Treatment of cows with milk fever using intravenous and oral calcium and phosphorus

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Summary

Fifteen cows with milk fever were treated with 500 ml of 40% calcium borogluconate (group A) intravenously. Fifteen other cows with milk fever received the same treatment, supplemented with 500 ml of 10% sodium phosphate intravenously, and 80 g calcium as calcium lactate and 70 g inorganic phosphorus as sodium phosphate administered orally in drinking water. The cows were monitored and blood samples collected for 3 days to measure the concentrations of total and ionized calcium, inorganic phosphorus and magnesium and the activity of creatine kinase. The two groups did not differ significantly with respect to the course of the disease. In each group 14 cows were cured. A rapid and significant increase in serum calcium concentration from the hypo- to the hypercalcaemic range occurred in both groups within 10 min of the start of treatment, followed by a slow and steady decrease to the hypocalcaemic range. Calcium lactate did not prevent the calcium concentration from returning to the hypocalcaemic range, and the calcium profiles of the two groups did not differ significantly. As expected, treatment had little effect on the concentration of inorganic phosphorus in group A. In group B, treatment caused a rapid increase in the concentration of inorganic phosphorus to a maximum 20 min after the start of treatment. This was followed by a slow decrease in the phosphorus concentration to the normophosphataemic range. Our findings confirmed that combined intravenous and oral administration of sodium phosphate in cows with periparturient paresis attributable to hypocalcaemia and hypophosphataemia results in a rapid and sustained increase in serum phosphorus, but not in serum calcium concentration. This modified therapy did not improve the success rate of milk fever treatment and further studies are needed to improve treatment of periparturient paresis.

Keywords: cattle, parturient paresis, treatment, calcium, phosphorus

Intravenöse und perorale Behandlung von Gebärparese-Kühen mit Kalzium und Phosphor


Schlüsselwörter: Rind, Gebärparese, Therapie, Kalzium, Phosphor
Introduction

The pathogenesis, prophylaxis and treatment of milk fever (parturient paresis) in dairy cows have recently been discussed in several review articles (Thilsing-Hansen et al., 2002; DeGaris and Lean, 2008; Goff, 2008; Murray et al., 2008). Routine treatment of milk fever consists of intravenous administration of a calcium solution (Radostits et al., 2007). The percentage of hypocalcaemic cows that respond to a single treatment ranges from 47% (Salis, 2002; Braun et al., 2004) to 76% (Malz and Meier, 1992). Some cows relapse and require a second treatment, while others remain recumbent and are euthanized despite multiple treatments. Several studies carried out in our Clinic were aimed at improving the success rate of milk fever treatment. Modifications of routine treatment included the intravenous administration of calcium over several hours via an indwelling catheter (Salis, 2002; Braun et al., 2004a, 2004b), doubling the dose of calcium (Jehle, 2004; Braun et al., 2006) and supplementing the routine treatment with sodium phosphate administered either orally (Dumelin, 2005; Braun et al., 2007) or intravenously (Zulliger, 2008; Braun et al., 2009). However, none of these treatments improved the success rate compared with routine intravenous administration of calcium alone. None of these treatments led to a rapid increase and sustained elevation (48–72 hours) of serum calcium and inorganic phosphorus concentrations that lasted 48 to 72 hours. The goal of the present study was to investigate whether the combination of various treatment modifications that had a positive therapeutic effect improved the overall outcome of milk fever treatment. To achieve this, initial intravenous treatment with calcium (Dumelin, 2005; Braun et al., 2007; Zulliger, 2008; Braun et al., 2009) and phosphorus (Dumelin, 2005; Braun et al., 2007) was followed immediately by oral administration of sodium phosphate (Zulliger, 2008; Braun et al., 2009). In addition, calcium lactate dissolved in water was provided for the cows in an attempt to stabilize the blood calcium concentration (Geishauser et al., 2008).

Animals, Material and Methods

Animals

Thirty cows from 22 different clients of the ambulatory Clinic of the Department of Farm Animals, University of Zurich, were used. The patients were 4 to 10 years old (mean ± sd = 7.4 ± 1.54 years) and included 15 Simmental, 10 Swiss Braunvieh and 5 Holstein Friesian cows. Lactation numbers ranged from 3 to 8 (5.5 ± 1.43) and milk production of the previous lactation was 5400 to 12'000 kg (8043 ± 1613 kg). All cows had periparturient paresis within 24 hours of calving. Fourteen cows had milk fever during a previous lactation. Eighteen of the cows were treated prophylactically before signs of hypocalcaemia occurred using oral calcium products, which were administered immediately before or after parturition and in some cases combined with the intramuscular injection of vitamin D₃ between 3 and 8 days before the anticipated date of calving. Light manual traction was used to deliver 8 of the calves, and 3 cows had a retained placenta. Treatment was started 1 to 10 hours (3.4 ± 1.99 hours) after periparturient paresis was diagnosed; this interval did not differ among the various treatment groups.

