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ORAL 1,25-DIHYDROXYVITAMIN D_3 IN PREVENTION OF MILK FEVER

By

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HOVE, K. and T. KRISTIANSEN: *Oral 1,25-dihydroxyvitamin D_3 in prevention of milk fever.* Acta vet. scand. 1984, *25*, 510—525. — The effect of daily oral doses of 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) on plasma mineral concentrations and incidence of milk fever was tested in 39 aged cows. Three dose levels of 1,25-$(OH)_2D_3$ (0, 100 and 200 µg/d) were compared in cows supplemented with 100 g Ca/d (250 g $CaCO_3$) and in cows receiving no Ca supplement. 1,25-$(OH)_2D_3$ treatments were given from day 5 before expected calving (day —5) until the day after calving (Calving = day 0).

Expected minima in Ca concentrations in plasma were seen on day 1 in placebo treated cows, while Ca concentrations in 1,25-$(OH)_2D_3$ treated cows were normal or increased in the period from start of treatment until day 3—5. In the parturient period (day —1 to +2) 1 of 21 treated cows developed milk fever, as compared to 4 of 18 untreated. A pronounced hypocalcaemia developed, however, in the 1,25-$(OH)_2D_3$ treated cows from day 3 to 5 onwards, culminating day 8—11 with 7 cases of milk fever. Ca supplements reduced the development of hypocalcaemia in the 1,25-$(OH)_2D_3$ treated cows, but could not completely prevent the occurrence of milk fever.

milk fever; prevention; 1,25-dihydroxyvitamin D_3; hypocalcaemia; dairy cows.

The positive effect of 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) on intestinal calcium absorption has prompted the use of 1,25-$(OH)_2D_3$ and the synthetic analog 1α-hydroxyvitamin D_3 (1-$(OH)D_3$) to prevent milk fever. In most studies on milk fever prevention the vitamin D metabolites were administered parenterally (*Sansom et al.* 1976, *Gast et al.* 1979, *McMurray et al.* 1980, *Sachs et al.* 1983), but recent studies have demonstrated their efficacy by oral administration (*Hove et al.* 1983, *Hove* 1984 a, b).

A major problem with both parenteral and oral prevention regimes is the difficulty in predicting the actual day of calving. This is probably why a single oral dose of 1,25-$(OH)_2D_3$ before parturition protected only about 50 % of treated cows (*Hove &*

Kristiansen 1982). Induction of parturition has been used as a means of synchronizing vitamin D metabolite treatment and calving (*McMurray et al.* 1980, *Sachs et al.* 1983). In the present study we have tried to overcome the difficulty by feeding daily oral doses of 1,25-$(OH)_2D_3$ from about day 5 before expected parturition until the calving.

MATERIALS AND METHODS

Animals

Fifty-eight cows of Norwegian dairy breed were used when at third or later parturition. The cows were fed according to, or slightly above Norwegian standards (*Ekern & Vik-Mo* 1983). The experiment was conducted during the indoor season and available feeds changed somewhat during the experiment. Silage and concentrates were used throughout, while freshly cut grass and turnip leaves were added in early autumn and turnip roots in winter. The diet was supplemented with minerals (especially Mg) and daily intakes from the basal ration in the last weeks before calving were 45—60 g Ca, 25—30 g Mg and 33—43 g P. Cholecalciferol added to the concentrate supplied at least 9000 U/d of vitamin D. Observations started 10—14 d before expected calving. In the presentation of data from individual animals days were numbered relative to the day of parturition (Day 0), days after parturition being positive and days before parturition negative.

Experimental plan

The experiment was planned with 6 groups of 10 cows per group, but was terminated when 39 cows had completed the observation period because of a high incidence of milk fever in some of the groups. The actual number of cows in each group is shown in Table 1. The groups were initially matched for age, but no account was taken of earlier episodes of milk fever. The groups were designed to compare the effect of 3 dose levels of 1,25-$(OH)_2D_3$ (0, 100 and 200 µg/d) in cows receiving the basal ration and in cows fed a Ca supplement (250 g $CaCO_3$/d, Table 1).

