The Treatment and Prophylaxis of Bovine Parturient Paresis (Milk Fever)

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It is well documented that the amelioration of hypocalcaemia is the most essential component in the treatment of parturient paresis (P.P.) in the bovine. Results are, however, not clear as to the possible value in also correcting the accompanying hypophosphataemia. Other unresolved problems concern the optimal route of administration and the prophylaxis of the disorder.

In several countries such as the United States of America, Great Britain and Israel, phosphorus is added to the standard solution of calcium in the form of calcium or magnesium hypophosphite ($Ca(H_2PO_2)_2$. In Germany it is often added in the form of an organic salt such as 1-(n-butylamino)-1-methyl-phosphorous acid which is claimed to have a "tonic" effect.

In 1916 Mariot (1) showed that hypophosphite was rapidly eliminated through the kidneys without any significant modification. Delaine (2) concluded that only a trace of injected hypophosphite undergoes oxidation to orthophosphate (PO_4) in the body. Milks (3) confirmed these findings and concluded that the hypophosphites are without any value as a source of phosphate in the body.

Experiment 1.
The Efficacy of Calcium Hypophosphite in Raising Plasma Calcium and Inorganic Levels in the Blood of Normal Dairy Cows.

Materials and Methods

Six cows, 2-7 years old, four of which were dry and two in full lactation, received an intravenous (jugular vein) dose of Calciphos. This material contains 30 g calcium gluconate, 31 g calcium hypophosphite and 8 g boric acid in 500 ml water and supplies 9.6 g of calcium and 11.3 g of phosphorus.

Three lactating cows received a solution of calcium borogluconate supplying 9.6 g of calcium in 525 ml of sterile water intravenously into the jugular vein of one side of the neck and a buffered solution of sodium monophosphate and diphosphate supplying 5 g of phosphorus into the jugular vein of the other side. This solution supplied half the dose of phosphorus of Calciphos.

Two lactating cows received the phosphate solution as above without any calcium treatment. Blood samples were taken at various time intervals into heparinized vacuum tubes up to 295 minutes post-injection and processed for calcium and inorganic phosphorus estimation.

Results

The results are presented in Fig. 1.

Plasma calcium levels rose after the injection of either Calciphos or calcium borogluconate and sodium phosphate. When only phosphate was injected, the calcium level fell slightly.

Plasma inorganic phosphate increased significantly ($p<0.05$) following the injection of the orthophosphate given either with calcium or without calcium.

When hypophosphite was injected, the effect on plasma inorganic phosphate was insignificant.

Phosphorus is found in the body mainly as orthophosphate, although traces of condensed phosphate can be found. The body cannot "recognize" hypophosphite and put it to any physiological use despite its phosphorus content. Furthermore, its inability to raise the inorganic phosphate concentration in plasma suggests that its oxidation in the body is insignificant. Our results show that there is no justification in using a hypophosphite compound as a source of phosphorus (4,5).

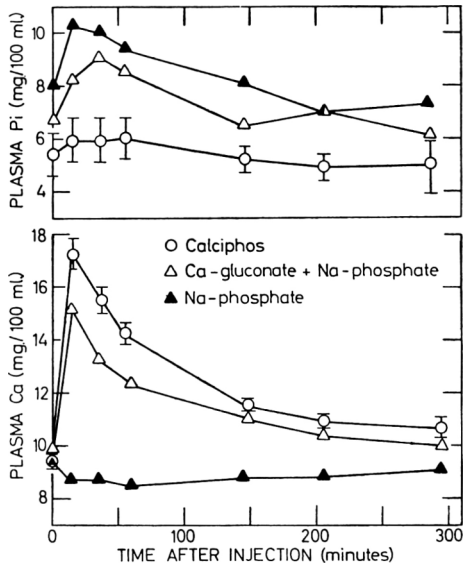

Figure 1. The response of plasma calcium (lower diagram) and inorganic phosphate (upper diagram) in cows given an intravenous injection of Calciphos, calcium borogluconate and sodium phosphate, and sodium phosphate only.