Clinical examination and diagnosis

The clinical examination included assessment of the demeanour and general condition, appetite, defaecation and micturition, rectal temperature, heart and respiratory rates, rumen motility, intestinal sounds, body posture, behavior, level of consciousness and sensitivity in the hind limbs. In addition, transrectal, vaginal and udder examinations including a California mastitis test were carried out. A urine sample was collected immediately before treatment and examined for acetocetic acid (Keto-Diastix®, Bayer Consumer Care AG, Basel). The clinical findings have been described in detail (Blatter, 2011). A diagnosis of parturient paresis was made when clinical signs typical of this condition (Radostits et al., 2007) occurred within 24 hours after parturition.

Treatment

The cows were alternately assigned to group A or B depending on treatment. Both groups consisted of 15 cows that received 500 ml of a solution containing 40% calcium borogluconate (15.65 g calcium gluconate and calcium borogluconate) and 6% magnesium hypophosphite (9.85 g magnesium hypophosphite) (Calcamyl-40MP, Gräub, Bern) via an indwelling jugular vein catheter. Treatment was given slowly during 10 minutes and the heart rate was monitored continuously. Immediately after treatment with calcium, cows of group B received 500 ml of a 10% solution of sodium phosphate (NaH₂PO₄ * 2 H₂O, Streuli, Uznach), yielding 10 g of inorganic phosphorus, which was also given slowly during 10 minutes. After the second infusion, cows of group B were offered 20 litres of water containing calcium lactate to provide 80 g calcium (Propeller Calcium Drink®, Provet, Lyssach). Water that was refused was administered via stomach tube 10 minutes later. Then 350 g sodium phosphate (NaH₂PO₄ * 2 H₂O, Streuli), yielding 70 g of inorganic phosphorus, was administered via stomach tube to all cows of group B. The hind legs were hobbled before treatment and the cows were rolled onto the other side. The cows were then monitored for 8 hours and futile and successful attempts to rise were noted. The demeanour and general condition, heart and respiratory rates, rectal temperature, rumen motility, appetite and defaecation were assessed hourly.
Follow-up treatment of non-responding and relapsing cows

Cows that did not respond to treatment within 8 hours or that relapsed were treated a second time with 500 ml of 40% calcium borogluconate (300 ml were given intravenously and 200 ml subcutaneously). Cows that did not respond to the initial treatment received a second treatment with 500 ml of 40% calcium borogluconate (300 ml were given intravenously and 200 ml subcutaneously) eight hours later. Cows that went down again received 500 ml calcium borogluconate intravenously at the time of the relapse.

Serum electrolytes and creatine kinase

Blood samples were collected from all cows into evacuated tubes without anticoagulant (Vacuette® Serum Sep. Clot Activator, 5 ml, Greiner bio-one GmbH, Kremsmünster, Austria) immediately before treatment and 10, 20, 40, 60 and 90 min and 2, 3, 4, 5, 6, 7, 8, 24, 48 and 72 hours after the start of treatment. The concentrations of total and ionized calcium, inorganic phosphorus and magnesium and the activity of creatine kinase (CK) were measured in serum. Ionised calcium was measured using an ion-selective electrolyte analyser (Nova CRT 8, Nova Biomedical, Germany) and the remaining variables were measured using a Cobas Integra 700 Analyzer (Roche Diagnostics, Rotkreuz) using the manufacturer’s reagents (Roche-Reagents) according to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) at 37 °C.

Statistics

The data were analyzed using Stata (StataCorp., 2009; Stata Statistical Software: Release 11.0; College Station, Texas, USA). The frequencies, means and standard deviations were calculated. The clinical findings and electrolyte concentrations of the cows of the two groups before treatment were compared using a chi-squared test for association and a two-sided Student’s t-test, respectively. Differences between the electrolyte concentrations in the two groups after treatment were analyzed using the Bonferroni/Dunn test. The response to treatment was analyzed in three different ways. A general linear model (GLM, <xtmixed var1 var2 time || time:>) was used to analyze the differences between the clinical variables (demeanour, rectal temperature, superficial body temperature, ruminal motility, defaecation) before and after treatment within and among the groups. The numbers of cows that stood by 8, 24, 48 and 72 hours after treatment were compared among the time points and between the two groups. The various outcomes (cured after one treatment, cured after more than one treatment, relapsed after standing, unable to stand) were calculated and the results of the groups compared. The significance of correlation coefficients was analyzed using the r to z test.