Treatments

Synthetic 1,25-$(OH)_2D_3$ (F. Hoffman la Roche, Basel, Switzerland) was incorporated in fatty acid pellets by Rumen Kjemi

A/S, Oslo. The fatty acid pellets contained 10 μg 1,25-$(OH)_2D_3$/g and the average pellet size was 40 mg. The matrix consisted of (g/kg): 540 C_{18}—C_{20} fatty acids, 370 glucose, 60 calcium carbonate, 30 adjuvants (emulgator, antioxidant). Pellets were given orally by bottle, or mixed into the concentrate.

The pellets were given daily from day 5 before expected parturition until the day after parturition. Treatments were started earlier in animals which showed clear signs of approaching parturition (relaxation of pelvic ligaments and rapidly enlarging udders). Finely ground limestone (> 98 % $CaCO_3$) was used to supply 100 g of Ca extra per day. The supplement was mixed with silage or concentrates. All treatments were given in the morning.

Blood sampling and analysis

Samples of venous blood (30 ml) were drawn daily about 3 h after start of morning feeding from day —10 until day 14. Collected blood was stored in ice until plasma was separated, usually within 2 h. Plasma was kept frozen (—20°C) until analyzed. Plasma concentrations of Ca and Mg were determined by atomic absorption spectrophotometry. Standard colorimetric procedures (Technicon autoanalyzer) were used for inorganic phosphorous (P) and hydroxyproline. Plasma 1,25-$(OH)_2D$ concentrations were measured by radioimmunoassay on extracts of plasma purified by high pressure liquid chromatography as described earlier (*Hove* 1984 b). The metabolite was measured in samples taken around calving from 4—6 cows per dose level of 1,25-$(OH)_2D_3$.

Clinical examination

All cows were examined daily for signs of hypocalcaemia during the first 14 d of lactation. A milk fever diagnosis was assigned to cows that were unable to respond to the various stimuli used to try to make the cow stand. Cows with milk fever were treated with iv infusions of $CaCl_2/MgCl_2$ solution.

Statistics

Effect of the treatments on plasma components were tested by t-test both within and between groups, while a chi square test was used to compare frequencies of milk fever in the different groups.

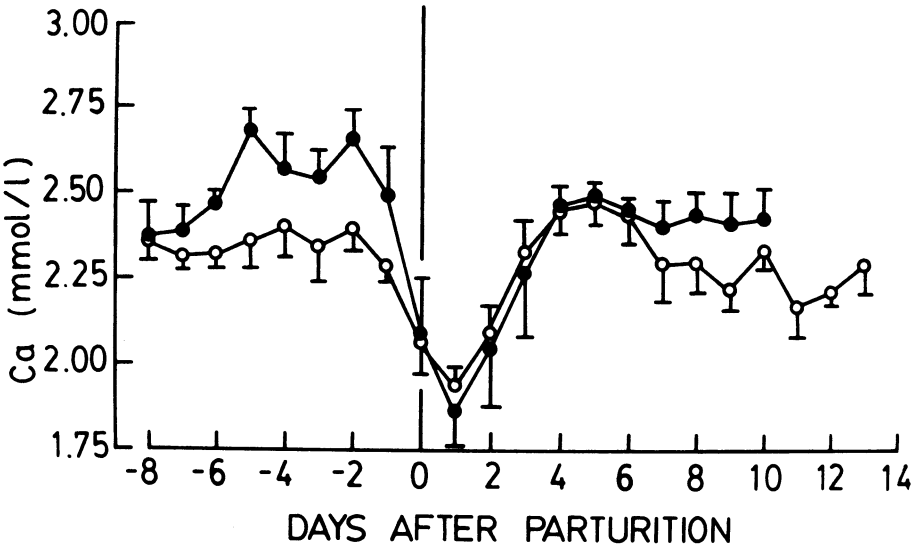

Figure 1. Plasma Ca concentrations in control animals supplemented with no (O) or 250 g/d $CaCO_3$ (●). Averages with their standard errors.