Experiment 2.
Treatment of Bovine Parturient Paresis: Is Phosphate Needed?

The purpose of this trial was to prepare an injectable solution containing both calcium and orthophosphate, to test its efficacy in raising plasma calcium and inorganic phosphate levels, and to compare its efficiency in the treatment of parturient paresis with that of a preparation supplying calcium without any phosphate.

Experiment 2a. Materials and Methods

A solution of calcium glycerophosphate was prepared in the laboratory of the Agricultural Research Organisation, Institute of Animal Science, The Volcani Centre, Rechovoth. Two cows, one dry and one in lactation, each received a dose of the above solution supplying 6.25 g of calcium and 4.8 g of phosphorus. The material was injected intravenously into the jugular vein and blood samples were collected until 360 minutes post-injection.

Results

The results are presented in Fig. 2 and compared to a parallel experiment described in Trial 3 in which 9.6 g of calcium in the form of a 25% solution of calcium borogluconate was given intravenously to a group of normal cows.

The more distinct response of plasma calcium in the calcium borogluconate group compared with the animals receiving calcium glycerophosphate is the result of the larger amount of calcium supplied by the former preparation. The ensuing decline in plasma calcium concentration was parallel in both groups of cows.

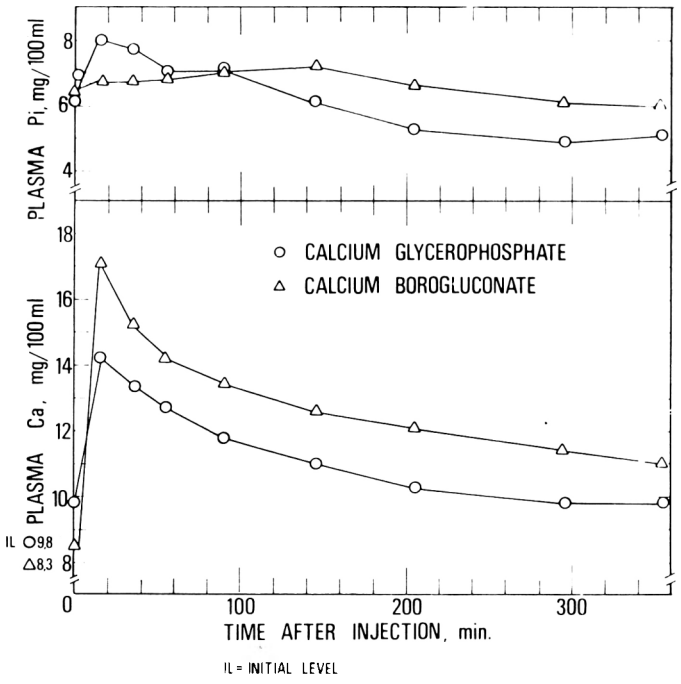

Figure 2. The response of plasma calcium (lower graph) and plasma inorganic phosphate (upper graph) of normal cows treated with either calcium borogluconate (△) or calcium glycerophosphate (○).

Only slight changes in plasma inorganic phosphate levels were elicited by calcium borogluconate; plasma phosphate concentrations hardly changed for two hours after administration. On the other hand, administration of calcium glycerophosphate resulted in a rise of 2 mg Pi/dl plasma 15 min. after administration, a rise of 30%. A rapid decrease followed this peak value. In both groups plasma phosphate levels gradually decreased from 2-6 hours p.i. to levels lower by about 1 mg/dl than the initial values. The decline was parallel in both groups.

Experiment 2b. Materials and Methods

The purpose of this trial was to test calcium borogluconate and calcium glycerophosphate in the treatment of parturient paresis.

The experiment involved six cows. They were used alternately for the two treatments, in order to avoid the influence of time and season in the response of the cows to these two treatments.

