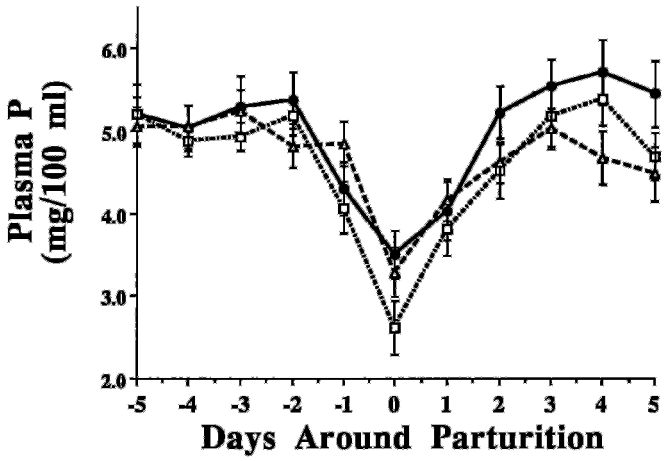

Figure 2. Profiles of plasma P concentration in cows fed a 1.1% (●), 2.1% (□), or 3.1% (△) K diet prior to calving. Bars represent standard errors of the means.

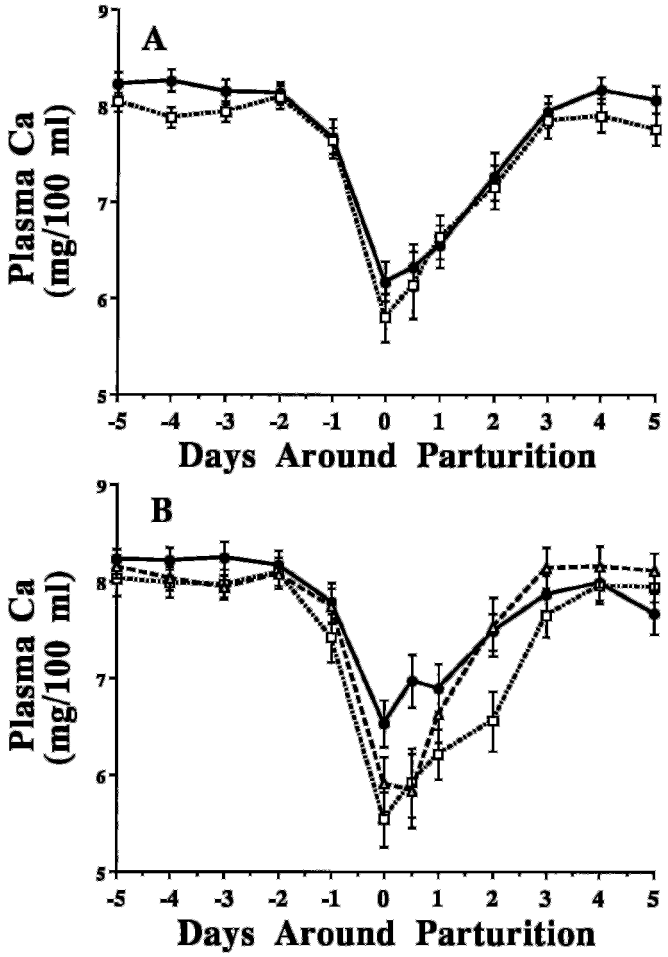

Figure 1. A. Profiles of plasma Ca concentration in cows fed a 1.5 % (□) or 0.5% (●) Ca diet prior to calving. B. Profiles of plasma Ca concentration in cows fed a 1.1% (●), 2.1% (□), or 3.1% (△) K diet prior to calving. Bars represent standard errors of the means.

Plasma Ca concentrations declined at calving for all cows ($P < 0.001$). Dietary Ca had no significant effect on profiles of plasma Ca concentration (Figure 1A). Plasma Ca concentration was significantly decreased in cows fed the 2.1 and 3.1% K diets compared with plasma Ca concentration of cows fed the 1.1% K diet ($P < 0.01$)(Figure 1B). Cows fed the high (3.1%) K diet had higher plasma Ca concentrations around calving than did cows fed the 2.1% K diet ($P < 0.05$). There was an effect ($P < 0.001$) of the interaction between dietary Ca and dietary K on plasma Ca con-centration. When dietary Ca and K were highest, the plasma Ca concentration was elevated above the concentration predicted by the model based on dietary K effects alone (Table 3). Plasma Ca concentrations of cows fed the diet containing 1.5% Ca and 3.1% K were higher ($P < 0.05$) than those of cows fed the diet

TABLE 3. Mean effects of the interactions of dietary Ca and K on plasma Ca concentration in blood samples obtained at calving and at 12 h after calving.[1]

Dietary treatment	$\bar{X}$	SEM
0.5% Ca, 1.1% K	6.57	0.29
0.5% Ca, 2.1% K	6.07	0.33
0.5% Ca, 3.1% K	5.22	0.39
1.5% Ca, 1.1% K	6.90	0.21
1.5% Ca, 2.1% K	5.27	0.24
1.5% Ca, 3.1% K	6.39	0.23

[1]Significant mean comparisons using Fisher's least significant difference test: 0.5% Ca, 1.1% K vs. 0.5% Ca, 3.1% K ($P < 0.05$); 0.5% Ca, 1.1% K vs. 1.5% Ca, 2.1% K ($P < 0.05$); 0.5% Ca, 3.1% K vs. 0.5% Ca, 1.1% K ($P < 0.01$); 0.5% Ca, 3.1% K vs. 1.5% Ca, 3.1% K ($P < 0.05$); and 1.5% Ca, 1.1% K vs. 1.5% Ca, 2.1% K ($P < 0.01$).