RESULTS

Plasma calcium

Untreated cows showed constant plasma Ca values until 1 d before parturition, followed by a decline to a minimum of 1.90 mmol/l on day 1. Supplements of $CaCO_3$ increased plasma Ca about 0.25 mmol/l before parturition (Fig. 1, $P < 0.01$), but could not prevent the fall in plasma Ca after parturition (Fig. 1). Similar minimum values were seen in both groups on day 1. Plasma Ca concentrations in the control cows returned to normal within 1—2 d after the minimum seen at parturition. A tendency to reduced levels was, however, seen in the unsupplemented group on days 8—11 (Fig. 1).

Plasma Ca rose in all animals treated with 1,25-$(OH)_2D_3$ when values the day before start of treatment were compared to values 2 d before parturition (Figs. 2 and 3). Average increments ranged from 0.25—0.43 mmol/l, with the highest values in cows receiving $CaCO_3$ supplements and the 200 µg dose of 1,25-$(OH)_2D_3$ (Fig. 3). Plasma Ca fell around parturition also in the 1,25-$(OH)_2D_3$-treated groups, starting at day —1 and reaching a minimum on day 0 or 1. In contrast to the untreated animals,

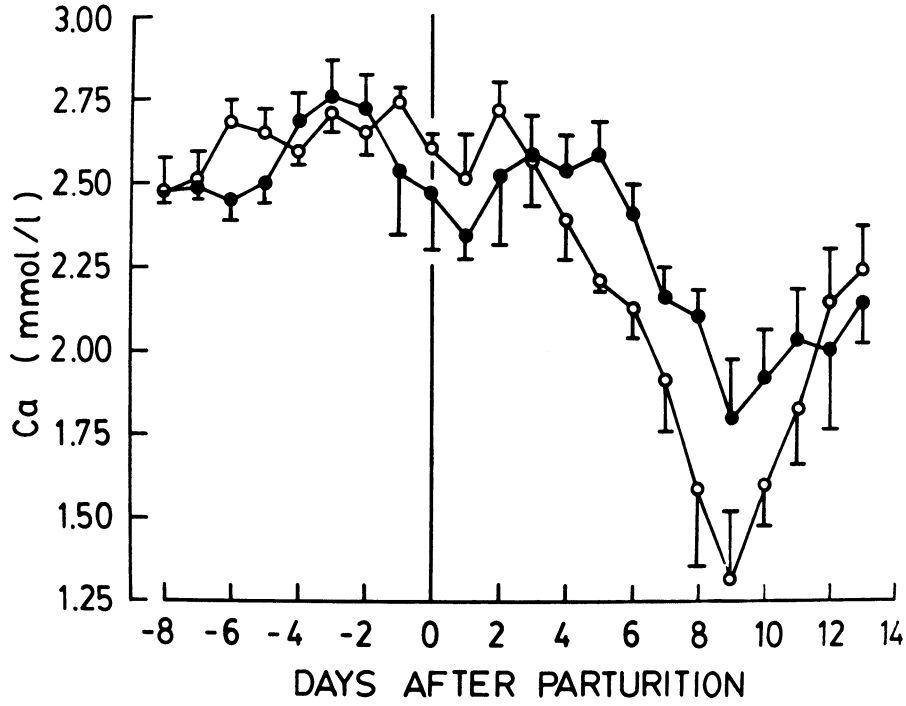

Figure 2. Plasma calcium concentrations in cows treated with daily oral doses of 100 µg 1,25-$(OH)_2D_3$ and supplemented with no (○) or 250 g/d $CaCO_3$ (●) for the 5 last days before parturition. Averages with their standard errors.

plasma Ca concentrations at parturition were in the range normally found outside the month of calving (i.e. 2.2—2.7 mmol/l). On day 1 differences between 1,25-$(OH)_2D_3$ treated and non-treated groups were highly significant in all groups ($P < 0.001$). A difference between the group receiving both 200 µg 1,25-$(OH)_2D_3$ and $CaCO_3$ (minimum Ca 2.77 mmol/l) and the other groups receiving 1,25-$(OH)_2D_3$ (average Ca minima 2.53—2.34 mmol/l) was also evident ((Figs. 2 and 3).