Three cows received 9.6 g of calcium in 525 ml of a 25% solution of calcium borogluconate, and three cows received calcium glycerophosphate in 600 ml. The dose supplied to different cows ranged between 7.4 - 10.0 g of calcium and 3.6 - 5.4 g of phosphorus per injection.

During the experiment, blood samples were taken for plasma calcium and inorganic phosphate determination. The clinical observations included measurements of heart rate, borborygmi, ruminal movements, defecation and rectal temperature.

A summary of the initial condition of the cows is given in Table 1, together with their age and weight. The cows treated with calcium borogluconate were somewhat older than those of the calcium glycerophosphate group, but were of similar body weight and all belonged to the Israeli Friesian breed. Both plasma calcium and inorganic phosphate levels were extremely low. Their heart rate was somewhat above normal. Typically, parameters associated with the functioning of the gastrointestinal tract, i.e., borborygmi, ruminal movements and defecation, were absent in most of the cows. The general state varied between paraplegic and comatose.

The solutions were injected slowly (7-10 min.) into the jugular vein. Blood samples were taken at various time intervals (first samples before injection and then 15, 35, 55, 90, 145, 205, 295, 355, 415, 475, 535, 595 minutes and at 24, 48 and 96 hours after treatment) into heparinised vacutainer tubes which were then processed.

Results

Haematological results are presented in Fig. 3 and clinical ones in Tables 2 and 3. In both groups there was an initial marked elevation in the plasma calcium levels in proportion to the dose of calcium given. This peak was followed by a decrease, with a leveling off at concentrations above 6 mg/dl. In no case did the plasma calcium values fall to the pre-treatment levels. Approximately 24-48 hours after injection plasma calcium concentrations returned to

Table 1
Initial Clinical Condition of Six Parturient Paretic Cows Used in Trial 2B

Assigned treatment	*Calcium borogluconate*			*Calcium glycerophosphate*		
Name of cow	Eilata	Ahuva	Lapida	Delila	Mimosa	Herda
	▲	□	○	△	■	●
Age, years	7	8	9	5	5	7
Body weight, kg	550	600	625	550	650	580
Plasma Ca, mg/100 ml	3.6	3.6	3.9	3.9	3.3	4.2
Plasma Pi, mg/100 ml	0.8	1.3	0.9	2.2	1.6	1.1
Heart rate, per minute	76	inaudible	88	88	76	96
Borborygmi	none	none	none	weak	none	none
Ruminal movements	none	none	none	none	none	none
Defecation	none	none	none	none	none	none
Rectal temperature, °C	37.8	37.2	37.8	38.5	37.2	38.0
General state	Comatose	Comatose	Unsteady	Paraplegic	Paraplegic	Paraplegic