TABLE 4. Acid-base status of cows fed diets varying in Ca and K.

	Dietary K						Effect of dietary Ca	
	1.1%		2.1%		3.1%			
	$\bar{X}$	SEM	$\bar{X}$	SEM	$\bar{X}$	SEM	$\bar{X}$	SEM
0.5% Dietary Ca								
Urine pH	5.80	0.22	7.99	0.08	8.09	0.11	7.32	0.20
Blood pH	7.373	0.015	7.470	0.065	7.406	0.008	7.418	0.009
Blood HCO_3	20.5	1.0	25.2	0.6	24.6	0.5	23.5	0.6
1.5% Dietary Ca								
Urine pH	5.70	0.09	7.85	0.11	8.23	0.06	7.33	0.24
Blood pH	7.360	0.020	7.400	0.009	7.417	0.006	7.394	0.025
Blood HCO_3	23.6	1.0	24.1	0.9	26.0	0.6	24.6	0.5
Effect of dietary K								
Urine pH	5.75	0.10	7.92	0.07	8.17	0.06	. . .	. . .
Blood pH	7.367	0.012	7.437	0.035	7.412	0.005	. . .	. . .
Blood HCO_3	21.9	0.8	24.7	0.5	25.3	0.4	. . .	. . .

containing 0.5% Ca and 3.1% K and similar to the concentrations of cows fed the 1.1% K diets.

Plasma P concentration decreased in all cows at calving, regardless of diet ($P < 0.001$). Dietary Ca and K both had significant effects on the profiles of plasma P. Cows fed the low Ca diets had higher plasma P concentrations prior to calving than did cows fed the high Ca diets ($P < 0.05$). Plasma P concentrations declined less in cows fed the 1.1% K diet than in cows fed either the 2.1 or 3.1% K diets ($P < 0.05$) (Figure 2). Plasma Mg concentration increased at calving, regardless of dietary Ca or K treatment. The elevation in plasma Mg concentration (Figure 3A) was less in cows fed the high Ca diets (lower dietary Mg) than in cows fed the low Ca diets ($P < 0.05$). Dietary K had no effect on plasma Mg concentration (Figure 3B). Plasma Na and K concentrations were not affected by dietary Ca treatment, dietary K treatment, or calving.

Plasma PTH and $1,25(OH)_2D$ concentrations increased in all cows during the first 24 h after calving. Dietary Ca had no significant effect on profiles of plasma PTH or $1,25(OH)_2D$ concentration. Plasma PTH concentrations were lower in cows fed the 1.1% K diet than in the cows fed the 2.1 and 3.1% K diets ($P < 0.01$; Figure 4). No significant interaction between dietary Ca and dietary K on plasma PTH was observed. Plasma $1,25(OH)_2D$ concentration increased twofold at calving in cows fed the 1.1% K diet and increased threefold in cows fed the 2.1% K diet (Figure 5). Plasma $1,25(OH)_2D$ concentration in cows fed the 3.1% K diet increased twofold at calving.

Profiles of plasma hydroxyproline concentration were not affected by dietary Ca. Profiles of plasma hydroxyproline concentration of cows fed the 1.1% K diet shortly before calving were increased over those of cows fed the 2.1 or 3.1% K diets (Figure 6). Plasma hydroxyproline concentration was increased in all cows by d 2 after calving.

Cows fed the 1.1% K diets had lower urine and blood pH and lower blood HCO_3 concentrations than did cows fed the higher K diets (Table 4). Urine pH was significantly higher in cows fed the 3.1% K diets, but no significant difference in blood HCO_3 or blood pH was observed between cows fed the 2.1 and 3.1% K diets. Dietary Ca treatment had no significant effect on urine, blood pH, or blood bicarbonate concentrations.

TABLE 5. Incidence of retained placenta, displaced abomasum, mastitis, and primary ketosis observed within each dietary treatment block.

	Dietary K			Effect of dietary Ca
	1.1%	2.1%	3.1%	
0.5% Dietary Ca				
Retained placenta	2/10[1]	1/11	0/10	3/31
Displaced abomasum	2/10	1/11	0/10	3/31
Mastitis	0/10	0/11	0/10	0/31
Ketosis	0/10	1/11	1/10	2/31
1.5% Dietary Ca				
Retained placenta	0/10	1/9	2/13	3/32
Displaced abomasum	1/10	0/9	0/13	1/32
Mastitis	3/10	0/9	2/13	5/32
Ketosis	0/10	0/9	0/13	0/32
Effect of dietary K				
Retained placenta	2/20	2/20	2/23	. . .
Displaced abomasum	3/20	1/20	0/23	. . .
Mastitis	3/20	0/20	2/23	. . .
Ketosis	0/20	1/20	1/23	. . .

[1]Number of cases per number of cows in each dietary block.

