A Comparative Study of the Effectiveness of Calcium Propionate and Calcium Chloride for the Prevention of Parturient Paresis in Dairy Cows

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ABSTRACT

The efficacy of calcium propionate for the prevention of parturient paresis (milk fever) was compared with that of calcium chloride using 194 cows that had experienced milk fever during the previous calving. The cows were mainly of the Swedish Red and White and Swedish Friesian breeds and were divided randomly into an experimental group (n = 99) and a control group (n = 95). The cows in the experimental group received up to six boluses of 20 g of calcium as calcium propionate between 36 h before and 24 h after calving; the cows in the control group received up to four doses of 54 g of calcium as a commercially available oily solution of calcium chloride during the same period. Incidence of milk fever was recorded as the percentage of cows that were treated by a veterinarian because they showed clinical signs of the disease and had a blood calcium concentration less than 8.0 mg/dl. Twenty-five (25.3%) cows in the experimental group and 22 cows (23.2%) in the control group developed milk fever. The incidence of milk fever for cows in both groups was significantly lower than the 36.0% found in 713 cows that had experienced milk fever during their previous calving but received no prophylactic treatment. Therefore, calcium propionate was considered to have had a significant preventive effect, comparable with that of calcium chloride.

(Key words: parturient paresis, milk fever, calcium propionate, calcium chloride)

INTRODUCTION

Parturient paresis (milk fever) is a metabolic disorder of cows that is associated with parturition and the initiation of lactation. Milk fever is characterized by hypocalcaemia, general muscular weakness, circulatory collapse, and depressed consciousness (17). In 1995, the incidence of the disease in Swedish dairy cows was 4.4% (20) but probably would have been significantly higher if effective preventive treatments had not been widely used.

In the US, adjustment of the acid-base balance in the diet during the last weeks of pregnancy is a method often used to prevent milk fever (1, 12). This method is not used in Sweden where the most common method is oral administration of calcium chloride during the peripartal period. Since the early 1970s, many Swedish farmers have treated their cows with three to four doses of 150 g of calcium chloride mixed to a gel with hydroxycellulose between 24 h before and 48 h after calving. The method is a modification of a procedure introduced by Ringarp et al. (18) and has been shown to reduce the incidence of milk fever by about 50% (10). This method, sometimes in a modified form, has also been used in other countries. One modification uses an oily solution of calcium chloride, which reduces the bitter taste of the salt. Schültken (19) considered calcium chloride in soybean oil to be as effective as calcium chloride in gel, although Goff and Horst (7) found that calcium chloride in soybean oil was poorly absorbed. The bitter taste may also be overcome by the administration of calcium chloride in a capsule, a method that also helps to reduce the risk of aspiration pneumonia and has been shown to be at least as effective as the gel (15).

Jørgensen et al. (11) reported that calcium chloride, administered as a gel, caused focal inflammation of the mucosa of the forestomachs; similar findings were recorded by Wentink and van den Ingh (22) who also observed extensive necrotic lesions in the abomasum, probably the result of elicitation of the esophageal groove reflex by the salt. Pehrson and Jönsson (14) also found inflammatory reactions in the rumen after the administration of capsules of calcium chloride, although the reactions did not apparently yield any clinical signs. No increase in the

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concentration of protein fibrinogen in the blood was observed during the acute phase, and no decrease in milk yield occurred. In contrast, the administration of oily solutions of calcium chloride caused only mild reactions in the forestomachs (11, 22).

The use of a source of calcium that would have no adverse effects on the forestomach is preferable, provided that the calcium is equally available for absorption. Large amounts of propionic acid are produced in the rumen as a result of carbohydrate metabolism, and no adverse effects are obvious. Therefore, calcium propionate might be expected to be a satisfactory source of calcium. The salt has a neutral taste, and Goff and Horst (6) found that an aqueous solution of calcium propionate was at least as effective at increasing plasma calcium concentration as a calcium chloride gel but was not as effective as aqueous calcium chloride. Those researchers (6) reported promising results from the prophylactic administration of two doses of a calcium propionate paste to a herd of Jersey cows (8). Moreover, Higgins et al. (9) found increased serum concentrations of calcium (SCa) when calcium propionate and propylene glycol were administered to Holstein cows at parturition.

The aim of the present investigation was to evaluate further the use of calcium propionate for the prevention of milk fever in cows highly predisposed to the disease by comparing its effect with a commercially available oily solution of calcium chloride.

