A Pharmacokinetic Study of Plasma Calcium Concentration in Dairy Cows Following Four Oral Administrations at 12 Hour Intervals Around Calving of a Calcium Chloride Paste Formulation

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Introduction

Despite intensive research during the last decades, milk fever is still widespread among high yielding dairy cows with considerable negative economic impact for the farmer. Furthermore, subclinical milk fever occurs more frequently than clinical milk fever.[1] The negative economic impact is intensified by an increased risk of secondary diseases following milk fever at the time when the cow is ready for milk production. The incidence of dystocia, uterine prolapse, retained placenta, ketosis, mastitis, and left displacement of the abomasum is greatly increased in milk fever cows compared with cows with normal parturition.[2]

Oral supplementation of calcium at strategic correct times around calving for the prevention of milk fever has been practised during the last 20-25 years.[3] Several calcium products containing different calcium salts have been introduced over the years.[4]

This article describes a pharmacokinetic study of plasma calcium concentration following oral administration of a newly developed calcium paste product (BOVIVET® Calcium Paste, Jørgen Kruuse A/S) to third or fourth parturient Holstein cows. One cartridge of calcium paste consists of 180 g calcium chloride and 6 g magnesium chloride. The salts are distributed in and protected by a special two-component oil. By using this special oil formulation the caustic effect of calcium chloride on the mucosal wall of the gut is eliminated.[5] This side effect is described for other calcium chloride formulations.[6,7]

The calcium paste formulation was developed in cooperation with the Royal Danish School of Pharmacy.

Materials and methods

Design and animals

Four Danish bovine veterinary practitioners were asked to identify one or two Holstein herds with two highly pregnant cows (3rd or 4th parturity) in each herd. The selected cows had not shown clinical signs of milk fever in any of the preceding parturitions.

This manuscript was received after the program was completed and in press.

In each herd the cow that calved first was selected as the test cow. Consequently, the other cow was the control cow in the study.

Study protocol

In order to establish baseline plasma calcium values, 2 heparin-stabilized blood samples of all cows in the study were drawn at least 24 hours prior to and at least 36 hours post partum.

The **test cows** were orally dosed with the calcium chloride paste formulation at the following times:

1st administration: 1 cartridge 10-14 hours prior to expected calving
2nd administration: 1 cartridge at calving
3rd administration: 1 cartridge approx. 12 hours post calving
4th administration: 1 cartridge approx. 24 hours post calving.

This preventive program has been used in Denmark since the late 1970's.

In addition to the above mentioned blood samples, other blood samples were drawn from the test cows at the following four time points around each dosing:

Immediately prior to dosing, 30 minutes, 1 hour, and 2-6 hours after dosing.

The **control cows** remained untreated.

Blood samples of control cows were drawn at the same time around calving as the test cow in the herd.

In case of clinical milk fever the cow was treated therapeutically with calcium intravenously. A blood sample was drawn immediately prior to treatment.

All blood samples were centrifuged and plasma samples were kept frozen until all samples were collected.

Calcium measurement

The plasma samples were analyzed for total calcium on VetTest® 8008 (Idexx Labs. Inc.). In a Danish study VetTest® 8008 is described as user-friendly for dry chemical analyses in veterinary practice.[8] Dublicate analyses of all samples were performed.

Results

Seven Holstein herds were selected. The oral dosing of the seven test cows was performed without any problem and without any major waste of calcium chloride paste.

All treated cows showed increased salivation for a couple of minutes following administration.

The mean plasma calcium concentration in the test cows is given in figure 1. The B´s in figure 1 represent the average time points for the four calcium administrations. One test cow showed clinical milk fever approx. 48 hours post calving and was treated therapeutically.

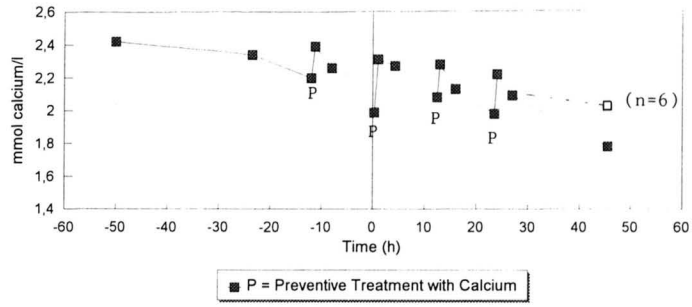

Figure 1. Calcium Conc. in Cows around Calving Calcium Paste Treated Group (n=7)

Three of seven control cows showed clinical milk fever as well. One of the cows had several relapses and was treated five times with calcium intravenously.