Feed intake from 10 to 2 d prior to calving averaged 7.2 kg/d. Across all dietary treatment groups, feed intake at calving declined 17% (Figure 7). During the 10 d before calving (including the day of calving), both dietary Ca and K had small but significant effects on feed intake. Feed intake of cows fed the high Ca diets was greater than that of cows fed the low Ca diets (7.03 ± 0.05 vs. 6.81 ± 0.06 kg/d, respectively; $P < 0.05$). Feed intake prior to calving for cows fed the 2.1% K diet (7.17 ± 0.04 kg/d) was greater than that for cows fed the 3.1% K diet (6.95 ± 0.06 kg/d; $P < 0.05$), which, in turn, was greater than the prepartum feed intake for cows fed the 1.1% K diet (6.65 ± 0.09 kg/d; $P < 0.05$). However, during the first 2 wk after calving, those cows fed the 2.1% K diets prepartum ate significantly less of the postpartum diet (containing 1.5% Ca and 3.2% K) (7.43 ± 0.13 kg/d) than did cows fed the 3.2% K diet (8.04 ± 0.16 kg/d) or the 1.1% K diet (8.10 ± 0.16 kg/d; $P < 0.05$). Feed intake during the first 2 wk after calving was not affected by dietary Ca treatment. Dietary Ca and K treatments had no significant effect on the incidence of ketosis, displaced abomasum, or retained placenta (Table 5), probably because the incidence of these diseases was too low to detect differences with such small sample sizes.

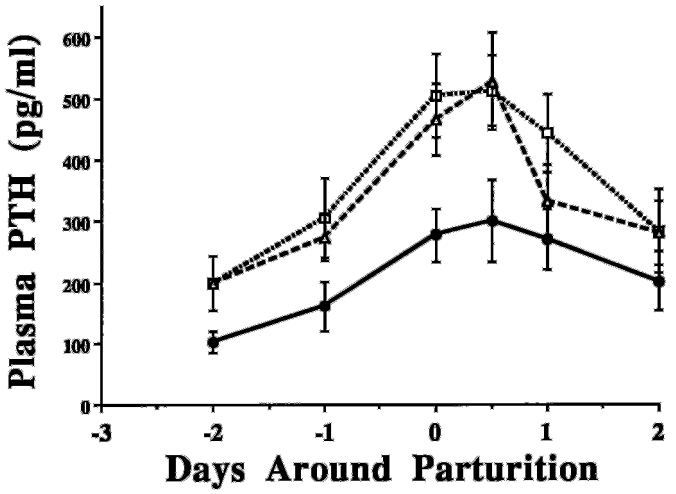

Figure 4. Profile of plasma parathyroid hormone (PTH) in cows fed a 1.1% (●), 2.1% (□), or 3.1% (△) K diet prior to calving. Bars represent standard errors of the means.

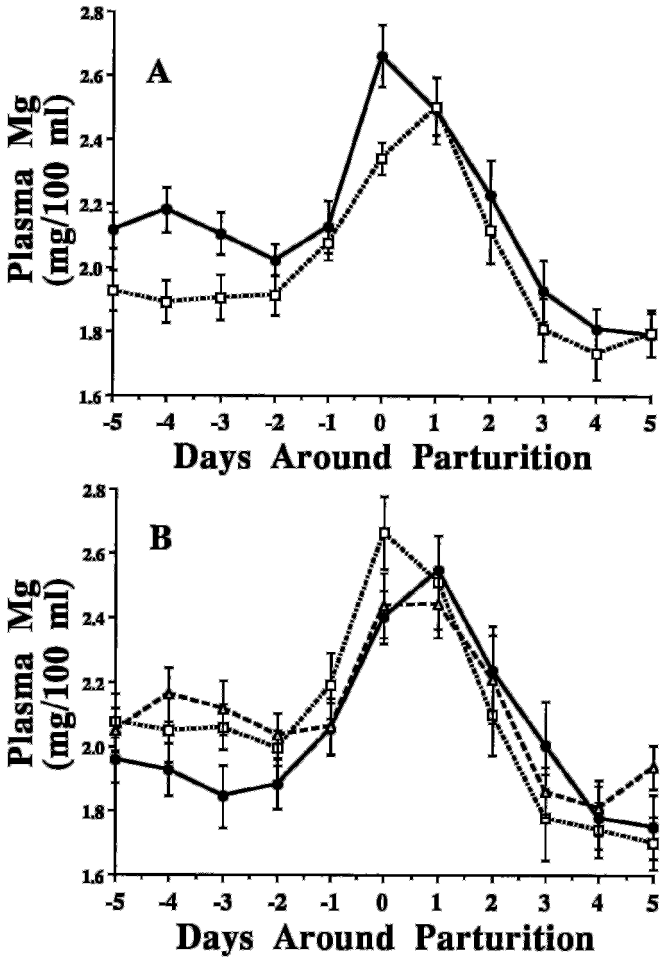

Figure 3. A. Profiles of plasma Mg concentration in cows fed a 0.5% (●) or 1.5% Ca (□) diet. B. Profiles of plasma Mg concentration in cows fed a 1.1% (●), 2.1% (□), or 3.1% (△) K diet prior to calving. Bars represent standard error of the means.

Effects of Dietary Na

Five of 8 cows fed the diet that was high in Ca and Na developed clinical milk fever, a significantly higher number than that for cows fed the diet that was high in Ca and low in K (2 of 10 cows). Eleven i.v. Ca treatments were administered to treat recumbency and paresis in the 8 cows fed the diet that was high in Ca and Na compared with two treatments for the 10 cows fed the diet that was high in Ca and low in K. In cows fed the diet that was high in Ca and Na, profiles of plasma Ca and P exhibited a significant decline at calving, and plasma PTH, $1,25(OH)_2D$, and Mg increased significantly at calving. The decline in plasma Ca at calving of cows fed the diet that was high in Ca and Na was significantly greater than that of cows fed the diet that was high in Ca and low in K (Figure 8; $P < 0.001$). The plasma Ca nadir of cows fed the diet that was high in Ca and Na was significantly lower than that of cows fed the diet that was high in Ca and low in Na and K (4.78 ± 0.44 vs. 6.81 ± 0.27 mg/100 ml).