**MATERIALS AND METHODS**

Cows (n = 255) from Skaraborg in southwestern Sweden that had been treated for milk fever during their previous calving and that were expected to calve between January and June 1996 were selected from a database of the Swedish Association for Livestock, Breeding, and Production (Hålsta). The cows were allocated at random into an experimental group and a control group. The owners of the cows in the experimental group (n = 121) were instructed to administer to their cows six boluses of calcium propionate, each containing 20 g of calcium, by balling gun; the boluses were cylinders that were 15 cm long and 3.4 cm in diameter. One bolus was to be administered about 24 h before the cow was expected to calve, two boluses were administered close to calving, two were administered about 12 h after calving, and one bolus was administered about 24 h after calving. The owners of the control cows (n = 134) received four bottles of a commercially available oily calcium chloride solution (lycine oil; Paregel vet®; Pherrovet AB, Malmö, Sweden). Each bottle contained 54 g of calcium. Those owners were instructed to follow the recommendations of the manufacturer and administer one bottle about 24 h before expected calving, one bottle close to calving, one bottle about 12 h after calving, and the final bottle about 24 h after calving. Many Swedish cows that have suffered milk fever are treated prophylactically with calcium chloride at the subsequent calving, and it was not considered ethically acceptable to use a control group treated with a placebo.

For practical reasons, we preferred to administer the calcium propionate as boluses. However, it was not physically possible to incorporate more than 20 g of calcium in a bolus of a size that could be easily administered to a cow. In this trial, we wanted to compare the effect of the commercial product with that of calcium propionate in a dose that could be considered obtainable under practical circumstances. Therefore, we used a number of boluses that we considered realistic for the owners to administer. Consequently, we could not use equal doses of calcium from the two salts.

All cases of milk fever were treated by veterinarians who were requested to take blood samples and send them to our laboratory to determine SCa, the serum concentration of magnesium (SMg), and the serum activity of aspartate aminotransferase (SASAT). The SCa and SMg were measured by atomic absorption spectrophotometry, and SASAT was measured with a commercial kit (Boehringer Mannheim Diagnostica, Mannheim, Germany). The veterinarians also sent data on the time of treatment and a description of the clinical signs exhibited by each cow. The owners were provided with a form on which they were requested to record the exact time of calving, the appearance of possible signs of milk fever, and the times at which the boluses or bottles were administered.

Cows were considered to have milk fever if they showed clinical signs of the disease between 2 h after the administration of the first dose of either of the two treatments and 7 d after calving, if they had an SCa below 8.0 mg/dl, and if no other main disease could be suspected on the basis of either the description provided by the veterinarian or the results of the analyses of SMg and SASAT. Staggering and muscle twitching were accepted as signs of milk fever. Cows were recorded as not diseased only if at least three of the four treatments had been administered close to the scheduled times. The first dose was administered between 36 h before calving and 3 h after calving.

In total, 99 (82%) of the 121 cows in the experimental group and 95 (71%) of the 134 cows in the control group fulfilled the previously mentioned...
TABLE 1. Breed and age distribution of two groups of cows.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cows (no.)</th>
<th>SRB (%)</th>
<th>SLB (%)</th>
<th>Other (%)</th>
<th>Age (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95</td>
<td>31.6</td>
<td>64.2</td>
<td>4.2</td>
<td>7.95 ± 2.00</td>
</tr>
<tr>
<td>2</td>
<td>99</td>
<td>47.5</td>
<td>47.5</td>
<td>5.0</td>
<td>7.89 ± 1.75</td>
</tr>
<tr>
<td>Total</td>
<td>194</td>
<td>39.7</td>
<td>55.7</td>
<td>4.6</td>
<td>7.81 ± 1.88</td>
</tr>
</tbody>
</table>

1SRB = Swedish Red and White breed; SLB = Swedish Friesian breed.
2Cows in group 1 were treated prophylactically with Paregel vet® (Pherrovet AB, Malmö, Sweden), and cows in group 2 were treated with calcium propionate boluses.

Evaluation of Effect

In June 1997, all Swedish cows that calved between February and May 1997 and that had experienced milk fever during the previous calving were selected from the database of the Swedish Association for Livestock, Breeding, and Production. This database also included information about whether the cows had been treated for milk fever in 1997. The owners of these 2047 cows were requested to fill out a questionnaire to check the accuracy of the information in the database of the Swedish Association for Livestock, Breeding, and Production. Owners were asked whether the cows had been treated prophylactically with at least one dose of calcium chloride at their last calving. Any cow that had calved more than 10 d before the expected calving date and any cow for which the owners were uncertain about the events were excluded. The incidence of milk fever among cows that had not been treated prophylactically was used as a reference value against which to assess the effectiveness of the two treatments investigated.