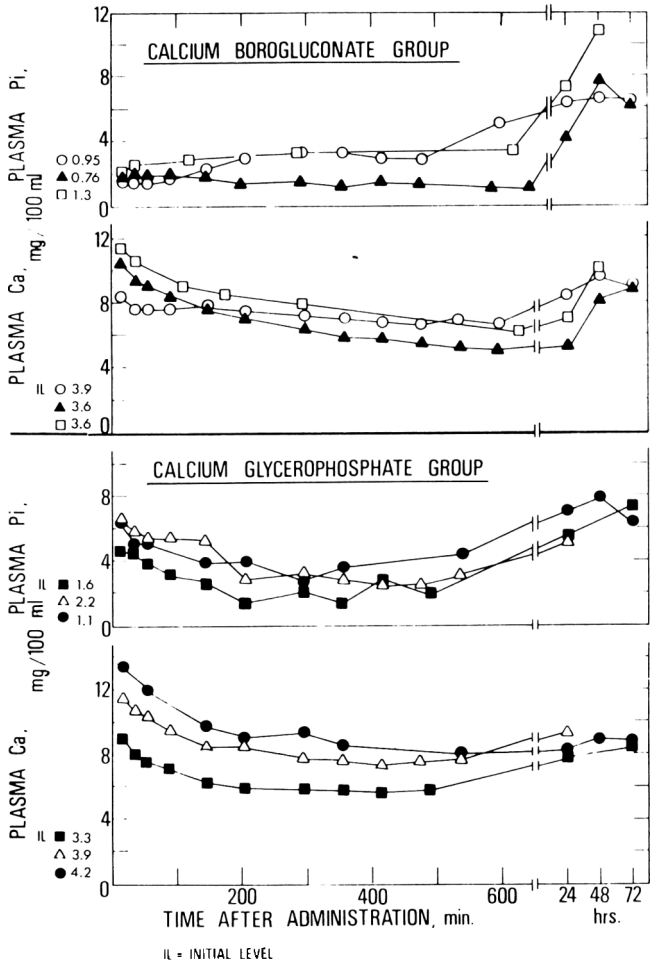

Figure 3. The response of plasma calcium and inorganic phsophate in cows with parturient paresis given either calcium borogluconate (upper two graphs) or calcium glycerophosphate (lower two graphs).

Table 2
Recovery Time (in minutes) of Selected Physiological Functions in PP Cows After Administration of Calcium-Containing Preparations.

Calcium borogluconate group				
Name of Cow	Borborygmi	Rumenal Movement	Defecation	Rising
Eilata	20	205 minutes	17	17
Ahuva	10	10 minutes	4	27
Lapida	3	67 minutes	17	17
Average	11	94 minutes	13	20
Calcium glycerophosphate group				
Delila	10	35 minutes	10	63
Mimosa	3	3 minutes	3	57
Herda	10	145 minutes	10	40
Average	8	61 minutes	8	53

normal (8-10 mg/dl) irrespective of the type of treatment.

The administration of calcium borogluconate resulted in only slight changes in plasma inorganic phosphate values. On the other hand, calcium glycerophosphate administration resulted in an increase of about 4 mg/dl and was dose dependent.

Boroborygmi and defecation occurred within 15 minutes after treatment in both groups. Ruminal movements were heard at various intervals after administration, in most cases within 1-1½ hours after treatment. All cows rose within one hour after treatment. Comparisons of the two groups suggests that in the glycerophosphate group the gastrointestinal functions recovered more rapidly, but the cows in the calcium borogluconate group could stand earlier. However, variations of the various criteria within each group are too distinct to permit an accurate comparison between the two treatments; both appeared to be effective in relieving the clinical symptoms of P.P.

Cardiac arrythmia was observed in most cows immediately after calcium administration. Arrythmia also occurred in one case several hours after therapy. There appears to be no difference in the occurrence of cardiac arrythmia between the two groups of cows.

Table 3. Occurrence of Cardiac Arrhythmia Following Administration of Either Calcium Borogluconate or Calcium Glycerophosphate to Cows With Parturient Paresis

Calcium borogluconate group					
Time after administration, min.	0 - 5	6 - 30	31 - 60	61 - 135	136 - 415
Eilata	x	-	-	x	-
Ahuva	-	x	-	-	-
Lapida	x	-	-	-	-
Calcium glycerophosphate group					
Delila	-	x	x	x	-
Mimosa	x	-	-	-	x
Herda	x	-	-	-	-

x = time of cardiac disturbance

It appears that the temporary addition of an active phosphate into the circulation of paretic cows does not modify the beneficial effects produced by calcium. There is no justification for its use. According to some authorities it can even do harm by interfering with the efficient use of Vitamin D (6,7,8).

Experiment 3.
The Effect of the Administration of Calcium by Different Routes on the Plasma Calcium Levels of Normal Cows.

The route of administration and the optimal dosage of calcium required are still a matter of considerable controversy.

It has been suggested (9) that the intravenous administration of calcium causes an immediate rise in the level of that ion in the plasma, whereas an added subcutaneous dose of the same ion has a depot effect.

Workers in Holland (10,11) found that there was no difference in recovery and relapse rates between cows given 7.4 g calcium intravenously and those given an additional subcutaneous dose of the same amount.