Results

Clinical findings before treatment

The clinical findings before treatment did not differ between the groups and they are therefore analyzed together. Eight cows had a normal demeanour, 16 were listless, 4 were somnolent and 2 were comatose. The latter 6 cows were in lateral recumbency and the remaining 24 were in sternal recumbency. The rectal temperature ranged from 35.6 to 39.8 °C (38.1 ± 0.86 °C) and the body surface of 27 cows was cold to the touch. Twenty-nine cows were anorexic and one ate very little. Ruminal motility was reduced in 3 cows and absent in 27. Intestinal atony occurred in 29 cows and 19 cows had dry hard faeces. Two cows had low levels of ketones in the urine.

Clinical findings after treatment and outcome

There was no difference between the two groups with respect to outcome of treatment. Awareness normalized in all cows following treatment. Of the 6 cows that were stuporous before treatment, 4 were still mildly listless one hour after treatment. The rectal temperature normalized in all cows within 1 hour and the appetite normalized in 15 cows within 8 hours. Of the remaining 15 cows, 14 were still anorexic 8 hours after the start of treatment and one had a reduced appetite. Ruminal motility resumed within 1 hour in all cows. A total of 22 cows (73.3%), 11 from each group, stood within 8 hours of treatment (Tab. 1) and 11 of these (3 from group A and 8 from group B) relapsed between 8 and 24 hours after the initial treatment. Thus, 8 cows of group A and 3 of group B were cured after one treatment. The 11 cows that relapsed after successful initial treatment and the 8 cows that did not respond to initial treatment were treated two to six times. The overall success rate did not differ between the two groups (14 of 15 cows were cured in each).

Table 1: Treatment outcome in 30 cows with milk fever.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Group A</th>
<th>Group B</th>
<th>Total Cows</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rising within 8 hours</td>
<td>11</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Recurrence after rising</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Cured after single treatment</td>
<td>10</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Cured after multiple treatments</td>
<td>6</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Euthanasia because of failure to respond to treatment</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total cured</td>
<td>14</td>
<td>14</td>
<td>28</td>
</tr>
</tbody>
</table>
Electrolyte concentrations before treatment

The electrolyte concentrations before treatment did not differ between the two groups. All cows had hypocalcaemia with concentrations of total calcium lower than 2.0 mmol/l and concentrations of ionized calcium lower than 1.15 mmol/l. There was also hypophosphataemia in all cows with concentrations of inorganic phosphorus lower than 1.30 mmol/l. The magnesium concentrations ranged from 0.81 to 1.84 mmol/l (normal range, 0.80 – 1.20 mmol/l).

Electrolyte concentrations after treatment

Mean serum calcium concentrations increased rapidly and significantly, and within 10 min after the start of treatment reached the hypercalcaemic range in both groups (Fig. 1). After the peak the calcium concentration decreased gradually. Hypercalcaemia lasted 60 to 90 min, which was followed by normocalcaemia for 4 to 6 hours. Five to 7 hours after the start of treatment, the mean serum calcium concentration returned to the hypocalcaemic range, where it remained until 48 hours in both groups. The cows were normocalcaemic at 72 hours. The post-treatment profiles of total calcium differed significantly between the two groups. At 8 hours, seven cows of group A and 14 cows of group B had hypocalcaemia (P < 0.01) (Tab. 2). Hypocalcaemia occurred in 9 cows of group A and 12 cows of group B at 24 hours post treatment (difference P < 0.01).

The concentrations of ionized and total calcium were highly correlated (0.90 ≤ r ≤ 0.99, P ≤ 0.01) during the entire observation period, and the post-treatment profiles of ionised calcium did not differ between the two groups (Fig. 2). The profiles of ionized and total calcium concentrations were similar. After treatment, cows of group A only had a slight increase in inorganic phosphorus compared with cows of group B (Fig. 3). In group B, the mean concentration of inorganic phosphorus increased rapidly after treatment and at 20 min reached a maximum of 3.79 ± 1.23 mmol/l.