The incidence of hypercalcaemia cannot be deduced from the mean curves. The maximum plasma Ca observed in the whole study was 3.07 mmol/l, and values above 3.0 mmol/l were seen in 6 of 21 1,25-$(OH)_2D_3$ treated cows. In the 1,25-$(OH)_2D_3$ treated cows high or normal Ca levels were maintained for a few days following parturition. Then followed a period of several days where plasma Ca in all treated groups declined at an apparently similar rate of 0.2 mmol/day until in several cases

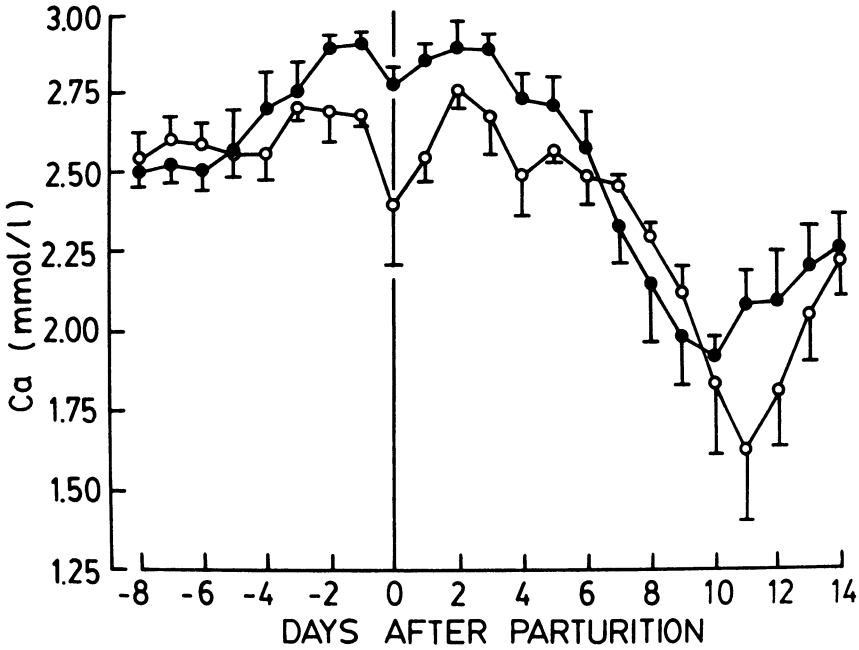

Figure 3. Plasma calcium concentrations in cows treated with daily oral doses of 200 µg 1,25-$(OH)_2D_3$ and supplemented with no (○) or 250 g/d $CaCO_3$ (●) for the last 5 days before parturition. Averages with their standard errors.

clinical milk fever occurred. Average minimal plasma Ca values appeared on day 9 in the groups treated with 100 µg 1,25-$(OH)_2D_3$ (Fig. 2), and on day 10 and 11 in the groups receiving 200 µg 1,25-$(OH)_2D_3$ before parturition (Fig. 3). Plasma Ca was better maintained when $CaCO_3$ supplements were given irrespective of the dose of 1,25-$(OH)_2D_3$ (Figs. 2 and 3). No relationship was found between the extent of hypercalcaemia during 1,25-$(OH)_2D_3$ treatment and the subsequent hypocalcaemia on days 7—13.

Fig. 4 compares individual minima of all cows in the two critical periods —1 to 2 d and 7 to 14 d after parturition. Values below 1.5 mmol/l indicating a high risk of milk fever were seen in all 1,25-$(OH)_2D_3$ treated groups. It should be noted that several of the control cows showed Ca minima below 2.0 mmol/l in this period.