The experiment was undertaken in order to determine the efficacy of raising plasma calcium by intravenous or subcutaneous doses of calcium borogluconate and by a combination of the two.

Materials and Methods

Group 1: Four cows aged 4-8 years, three being dry and one in medium milk production, received 9.6 g of calcium intravenously and an additional dose of 5.3 g calcium subcutaneously.

Group 2: Four cows, 4-8 years old as above, received 9.6 g of calcium only intravenously.

Group 3: Four cows, ages as above, received 9.6 g of calcium only subcutaneously.

Results

The results are presented as deviations from pre-injection values in Fig. 4. At 15 minutes post-injection (p.i.) the mean plasma calcium levels in groups 1 and 2 increased by 8-9 mg/dl above the initial values. The small difference between the groups was not significant. A rapid decrease followed in both groups. The fall was slower in group 1, which received a subcutaneous dose in addition to the intravenous one. The difference between the two groups was apparent after 90 minutes, reached a maximum at 275

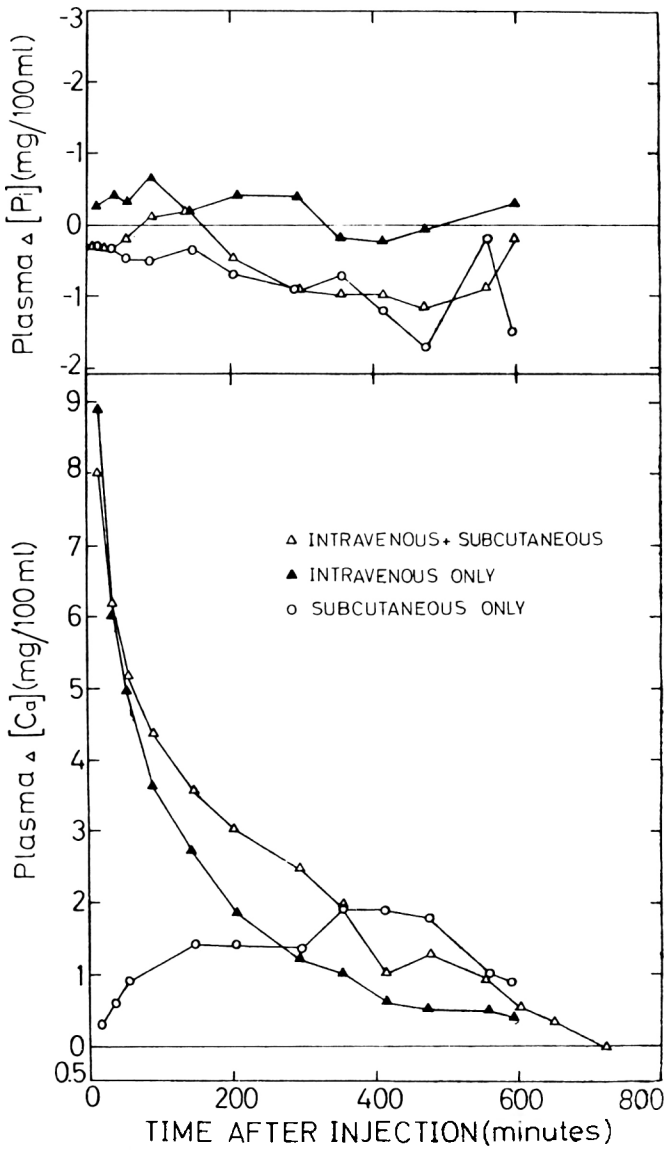

Figure 4. Changes from pre-injection levels of plasma calcium and inorganic phosphate in three groups of cows to which calcium was given by different routes.

minutes and completely disappeared after 600 minutes, when plasma calcium levels in both groups 1 and 2 approached the initial values. The additional subcutaneous dose of calcium had no true "depot" value.

In group 3 which received only a subcutaneous dose, the mean plasma calcium levels gradually increased to reach a peak 400 minutes p.i. They then declined to approach the initial value 600 minutes p.i. The maximum rise in plasma calcium concentration in this group was only 1.9 mg/dl.