*Figure 1: Profile of total calcium after intravenous administration of calcium borogluconate (groups A and B) and sodium phosphate (group B) and oral administration of calcium lactate and sodium phosphate (group B) (mean ± sd). The yellow bar indicates the normal range for total calcium (2.00 to 2.80 mmol/l). The values at 24, 48 and 72 hours may have been affected by the repeated calcium infusions in 19 cows that did not respond to the initial treatment or relapsed.*

*Figure 2: Profile of ionised calcium after intravenous administration of calcium borogluconate (groups A and B) and sodium phosphate (group B) and oral administration of calcium lactate and sodium phosphate (group B) (mean ± sd). The yellow bar indicates the normal range for ionised calcium (1.06 to 1.26 mmol/l). * P < 0.05. The values at 24, 48 and 72 hours may have been affected by the repeated calcium infusions in 19 cows that did not respond to the initial treatment or relapsed.*

*Table 2: Number of cows with hypocalcaemia and hypophosphataemia after treatment.*

<table>
<thead>
<tr>
<th>Hours after the start of treatment</th>
<th>Hypocalcaemia (calcium &lt; 2.0 mmol/l)</th>
<th>Hypophosphataemia (inorganic phosphorus &lt; 1.3 mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>group A</td>
<td>group B</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>0</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>24</td>
<td>9</td>
<td>12*</td>
</tr>
<tr>
<td>48</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>72</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

* Difference B to A P < 0.01
Milk fever using calcium and phosphorus

The concentration then decreased slowly to the normophosphataemic range, where it remained for the remainder of the study period. The profiles of inorganic phosphorus differed significantly between the two groups ($P < 0.01$). There was no difference between the two groups with respect to the proportion of cows that were hypophosphataemic at various time points (Table 2).

The profiles of the magnesium concentrations of the two groups did not differ. In both groups, the magnesium concentration increased rapidly and significantly ($P < 0.05$) within 10 min after the start of treatment (Fig. 4), which was followed by a gradual decrease to pre-treatment concentrations 3 to 4 hours later.

**Treatment outcome in relation to electrolyte concentrations and CK activity**

The calcium profile of the 22 cows that stood within 8 hours of treatment did not differ significantly from the profile of the eight cows that did not stand. In contrast, the cows that stood had significantly higher phosphorus profiles than the cows that did not stand ($P < 0.05$). The cows that remained recumbent 8 hours after treatment had higher serum CK activity at 2 hours after treatment than the cows that stood ($P < 0.05$).

**Discussion**

In this study, two different treatments for milk fever were compared in 30 dairy cows. One treatment consisted of a standard intravenous calcium borogluconate infusion and the other combined intravenous infusion and oral administration of both calcium and phosphorus. Eleven of 15 cows in each group (73.3%) stood within 8 hours of treatment, which was similar to success rates (70.0 and 73.5%) reported in our previous studies (Salis, 2002; Braun et al., 2004a; Jehle, 2004; Dumelin, 2005; Braun et al., 2006; Braun et al., 2007). In agreement with the previous results, the pre-treatment electrolyte concentrations were not related to the treatment outcome assessed 8 hours after treatment in the present study. The cows that did not stand within 8 hours received additional treatments. Cows that responded to treatment within 8 hours had significantly higher serum phosphorus concentrations than cows that did not, which confirmed previous suggestions that the post-treatment phosphorus profile has prognostic value (Goff, 2000). Eleven of 30 cows (37%) had a favourable response to treatment initially, but relapsed later. The recurrence rate was considerably lower in previous studies at 3.7% (Zulliger, 2008; Braun et al., 2009), 20.0% (Dumelin, 2005; Braun et al., 2007) and 23.3% (Jehle, 2004; Braun et al., 2006). Other authors (Oetzel, 1988; Martig, 2002) reported recurrence rates ranging from 23 to 40%. The recurrence rate was greater in group B than in group A (8 of 11 versus 3 of 11). It is possible that oral administration of sodium phosphate and calcium delayed the re-establishment of the calcium-phosphorus homeostasis.

Only 11 of 30 cows (37%) were cured of hypocalcaemia after a single treatment, which was considerably worse than cure rates previously reported at 46.7% (Salis, 2002; Braun et al., 2004a; Jehle, 2004; Dumelin, 2005; Braun et al., 2006; Braun et al., 2007), 56.7% (Zulliger, 2008;...
Electrolyte measurements confirmed previous findings that 5 to 10% (Martig, 2002) and up to 97% (Jehle, 2004; Braun et al., 2006) and also agreed by Braun et al., 2007; Zulliger, 2008; Braun et al., 2009) and of 90% (Salis, 2002; Braun et al., 2004a; Dumelin, 2005; Braun et al., 2007; Zulliger, 2008; Braun et al., 2009) and 97% (Jehle, 2004; Braun et al., 2006) and also agreed by findings that 5 to 10% (Martig, 2002) and up to 14% (Radostits et al., 2007) of cows with milk fever were euthanased because they did not respond to treatment. Electrolyte measurements confirmed previous findings of hypercalcaemia within the first hour of treatment with return to the hypocalcaemic range after 5 hours, followed by the re-establishment of normocalcaemia after 72 hours (Dumelin, 2005; Braun et al., 2007; Zulliger, 2008; Braun et al., 2009). The oral administration of calcium lactate to cows of group B was a novel adjunct to milk fever treatment, but it did not have an apparent effect on serum calcium concentration and did not prevent cows from becoming hypocalcaemic again. This was in agreement with recent observations that the oral administration of calcium lactate to healthy fresh cows does not cause an increase in the serum calcium concentration (Blatter, 2011).