Concentrations of plasma PTH were significantly higher in the cows fed the diet that was high in Na

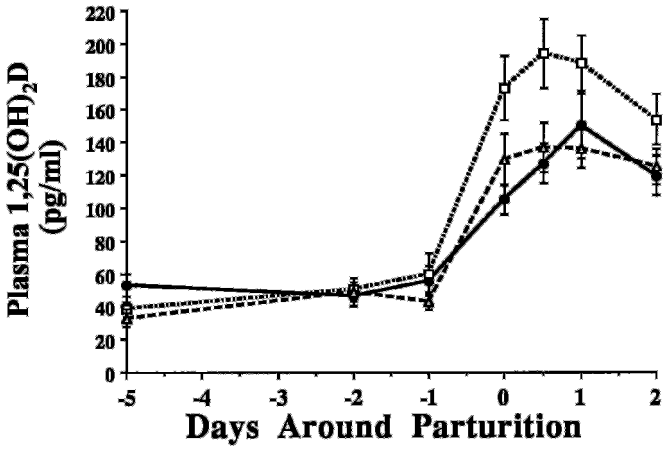

Figure 5. Profile of plasma 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] in cows fed a 1.1% (●), 2.1% (□), or 3.1% (△) K diet prior to calving. Bars represent standard errors of the means.

and Ca and low in K (high Na) than those in the cows fed the diet that was low in Na and K and high in Ca on the day of calving (Figure 8). Profiles of plasma 1,25$(OH)_2$D concentration were similar for cows fed the high Na and low Na diets, although concentrations of plasma 1,25$(OH)_2$D 24 h after calving tended to be higher in cows fed the low Na diet (Figure 8). Concentrations of plasma hydroxyproline were significantly greater in cows fed the low Na diet prior to calving than in cows fed the high Na diet (Figure 8).

Urine pH prior to calving of cows fed the high Na diet was higher than that of cows fed the low Na diet (8.26 ± 0.02 vs. 5.70 ± 0.09; $P < 0.01$). Blood pH (7.419 ± 0.010) and blood HCO_3 (27.8 ± 0.76 meq/L) were higher ($P < 0.05$) in cows fed the high Na diet than in cows fed the low Na diet (pH = 7.360 ± 0.020 and HCO_3 = 23.6 ± 1.0 meq/L).

DISCUSSION

Anecdotal evidence implicating the high cation-anion difference of prepartum rations as an important factor in the etiology of milk fever has also suggested that the high dietary K content of forages such as alfalfa is more important than the Ca content of the forages in predisposing cows to milk fever (2, 28). In this experiment, the incidence of milk fever was increased simply by increasing the K concentration in the prepartum diet from 1.1 to 2.1%. Within the groups fed the 0.5% Ca diet, the incidence of milk fever was 0% in cows fed the 1.1% K diet, 36% in cows fed the 2.1% K diet, and 80% in cows fed the 3.1% K diet. However, increasing dietary K from 2.1 to 3.1% at the 1.5% Ca concentration resulted in a lowered incidence of milk fever. We are unable to explain why cows fed the diet that was highest in Ca and K had a relatively low incidence of milk fever, although these results would argue against increased dietary Ca as a cause of milk fever.

Addition of Na to a basal diet that was low in K and Na also induced milk fever, corroborating the observations of Dishington (7). A major physiologic effect of the additional dietary Na was an increase in alkalinity of the blood and urine; the addition of K to the basal diet had a similar effect. The strong ion difference theory of acid-base balance as proposed by Stewart (40) suggests that $NaHCO_3$ and $KHCO_3$ bicarbonate would be equally able to alkalinize the blood of the cow because both Na and K are absorbed with nearly 100% efficiency from the diet. Calcium and Mg are also strong cations that might be able to alkalinize the blood if provided in the diet in the carbonate form rather than as chloride or sulfate salts. However, because Ca and Mg are absorbed from the diet with about 38 and 28% efficiency, respectively (27), they would have to be present in large amounts to alter blood pH significantly.

There is growing evidence that suggests that diets with a highly positive cation-anion difference cause a state of metabolic alkalosis in cows, reducing the responsiveness of bone and kidney to PTH (10, 12, 34). Perhaps one reason we did not see an increase in the incidence of milk fever when dietary K increased from 2.1 to 3.1% was because at both of these dietary K concentrations urine and blood pH indicated that the cows were in an alkaline state. When fed 1.1% dietary K, the cows were in a state of mild metabolic acidosis. Plasma hydroxyproline concentration, which

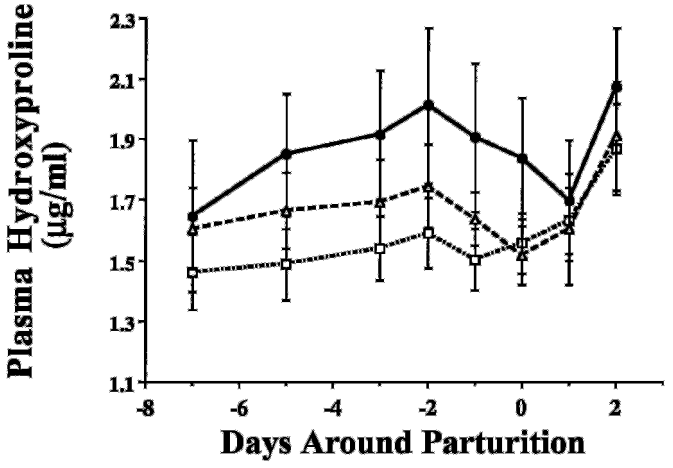

Figure 6. Profile of plasma hydroxyproline in cows fed a 1.1% (●), 2.1% (□), or 3.1% (△) K diet prior to calving. Bars represent standard errors of the means.