Plasma inorganic phosphate was hardly influenced by the intravenous injection of calcium; in group 2 a slight rise was noted immediately after injection. On the other hand those animals which had received the added subcutaneous or only the subcutaneous dose of calcium displayed a decrease in phosphate concentration from 200-450 minutes p.i.

In most clinical cases of parturient paresis the response to the intravenous injection of calcium is a fairly rapid one. In our cases during the years 1973-mid 1975, out of 62 cases, 50 recovered within 60 minutes, 7 within 7 hours, 3 relapsed and 2 died from possible toxic effects of the calcium therapy (no plausible cause for death found on post-mortem). The immediate effect of calcium is seen in the correction of the calcium deficiency at the neuro-muscular synapse and in the muscle fibres. Relapses occur usually 8-10 hours after the initial attack. As the effect of the additional subcutaneous dose on plasma calcium becomes apparent only about 90 minutes p.i. and as it wanes 535 minutes p.i., the usefulness of the additional subcutaneous dose is limited. In view of the potentially dangerous effects of excess calcium both on the heart and on the regulatory mechanism (12), as well as suppressing the normal physiological mechanism of the cow, it is suggested that this practice be discontinued (13,14,15).

Prophylactic Treatment

It was recently shown that the active hormonal form of vitamin D_3 is 1,25 dihydroxycholecalciferol (1,25$(OH)_2$-CC) (16). The hydroxylation occurs in two steps: (1) via a hydroxylase system in the liver producing 25 hydroxycholecalciferol (25(OH)CC) and (2) in the kidney yielding 1,25$(OH)_2$-CC. The second hydroxylation step is regulated by the calcium and/or phosphorus concentration in the plasma or in the kidney itself, and is believed to be dependent on parathyroid activity. The form 1,25$(OH)_2$-CC was found to be rapid acting and to be the most potent metabolite in stimulating absorption of calcium by the gut and the mobilization of calcium from bone (17). The form 1a-hydroxycholecalciferol (1a (OH)CC) is an active synthetic analog of 1,25$(OH)_2$-CC. The biological action of 1a(OH)CC is independent of kidney hydroxylation and therefore is not regulated by most of the mentioned stimuli (18). The compound apparently becomes active following hydroxylation in the liver to 1,25$(OH)_2$-CC (19).

In the chicken and rat, 1a(OH)CC has an antirachitogenic action 3-6 times more active on a weight basis and acts 3 times faster in inducing calcium absorption in the small intestine than Vitamin D itself (10). It has also been used extensively in treating human renal osteodystrophic complications following glomerulonephritis (21). It was decided to evaluate its prophylactic efficacy.

Varying doses of 1a-(OH)CC (50; 150; 250 and 350 micrograms) in propylene glycol were injected intramuscularly into dry adult Friesian Israeli cows (groups of 3 cows each).

Results

The results are presented in Fig. 5. Plasma calcium rose after 24 hours (0.5-1.0 mg/dl) at all dose levels except 50 microgram; a dose-dependent peak was reached at 3-4 days (0.9-2.5 mg/dl) with a return to base line 5-10 days after injection.

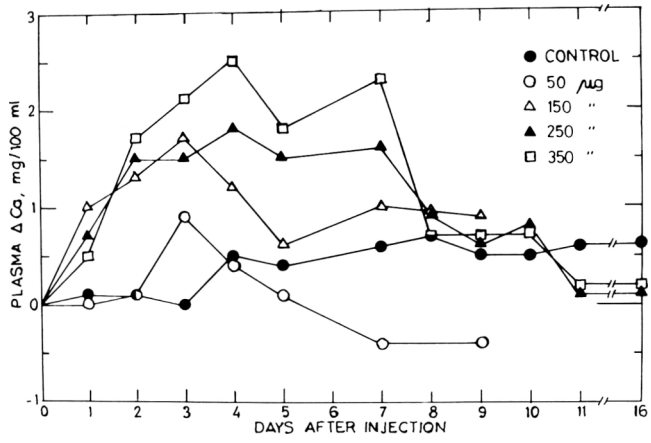

Figure 5. Plasma calcium of dry cows as influenced by a single intramuscular injection of varying doses of 1a-(OH)CC.