However, it contradicted observations by the inventors of the calcium lactate product who stated that it causes an increase in serum calcium when given to healthy fresh cows (Geishauser et al., 2008). We selected calcium lactate rather than another oral calcium product because questions about its efficacy had not yet surfaced. The combined intravenous and oral administration of phosphorus resulted in normal phosphorus concentrations throughout the entire study period. This was not possible in earlier studies: the oral administration of 350 g sodium phosphate alone caused a slow increase in the serum phosphate concentration (Dumelin, 2005; Braun et al., 2007), whereas the intravenous infusion of sodium phosphate alone caused only a temporary increase in the phosphate concentration (Zulliger, 2008; Braun et al., 2008). Thus, because combined treatment has a rapid and prolonged effect on serum phosphorus concentration, this finding supports an earlier recommendation to add phosphorus to the milk fever treatment in cows with severe hypophosphataemia (Forrester and Moreland, 1989; Cheng et al., 1998; Visser’t Hooft et al., 2005).

The high rate of recurrence at 8 hours after initial treatment for hypocalcaemia (70%) was a major problem in this study. Compared with group A, the recurrence rate for hypocalcaemia was two times higher in group B. It is therefore not surprising that recurrence of milk fever was considerably higher in group B.

**Traitement intraveineux et oral de la parésie puerpérale des vaches avec du calcium et du phosphore**

Dans ce travail, 15 vaches souffrant de parésie puerpérale ont été traitées avec 500 ml d’une solution de borogluconate de calcium à 40% par voie intraveineuse (groupe A) et 15 autres ont reçu en outre 500 ml d’une solution à 10% de dihydrogenophosphate de sodium, également par voie intraveineuse. En outre les vaches du groupe B ont reçu oralement 80 g de calcium sous forme de lactate de calcium et 70 g de phosphore sous forme de dihydrogenophosphate de sodium. Par la suite des prises de sang ont été réalisées durant 72 heures pour déterminer les electrolytes. Il n’y a pas eu de différence significative quant à l’évolution de la maladie entre les 2 groupes. Dans chaque groupe, 14 vaches ont guéri. Dans les 2 groupes on constatait une augmentation rapide et significative de la concentration en calcium. Celle-ci diminuait ensuite lentement et de façon constante. L’application orale de lactate de calcium dans le groupe B ne permettait pas d’empêcher cette baisse et les courbes de calcémie ne se différenciaient pas de façon significative entre les 2 groupes. Chez les vaches du groupe B, la concentration en phosphate anorganique augmentait considérablement en phosphate anorganique.

**Trattamento con calcio e fosforo per via endovenosa e orale nei bovini affetti da paresi puerperale**

Nel presente studio sono state trattate 15 mucche da latte affette da paresi puerperale per via endovenosa con 500 ml di una soluzione di boro gluconato di calcio al 40% (gruppo A). Altre 15 mucche (gruppo B) anch’esse affette da paresi puerperale, hanno ricevuto lo stesso trattamento e una ulteriore somministrazione di 500 ml di bifosfato di sodio al 10%, anche per via orale. Inoltre, alle mucche del gruppo B sono stati somministrati 80 g di calcio dal lattato di calcio e 70 g di fosforo dal bifosfato di sodio per via orale. Successivamente per 72 ore sono stati prelevati campioni di sangue per la determinazione degli elettrolini. Tra i due gruppi non si sono segnalate differenze significative in termini di progressione della malattia. In totale si sono guariute 14 mucche per gruppo. In entrambi i gruppi vi è stato un rapido e significativo aumento della concentrazione di calcio. Dopo che i livelli di calcio sono diminuiti lentamente ma in maniera costante. Il lattato di calcio somministrato per via orale non ha impedito la diminuzione dei livelli di calcio nel gruppo B e le curve di risposta del calcio tra i due gruppi non differivano in modo significativo. Nel-
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