can be used as an index of the activity of bone osteoclasts, was highest in the cows in metabolic acidosis. Because PTH is the major factor that controls bone osteoclast activity and because blood PTH concentrations were highest in the cows fed the alkalinizing diets, cows fed the high K or high Na diets should have had greater concentrations of plasma hydroxyproline at calving than cows fed the diet that was low in K and Na. However, these cows did not have greater concentrations of plasma hydroxyproline, suggesting that the bones of the cows consuming the high K or high Na diets were refractory to PTH stimulation, which has been a consistent finding in most studies of the mode of action of anionic diets (4, 12). Renal production of $1,25(OH)_2D$ is also under the control of PTH. Because concentrations of PTH were higher in cows fed the high K or high Na diets, the production of $1,25(OH)_2D$ might be expected to be highest in cows fed these diets. In this study, cows fed the 2.1% K diet exhibited a larger increase in plasma $1,25(OH)_2D$ than did cows fed the 1.1% K diet, as expected. However, cows fed the 3.1% K diet or the high Na diet had plasma $1,25(OH)_2D$ concentrations that were similar to those in cows fed the 1.1% K diet, suggesting impaired production of $1,25(OH)_2D$ in cows fed the 3.1% K and high Na diets. Earlier studies have demonstrated that renal production of $1,25(OH)_2D$ in response to PTH is significantly impaired in cows fed high cation diets (12, 34).

Urinary Ca losses are greatly increased in cows fed diets with a low cation-anion difference. This urinary Ca loss can be as much as 2 to 6 g of Ca higher than that in cows fed a high cation diet (10, 42). This Ca is capable of being reabsorbed by the kidney of the periparturient cow under the influence of PTH, which might partially explain the resistance to milk fever of cows fed the high anion diets (38).

High K diets interfere with ruminal absorption of Mg, which can be a major cause of hypomagnesemia (25). Hypomagnesemia can interfere with PTH secretion (24) and the responsiveness of tissue to PTH (36) and can cause hypocalcemia in the periparturient cow (32). In this study, concentration of plasma Mg increased at calving regardless of dietary K (probably as a result of enhanced renal Mg reabsorption, which was a result of PTH stimulation). This increase suggests that a reduction in Mg absorption was not a major factor in the increased incidence of milk fever that was seen in cows fed the high K diets.

High K diets might interfere with ruminal absorption of Ca, which might increase the risk of milk fever. However, this interference is unlikely to be a major factor because, despite evidence that high Na concentrations in the rumen enhance ruminal Ca absorption (16), high Na diets increased the risk of milk fever as much as did high K diets.

As in earlier studies (12, 17, 29), urine pH proved an easy and sensitive means of monitoring the acid-base status of cows shortly before calving. Urine pH has the advantage of being more stable and less expensive than blood gas and pH analysis. Urine pH may also prove more sensitive than blood pH, because blood pH was unable to distinguish between cows fed the 2.1 and 3.1% K diets.

Feed intake prior to calving was lowest in those cows fed the diet with the negative cation-anion difference. Other studies (37) have also shown that feed intake is increased with increased cation content in the ration. Adding K to the diet improved prepartum feed intake. Because all of the diets had the same high chloride and high sulfate concentrations, the adverse effect on feed intake in this experiment was related more to the low cation-anion difference (and perhaps the metabolic acidosis induced) than simply the presence of high chloride and sulfate. After calving, all cows were fed the diet containing 1.5% Ca and 3.1% K. During the first 10 d after calving, cows fed the low K diet (and a low cation-anion difference) prepartum had higher feed intake than did cows fed the higher K diets prepartum. Hypocalcemia and milk fever likely decreased postpartum feed intake in cows fed the higher K diets prepartum. Plasma NEFA concentrations (data not shown) were not significantly affected by dietary K, suggesting that the

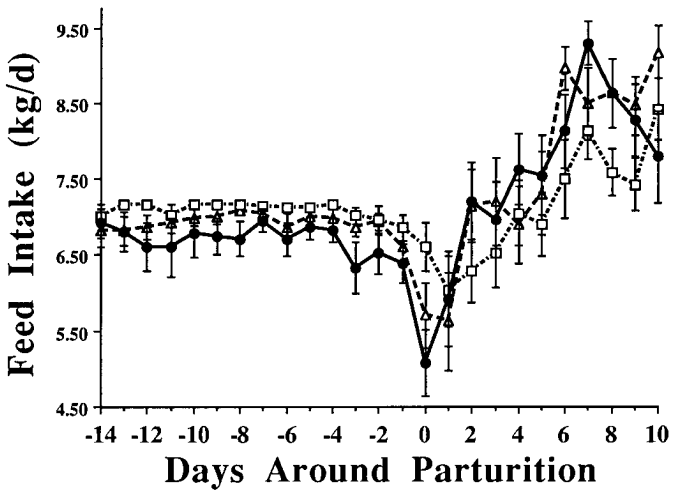

Figure 7. Feed intake of cows fed a 1.1% (●), 2.1% (□), or 3.1% (△) K diet prior to calving. Bars represent standard errors of the means.

reduction in feed intake prior to calving in cows fed the low K diet was not deleterious to energy balance, that the increase in feed intake after calving in cows fed the low K diet made up for the deficiency in feed intake prior to calving, or both.