Statistical Analyses

Differences between the incidences of milk fever in the two groups and the reference incidence deduced from the questionnaire were investigated by means of the chi-square test. The same test was used to evaluate the differences in incidence between cows of the different breeds and between cows 7 yr or younger (n = 96) and older cows (n = 97). Age could not be determined for 1 cow. The difference between the number of infusions of calcium administered to the diseased cows in the two groups was evaluated by the Mann-Whitney test.

The 95% confidence interval for the difference in the incidence of milk fever between the two groups was calculated according to the description of Gardner and Altman (5) from the formula for the standard error of the difference (SED):

$$\text{SED} = \sqrt{\frac{p_1(100 - p_1)}{n_1} + \frac{p_2(100 - p_2)}{n_2}}$$

where p1 and p2 = incidences (percentages) in the two groups, and n1 and n2 = numbers of cows in the groups. The confidence interval was then calculated as the measured difference \(- 1.96 \times \text{SED}\) to the measured difference \(+ 1.96 \times \text{SED}\).

RESULTS

A total of 2047 questionnaires was sent out. Of these, 88.1%, representing 1804 cows, was returned. However, for reasons previously mentioned, the questionnaires relating to 218 of these 1804 cows were excluded, leaving 1586 cows for which the information was satisfactory. Of these 1586 cows, 873 (55.0%) had been treated prophylactically, and the other 713 had not been treated. Of the 713 untreated cows, 257 (36.0%) had contracted milk fever.
Twenty-five (25.3%) cows treated with boluses of calcium propionate and 22 (23.2%) control cows developed milk fever as defined previously. For both groups, the incidence was significantly less than the 36.0% found in the reference material ($\chi^2 = 4.47$ and $P = 0.03$ for the experimental group; $\chi^2 = 6.16$ and $P = 0.01$ for the control group). The 95% confidence interval for the difference between the incidence of the disease in the two groups was –10.0 to 14.2 percentage units.

No differences were detected between the incidences of milk fever in the Swedish Red and White cows and Swedish Friesian cows (24.7% of 77 Swedish Red and Whites and 24.1% of 108 Swedish Friesians developed milk fever). A smaller proportion (19.8%) of cows that were 7 yr or younger developed milk fever compared with the older cows (27.6%), but the difference was not significant ($P = 0.25$).

The severity of disease was not different between groups. In the experimental group, 10 of the hypocalcemic cows were given one intravenous infusion of calcium chloride, 11 were given two infusions, and 4 were given more than two infusions; in the control group, 8 cows received one infusion, 10 received two infusions, and 4 cows were given more than two infusions. In the experimental group, 4 (16.0%) of the hypocalcaemic cows were not paretic, and, in the control group, 3 cows (13.6%) were not paretic. In the experimental group, the mean SCa at the first treatment was $4.88 \pm 0.27$ mg/dl ($\bar{X} \pm SE$) compared with $4.96 \pm 0.29$ mg/dl for the control group; the corresponding values for SMg were $2.72 \pm 0.15$ and $2.82 \pm 0.14$ mg/dl. None of the diseased cows had SASAT that exceeded 3 $\mu$kat/L at the first treatment, indicating that no serious muscle damage had occurred by that time.

**DISCUSSION**

The incidence of milk fever in each of the two groups of cows (25.3% in the experimental group; 23.2% in the control group) was significantly less than the 36.0% for cows that had previously had milk fever and had been allowed to calve without prophylactic treatment. Therefore, we concluded that both treatments had a preventive effect.

In the present trial, calcium chloride was suspended in lycine oil because Goff and Horst (7) found that calcium salts suspended in soybean oil were poorly absorbed. Studies of the availability of calcium from lycine suspensions have not been reported in the literature. Therefore, we cannot exclude the possibility that a better prophylactic effect might have been achieved if the calcium chloride had been administered in hydroxycellulose gel or in a water solution.