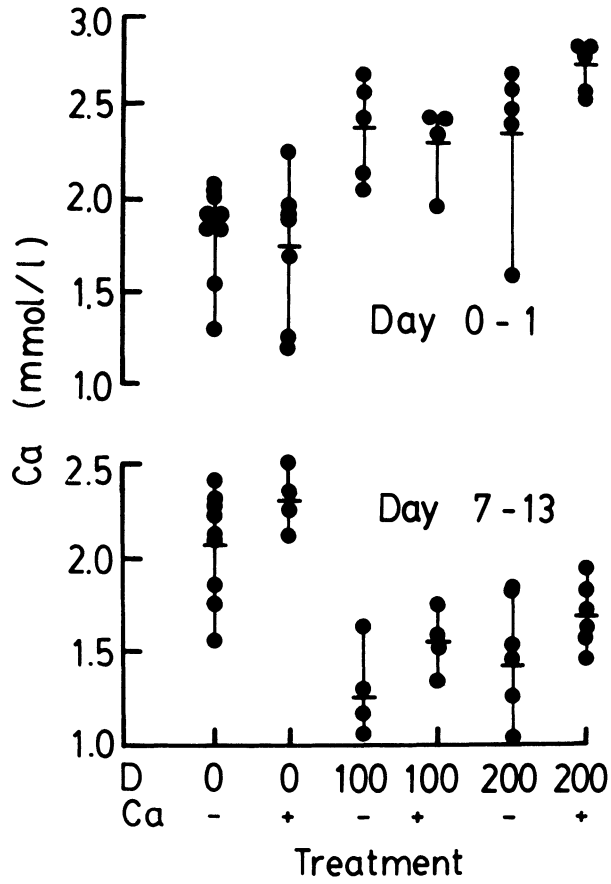

Figure 4. Minimal plasma calcium values in each of the experimental groups. Top graph: Minima days 0—1. Bottom graph: Minima days 7—13 after parturition. Treatments with 1,25-dihydroxyvitamin D_3 (D) and $CaCO_3$ are indicated under each column. Average Ca concentrations in each group and time interval are shown by horizontal bars.

Plasma phosphate

Changes in plasma P were not markedly influenced by $CaCO_3$ supplementation. Therefore only observations from the unsupplemented groups are given in Fig. 5. Cows treated with 1,25-$(OH)_2D_3$ had higher plasma P at calving (day 0 and 1) than untreated controls ($P < 0.01$; all treated groups). Low mean P values were prominent on day 8—11 in animals treated with 1,25-$(OH)_2D_3$.

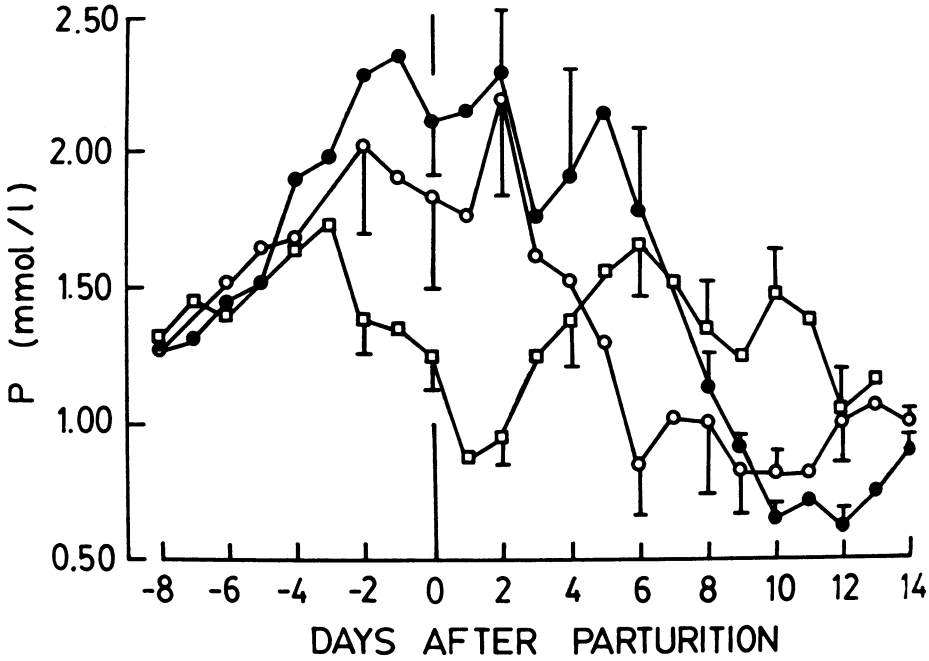

Figure 5. Plasma inorganic phosphate concentrations in cows treated with daily oral doses of 0 (□), 100 (○) or 200 (●) µg 1,25-$(OH)_2D_3$. Averages with their standard errors.