Cows fed a very low Ca diet (<20 g of Ca/d) prior to calving cannot meet Ca requirements for maintenance and fetal skeletal development from the diet. As a result, these cows are in negative Ca balance, stimulating secretion of PTH prior to calving. The secretion of PTH activates bone osteoclasts, stimulating bone Ca resorption, and activates renal tubules to resorb urinary Ca and to begin producing $1,25(OH)_2D$ prior to calving. Thus, at the onset of lactation, these Ca homeostatic mechanisms are active, preventing a severe decline in plasma Ca concentration in the cow. The experiments demonstrating the prophylactic effect of very low Ca diets contrasted the incidence of milk fever occurring in cows fed diets containing <20 g of Ca/d with the incidence of milk fever occurring in cows fed diets that had $CaCO_3$ added to raise dietary Ca to between 80 and 120 g of Ca/d, which was well above the requirement of the cow (14, 15, 22). Based on these experimental observations, it was routinely recommended that dietary Ca be kept as low as possible in the prepartum diet, and, despite the fact that it was generally possible to limit dietary Ca to only about 50 g/d, this strategy was often a successful means to prevent milk fever (5, 20). To achieve these reduced Ca diets required that high Ca forages, such as alfalfa, be removed from the ration and replaced with low Ca forages, such as corn silage or grass hays. In hindsight, this strategy also greatly reduced dietary K, because alfalfa is often 2.5 to 4% K and corn silage is generally <1.7% K. Traditionally, grass hays were not fertilized, which generally kept their K content <2.5%, although more recently, common agronomic practice is to fertilize (spread manure on) grass, allowing more accumulation of K. Our data suggested that the success of the

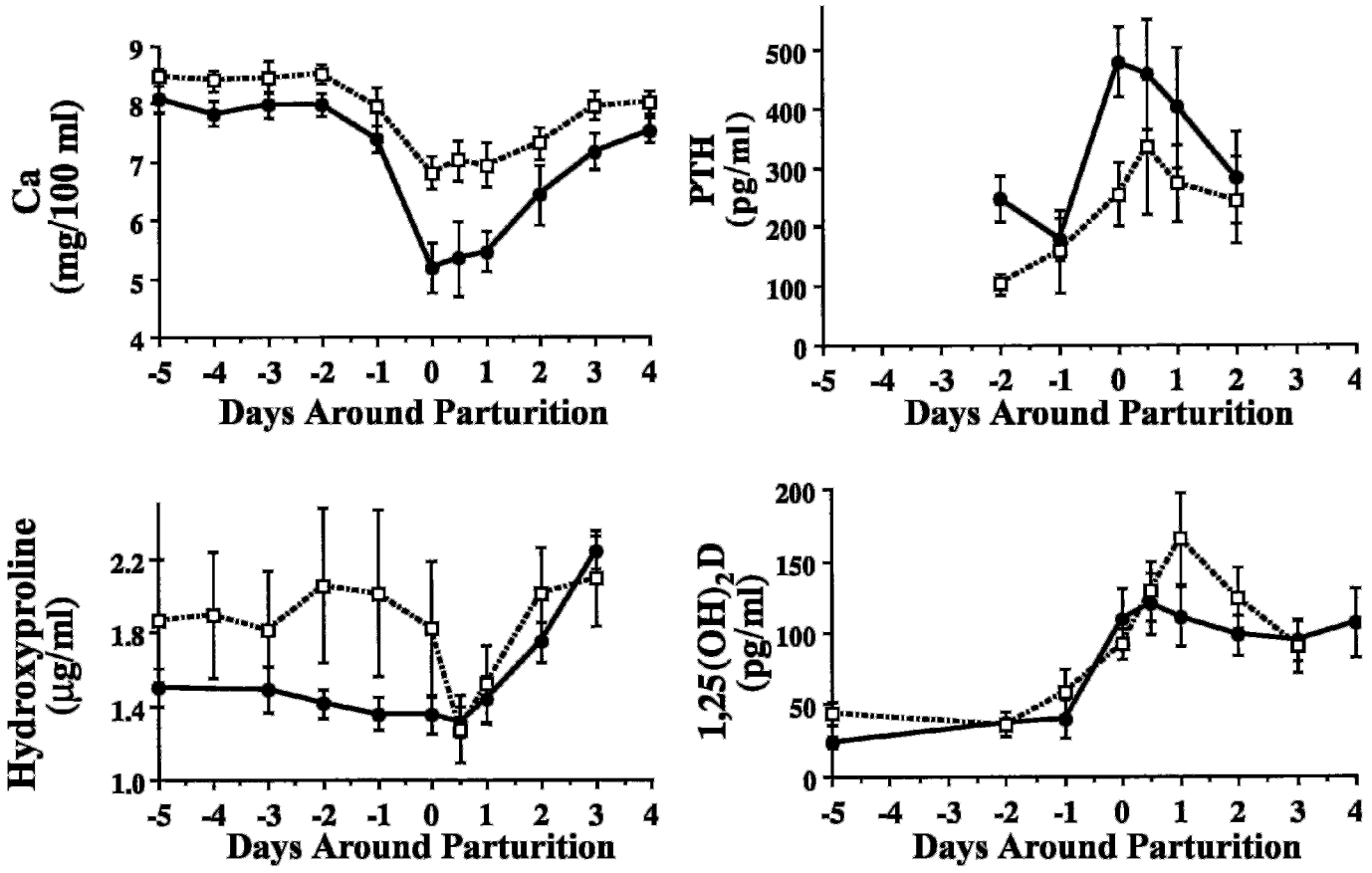

Figure 8. Plasma Ca, parathyroid hormone (PTH), hydroxyproline, and 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] concentrations in cows fed a diet that was high in Na and Ca and low in K (●) and in cows fed a diet that was low in Na and K and high in Ca (□). Bars represent standard errors of the means.

low Ca diets formulated in the field was primarily due to a reduction in dietary K, not Ca (because Ca could not be reduced to concentrations below the requirements of the cow). These data demonstrate that the most constructive step that can be taken to prevent milk fever is to reduce the dietary K content of the prepartum diet.