Although the field trial was considerably larger than the trial of Goff et al. (8), the wide confidence interval for the difference between the incidence of milk fever in the two groups indicated that too few cows were used for the trial to constitute an optimal equivalence study. According to the method cited by Pocock (16) for negative trials, groups of 604 cows would have been required to demonstrate equality with an upper confidence limit for the difference in incidence not exceeding 7 percentage units. Such a trial would be unrealistic to conduct. However, the results do suggest that treatment with calcium propionate was as effective in the prevention of milk fever as was treatment with calcium chloride, even though cows given calcium propionate received only 120 g of calcium compared with the 216 g received by cows treated with calcium chloride. The dose of calcium in all products available commercially is similar to that in the control product and is probably based on the original report by Jönsson and Pehrson (10). Those researchers found that the administration of four doses of 54 g of calcium was more effective than the administration of three doses of 36 g of calcium. However, whether the improvement was due to the higher dose of calcium or to the more frequent dosing has never been tested experimentally. The present results suggest that the quantity of calcium in the commercial products may be unnecessarily high. Moreover, our own unpublished data indicate that one to two peripartal doses of calcium propionate are less effective in the prevention of milk fever than are three or four doses. However, it is possible that an even better prophylactic effect of calcium propionate can be achieved when more than 120 g of calcium propionate are administered.

The incidence of milk fever among the untreated cows was 36.0%, a percentage that is considerably lower than the incidence (47 to 63%) that was observed in earlier trials (10, 13, 15, 18), including a total of 470 cows, most of them from the same areas of Sweden as the cows in the present trial. However, some of these trials (10, 18) took place several years ago and might have included a substantially different population of cows. Therefore, we decided to use 36.0% as the reference value, even though it might possibly underestimate the true incidence of milk fever among untreated cows. One reason for this possibility is that the questionnaires provided no information about the interval between the administration of the first dose of calcium chloride and the time when the cow was found to be paretic. In some cows, this interval might have been just 1 to 2 h; no prophylactic
effect can then be expected, and the cows might have been considered to be untreated. The 36.0% reference value may therefore be considered as being the minimal incidence of milk fever to be expected among untreated Swedish cows that are predisposed to the disease.

The effectiveness of calcium chloride is probably mainly due to the absorption of readily available calcium ions when blood calcium concentrations of the cow tend to decrease. However, it has also been reported that the acidifying effect of the chloride ions may be beneficial (7, 13). Previous research has shown that acidifying salts increase the rate of absorption of calcium from the digestive tract (3) as well as the rate of mobilization of calcium ions from the skeleton (2). However, provided in excess, calcium chloride could cause metabolic acidosis; Fløtla et al. (4) induced severe acidosis and death in young stock weighing 200 to 260 kg by dosing them orally with aqueous calcium chloride at 1.6 g/kg of BW.

Propionate, in contrast to the fixed chloride ion, is metabolized to a more rudimentary chemical level (1). Therefore, propionate should not have any acidifying or toxic effect. Calcium propionate is less soluble in water than is calcium chloride [49 g/100 ml of cold water compared with 75 g (21)] and is therefore likely to be absorbed more slowly from the digestive tract. However, calcium propionate is much more soluble than calcium carbonate, calcium sulfate, and calcium lactate, and the present results indicate that its solubility is adequate. In addition to not having any erosive effect on the mucosa of the digestive tract, calcium propionate has another advantage over calcium chloride; it is neutral in taste. The propionate ion is a source of energy after its conversion to glucose in the liver. The supplementation of about 85 g of propionate per bolus is, however, not quantitatively important compared with the amounts of propionate normally produced in the rumen.

The criteria used to include cows in the trial may be open to criticism. For example, it might be argued that cows from which no blood samples were taken and cows that had an SCA marginally above 8.0 mg/dl should have been included if they showed clinical signs of milk fever; it might also be argued that the cows that were still able to stand when they were examined by the veterinarian should not have been included. However, when these alternative criteria were considered, the incidence of milk fever in the two groups changed only marginally, and, more importantly, the relationship between the groups remained unchanged.

The number of cows excluded because they did not fulfil the criteria was higher in the control group (n = 39) than in the experimental group (n = 22). It is difficult to explain this difference, but one possible reason may be that the owners were more conscientious in the observation of these cows and in following the treatment protocol for a group treated with a previously untested drug.

In conclusion, the results of this trial verify preliminary results presented by Goff and Horst (6) and Goff et al. (8) that calcium propionate may be a satisfactory alternative to calcium chloride for the prevention of milk fever.

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REFERENCES