The actual calcium concentrations for each control cow with milk fever are given in figures 2A, 2B, and 2C.

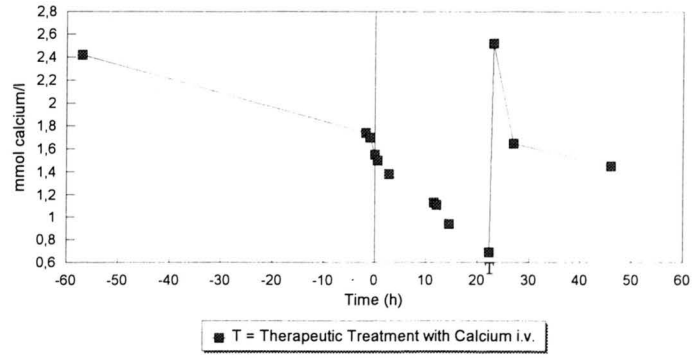

Figure 2A. Calcium Conc. in a Cow with Milk Fever Untreated Control Cow

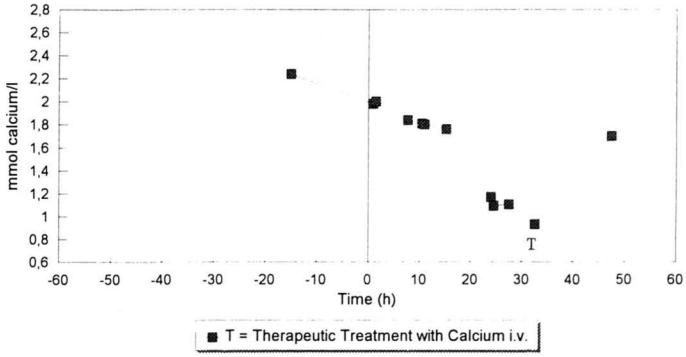

Figure 2B. Calcium Conc. in a Cow with Milk Fever Untreated Control Cow

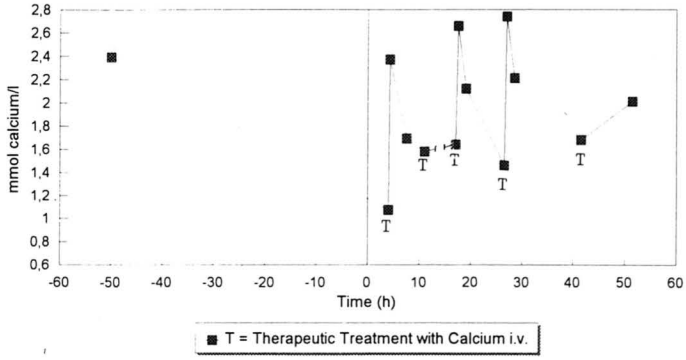

Figure 2C. Calcium Conc. in a Cow with Milk Fever Untreated Control Cow

The remaining four control cows did not show any signs of milk fever and the mean calcium concentration for these cows is shown in figure 3.

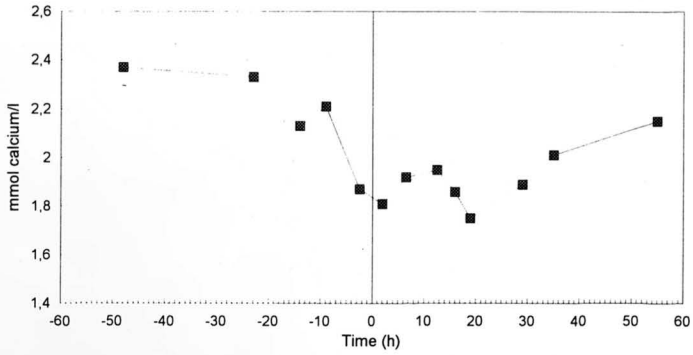

Figure 3. Calcium Conc. in Cows around Calving Untreated Control Group (n=4)

Each individual calcium measurement registered from calving onwards for all test and control animals (including the calcium treated animals) was placed in the following groups:

> 2.2 2.0-2.2 1.8-2.0 1.5-1.8 < 1.5 mmol Ca/l.

The results are illustrated in figure 4.