ACKNOWLEDGMENTS

The authors thank Ken Cummings (Church and Dwight Co., Inc., Princeton, NJ), who kindly supplied the $KHCO_3$ for the cattle diets. We also thank Norm Tjelmeland, Creig Caruth, and C. Eugene Rieks for their diligent care of the cows; Cynthia Hauber, Amy Peyton, K. C. Hummel, and Douglas Mashek for their technical assistance in completion of these studies; and Kathleen Kelderman for preparation of the manuscript.

REFERENCES

1 Abu Damir, H., M. Phillippo, B. H. Thorp, J. S. Milne, L. Dick, and I. M. Nevison. 1994. Effects of dietary acidity on calcium balance and mobilization, bone morphology and 1,25 dihydroxyvitamin D in prepartal dairy cows. Res. Vet. Sci. 56:310.
2 Beede, D. K. 1992. Dietary cation-anion difference: preventing milk fever. Feed Management 43:28.
3 Beitz, D. C., D. J. Burkhart, and N. L. Jacobson. 1974. Effects of calcium to phosphorus ratio in the diet of dairy cows on incidence of parturient paresis. J. Dairy Sci. 57:49.
4 Block, E. 1984. Manipulating dietary anions and cations for prepartum dairy cows to reduce incidence of milk fever. J. Dairy Sci. 67:2939.
5 Boda, J. M., and H. H. Cole. 1954. The influence of dietary calcium and phosphorus on the incidence of milk fever in dairy cattle. J. Dairy Sci. 37:360.
6 Dabev, D., and H. Struck. 1971. Microliter determination of free hydroxyproline in blood serum. Biochem. Med. 5:17.
7 Dishington, I. W. 1975. Prevention of milk fever (hypocalcemic paresis puerperalis) by dietary salt supplements. Acta Vet. Scand. 16:503.
8 Ender, F., I. W. Dishington, and A. Helgebostad. 1971. Calcium balance studies in dairy cows under experimental induction and prevention of hypocalcaemic paresis puerperalis. The solution of the aetiology and the prevention of milk fever by dietary means. Z. Tierphysiol. 28:233.
9 Gardner, R. W., and R. L. Park. 1972. Effects of prepartum energy intake and calcium to phosphorus ratios on lactation response and parturient paresis. J. Dairy Sci. 56:385.
10 Gaynor, P. J., F. J. Mueller, J. K. Miller, N. Ramsey, J. P. Goff, and R. L. Horst. 1989. Parturient hypocalcemia in Jersey cows fed alfalfa haylage-based diets with different cation to anion ratios. J. Dairy Sci. 72:2525.
11 Goff, J. P. 1992. Cation-anion difference of diets and its influence on milk fever and subsequent lactation: the good and the bad news. Cornell Nutr. Conf. Feed Manuf., Rochester, NY. Cornell Univ., Ithaca, NY.
12 Goff, J. P., R. L. Horst, F. J. Mueller, J. K. Miller, G. A. Kiess, and H. H. Dowlen. 1991. Addition of chloride to a prepartal diet high in cations increases 1,25-dihydroxyvitamin D response to hypocalcemia preventing milk fever. J. Dairy Sci. 74:3863.
13 Goff, J. P., T. A. Reinhardt, and R. L. Horst. 1989. Recurring hypocalcemia of bovine parturient paresis is associated with failure to produce 1,25-dihydroxyvitamin D. Endocrinology 125: 49.
14 Goings, R. L., N. L. Jacobson, D. C. Beitz, E. T. Littledike, and K. D. Wiggers. 1974. Prevention of parturient paresis by a prepartum, calcium-deficient diet. J. Dairy Sci. 57:1184.
15 Green, H. B., R. L. Horst, D. C. Beitz, and E. T. Littledike. 1981. Vitamin D metabolites in plasma of cows fed a prepartum low-calcium diet for prevention of parturient hypocalcemia. J. Dairy Sci. 64:217.
16 Holler, H., G. Breves, M. Kocabatmaz, and H. Gerdes. 1988. Flux of calcium across the sheep rumen wall in vivo and in vitro. Q. J. Exp. Physiol. 73:609.
17 Jardon, P. W. 1995. Using urine pH to monitor anionic salt programs. Compend. Cont. Educ. Pract. Vet. 17:860.
18 Johnson, M. M., and J. P. Peters. 1993. Technical note: an improved method to quantify non-esterified fatty acids in bovine plasma. J. Anim. Sci. 71:753.
19 Jonsson, G., B. Pehrson, K. Lundstrom, L. E. Edqvist, and J. W. Blum. 1980. Studies on the effect of the amount of calcium in the prepartum diet on blood levels of calcium, magnesium, inorganic phosphorus, parathyroid hormone and hydroxyproline in milk fever prone cows. Zentralbl. Veterinaermed. Reihe A 27:173.
20 Jorgensen, N. A. 1974. Combating milk fever. J. Dairy Sci. 57: 933.
21 Julien, W. E., H. R. Conrad., J. W. Hibbs, and W. L. Crist. 1977. Milk fever in dairy cows. VIII. Effect of injected vitamin D_3 on calcium and phosphorus intake on incidence. J. Dairy Sci. 60: 431.
22 Kichura, T. S., R. L. Horst, D. C. Beitz, and E. T. Littledike. 1982. Relationships between prepartal dietary calcium and phosphorus, vitamin D metabolism, and parturient paresis in dairy cows. J. Nutr. 112:480.
23 LeClerc, H., and E. Block. 1989. Effects of reducing dietary cation-anion balance for prepartum dairy cows with specific reference to hypocalcemic parturient paresis. Can. J. Anim. Sci. 69:411.
24 Littledike, E. T., J. A. Studemann, S. R. Wilkinson, and R. L. Horst. 1983. Grass tetany syndrome. Page 173 *in* Role of Magnesium in Animal Nutrition. J. P. Fontenot, G. E. Bunce, K. E. Webb, and V. G. Allen, ed. Virginia Polytechnic Inst. State Univ., Blacksburg, VA.
25 Martens, H., and Y. Rayssiguier. 1980. Magnesium metabolism and hypomagnesemia. Page 447 *in* Digestive Physiology and Metabolism in Ruminants. Y. T. Ruckebusch, ed. MTP Press Ltd., Lancaster, England.
26 Martig, J., and G. P. Mayer. 1973. Diminished hypercalcemic response to parathyroid extract in prepartum cows. J. Dairy Sci. 56:1042.
27 National Research Council. 1989. Nutrient Requirements of Dairy Cattle. 6th rev. ed. Natl. Acad. Sci., Washington, DC.
28 Oetzel, G. R. 1991. Meta-analysis of nutritional risk factors for milk fever in dairy cattle. J. Dairy Sci. 74:3900.
29 Oetzel, G. R., M. J. Fettman, D. W. Hamar, and J. D. Olson. 1991. Screening of anionic salts for palatability: effects on acid-base status and urinary calcium excretion in dairy cows. J. Dairy Sci. 74:965.
30 Oetzel, G. R., J. D. Olson, C. R. Curtis, and M. J. Fettman. 1988. Ammonium chloride and ammonium sulfate for prevention of parturient paresis in dairy cows. J. Dairy Sci. 71:3302.
31 Parekh, A. C., and D. H. Jung. 1970. Serum inorganic phosphorus determination using p-phenylenediamine as a reducing agent. Clin. Chim. Acta 27:373.
32 Payne, J. M., G. J. Rowlands, R. Manston, and S. M. Dew. 1973. A statistical appraisal of the results of metabolic profile tests on 75 dairy herds. Br. Vet. J. 129:370.
33 Perkin-Elmer Corp. 1965. Analytical Methods for Atomic Absorption Spectrophotometry. Perkin-Elmer Corp., Norwalk, CT.
34 Phillippo, M., G. W. Reid, and I. M. Nevison. 1994. Parturient hypocalcaemia in dairy cows: effects of dietary acidity on plasma minerals and calciotropic hormones. Res. Vet. Sci. 56: 303.