Field Trials

Several field trials were undertaken to test the efficacy of the compound in preventing P.P.

Trial 1.

350 micrograms of 1a-(OH)CC in propylene glycol was injected intramuscularly into 23 milk fever-prone cows of the same breed as above, 7 days to 6 hours pre-partum. Thirteen cows were injected once, six twice, and four three times at 48-hour intervals. Twenty-three animals served as controls, out of which nine contracted P.P.

Results

Results presented in Table 4 and Fig. 6.

1a(OH)CC caused a rise in plasma calcium before calving in those cows injected twice, but more importantly it prevented the physiological as well as the pathological hypocalcaemia associated with calving.

None of the cows injected within 72-24 hours prior to calving developed the condition. There were no signs of toxicity (22).

Trial 2.

This time a larger number of cows were used and

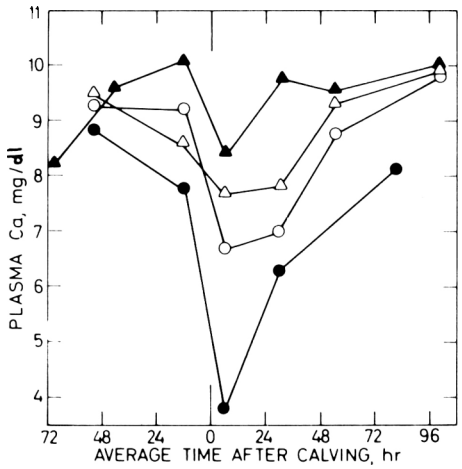

Figure 6. Plasma calcium concentrations in parturient-paresis-prone cows injected once △ (n = 8) or twice ▲ (n = 4) IM with 350 μg of 1α(OH)CC, compared with control ○ (n = 5) and parturient paresis cows ● (n = 3) which were not treated.

Table 5

Number of Injections (a)	Number of Cows	Number Contracting Parturient Paresis
0 (Control)	46	18
1	34	1 (b)
2	12	1 (b)
2 plus 5 mg Flumethasone	13	0 (c)

a) The injections were given 7 days to 14 hours before calving, and repeated up to 2 times at 72-hour intervals until calving took place.
b) The material was injected less than 18 hours prior to calving and did not have time to act.
c) Calving was induced by Flumethasone 48 hours after the second injection, and occurred 24-48 hours later.

the injection was given twice at an interval of 72 hours instead of 48 hours as above. Those cows which had not calved within 48 hours after the second injection were injected with 5 mg Flumethasone (Fluvet, Teva, Jerusalem) in order to induce calving. All these cows calved within 36-48 hours p.i. This method was adopted in order to avoid giving a third injection of 1a(OH)CC a) because of the cost and b) in case of possible toxicity.

Results

The results are presented in Table 5.

Further work has to be done in order to determine any toxic effects as a result of the Flumethasone treatment.

The conclusions from the second trial are that an interval of 72 hours between injections is permissable and that, even with the use of Flumethasone, the efficacy of 1a-(OH)CC in preventing bovine parturient paresis is very high.

Table 4

Prevention of Parturient Paresis by IM Injection of 350 μg of 1α-Hydroxycholecalciferol in 5 ml of Propylene Glycol*

No. of injections	No. of cows	No. with parturient paresis
0 (Control)	23	9
1	13	3**
2	6	0
3	4	0

*Injections were given 7 days to 6 hours before calving and repeated (up to 3 times) at 48-hour intervals until calving took place.
**Material was injected less than 18 hours prior to calving and had not enough time to be hydroxylated in the liver.

Acknowledgements

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