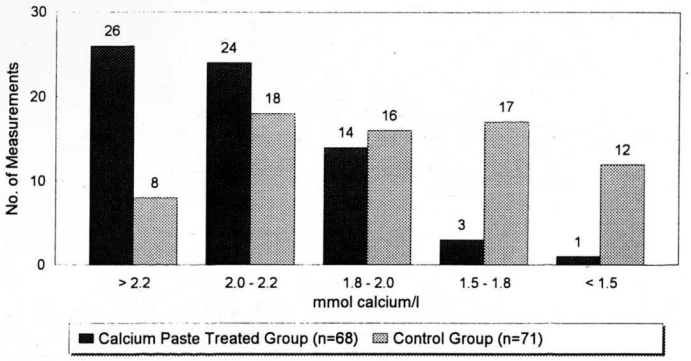

Figure 4. Calcium Conc. in Cows After Calving Distribution per Group

73.5% of all measurements in the test group had calcium concentrations above 2.0 mmolCa/l. The corresponding figure for the control group was 36.6%.

5.9% of all measurements in the test and 40.8% of all measurements in the control group had plasma calcium concentrations below 1.8 mmol Ca/l.

Discussion

This study has demonstrated that calcium chloride in a special two-component oil formulation and orally dosed to Holstein cows causes increased plasma calcium concentration around calving when the product is administered four times with approximately 12 hour intervals around calving starting approximately 12 hours prior to expected calving.

The observed increased salivation after administration is a normal occurrence in dairy cows when calcium chloride products are administered orally.

This study has also demonstrated how difficult it is for the farmer to predict exact calving time. Four of seven test cows received their first administration of calcium chloride paste an average of 17 hours (range 11-29 hours) prior to calving. The average first administration of the remaining three cows was 4 hours (range 2.5-5 hours) prior to calving.

The four administrations at 12 hour intervals of the calcium chloride paste formulation kept plasma calcium concentration above 2.0 mmol/l during the first 36 hours post calving. However, one test cow got milk fever approximately 48 hours post calving, i.e., 24 hours after the last dose. This cow was treated therapeutically and recovered instantly. In figure 1, two values at 48 hours post calving are given, one with and one without the value for the sick test cow.

Three of seven control cows had clinical milk fever. One had to be treated 5 times before she recovered. This cow and the test cow with milk fever came from the same herd.

The remaining four control cows represent normal cows around calving; 8-10 hours before calving the plasma calcium concentration started to drop from 2.2 mmol/l to 1.8 mmol/l at calving. 20-24 hours post calving the calcium homeostasis of the cows was in place and plasma calcium concentration started to rise and was back to baseline value within the next 24-36 hours.

This rise in plasma calcium concentration was not registered in the test group. The intensive calcium treatment might depress the cow's own calcium mobilization instead of supporting it. A similar situation is known from human patients with hypokalemia. Intensive treatment with potassium depresses the patient's own potassium mobilization. If this intensive potassium treatment is phased out in the latter part of the treatment period, the patient's own potassium mobilization takes over, and an interim period with hypokalemia is avoided.[9]

By taking the above mentioned observations into account, a new program for the prevention of milk fever can be suggested:

1st administration:	1 cartridge 6-8 hours prior to expected calving
2nd administration:	1 cartridge at calving
3rd administration:	1 cartridge 10-12 hours post calving
4th administration:	½ cartridge 20-24 hours post calving
5th administration:	½ cartridge 30-36 hours post calving.

This prophylactic program takes both the farmer and the cow into consideration. It will be easier for the

farmer to predict the correct time for the 1st administration, and the cow's lack of calcium mobilization will be replaced by heavy calcium administration in the first part of the treatment period followed by a less intensive calcium administration at the end of this period in order to let the cow's own calcium homeostasis take over.

This suggested preventive program using the newly developed calcium paste formulation will be tested in a controlled clinical field study.

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Abstract

Virulence, immunogenicity and reactivation of seven bovine herpesvirus 1.1 strains: clinical and virological aspects

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Specific pathogen-free calves were inoculated intranasally with one of seven strains of bovine herpesvirus 1.1 (BHV1.1) to identify a highly virulent strain for use in vaccination-challenge experiments. The calves were monitored clinically and virologically. Clear differences in virulence between the strains were observed. The Iowa strain was the most virulent; the four calves infected with the strain had the most severe clinical signs; two of them died and viraemia was detected in three of them. To evaluate the immunogenicity of the seven strains all the calves were challenged 16 weeks later with the Iowa strain. The calves of a control group showed the typical signs of a BHV1 infection, whereas all the other calves were protected against disease and shed little or no virus. Hence, the differences in virulence were not associated with differences in immunogenicity. After the calves had been treated with dexamethasone, differences were observed between the strains in the amount of virus that was excreted.

Presented at the XIX World Buiatrics Congress, Edinburgh, Scotland, July 8-12, 1996