35 Reinhardt, T. A., R. L. Horst, J. W. Orf, and B. W. Hollis. 1984. A microassay for 1,25-dihydroxyvitamin D not requiring high performance liquid chromatography: application to clinical studies. J. Clin. Endocrinol. Metab. 58:91.
36 Rude, R. K., J. S. Adams, E. Ryzen, D. B. Endres, H. Niimi, R. L. Horst, J. G. Haddad, Jr., and F. R. Singer. 1985. Low serum concentrations of 1,25-dihydroxyvitamin D in human magnesium deficiency. J. Clin. Endocrinol. Metab. 61:933.
37 Sanchez, W. K., D. K. Beede, and J. A. Cornell. 1994. Interactions of sodium, potassium, and chloride on lactation, acid-base status, and mineral concentrations. J. Dairy Sci. 77:1661.
38 Schonewille, J. T., A. T. van't Klooster, and A. C. Beynen. 1995. Urinary calcium losses in cows fed on a high-chloride ration are reduced when plasma calcium is stressed. Page 23 *in* Proc. 9th Int. Conf. Prod. Diseases Farm Anim., Freie Univ. Berlin, Berlin, Germany.
39 Shappell, N. W., M. H. Herbein, L. J. Deftos, and R. J. Aiello. 1987. Effects of dietary calcium and age on parathyroid hormone, calcitonin and serum and milk minerals in the periparturient dairy cow. J. Nutr. 117:201.
40 Stewart, P. A. 1983. Modern quantitative acid-base chemistry. Can. J. Physiol. Pharmacol. 61:1444.
41 Stott, G. H. 1968. Dietary influence on the incidence of parturient paresis. Fed. Proc. 27:156.
42 van Mosel, M., A. T. van't Klooster, F. van Mosel, and J. van der Kuilen. 1991. The effects of reducing dietary cation-anion balance on the rate of calcium mobilization by dairy cows at parturition. Page 65 *in* Research on the Mineral Supply of Dairy Cows During the Dry Period in Relation to Prevention of Milk Fever. M. V. Mosel, ed. N. V. Staatsdrukkerij & uitgeverij-Gravenhage, Utrecht, The Netherlands.