Plasma magnesium

Plasma Mg was variable during the last week of pregnancy. A peak in plasma Mg averages seen on day 0 and 1 in untreated cows was small or lacking in the 1,25-$(OH)_2D_3$ treated animals (Fig. 6). Higher Mg averages were again common in all groups on days 8—12, simultaneously with the hypocalcaemic episodes in the 1,25-$(OH)_2D_3$ treated cows.

Plasma 1,25-$(OH)_2D$

Average concentrations of 1,25-$(OH)_2D$ in plasma ranged from about 50 pg/ml in untreated, preparturient cows to a peak of 201 ± 21 (s.e.m.) pg/ml at day 0 in cows treated with 200 µg/d 1,25-$(OH)_2D_3$ ($P < 0.001$, Fig. 7). Intermediate concentrations were seen in cows treated with 100 µg/d (116 ± 12 pg/ml). On the day of calving, average 1,25-$(OH)_2D$ levels in all the 1,25-$(OH)_2D_3$ treated groups were higher than in untreated controls

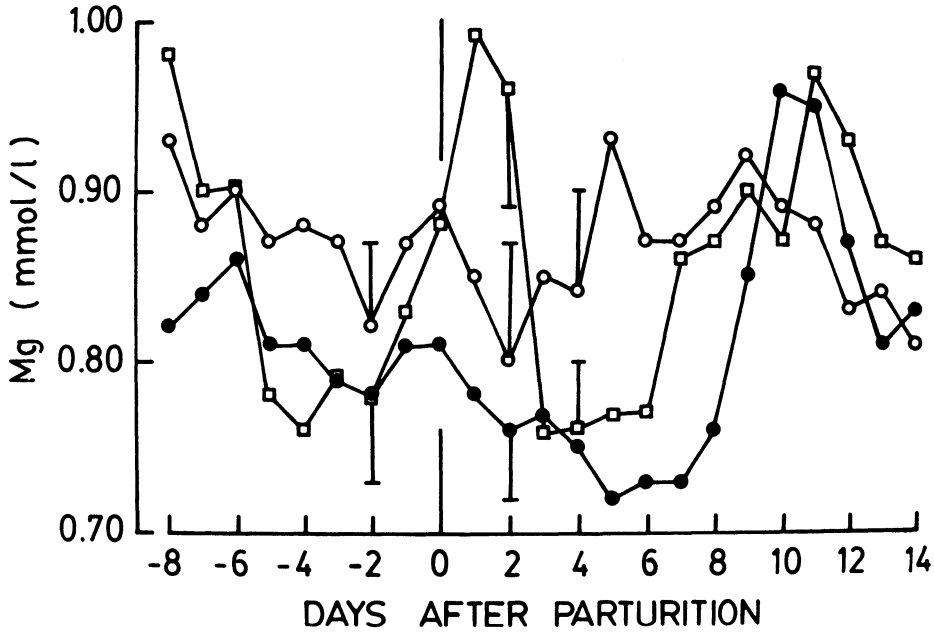

Figure 6. Plasma Mg concentrations in cows treated with daily oral doses of 0 (□), 100 (○) or 200 (●) μg 1,25-$(OH)_2D_3$. Averages with their standard errors.

($P < 0.01$). Plasma 1,25-$(OH)_2D$ increased rapidly immediately following parturition in the untreated controls, and from day 1 both treated and untreated cows showed similar values (Fig. 7).

Plasma hydroxyproline

Plasma hydroxyproline concentrations were relatively constant about 13 mg/l until parturition, followed by a remarkably parallel increase to nearly twice the pre-calving levels in both treated and control animals (Fig. 8).

Occurrence of milk fever

A comparison of milk fever cases at the time of parturition between untreated cows (22 %, groups 1 and 2) and 1,25-$(OH)_2D_3$ treated cows (5 %) showed a significant effect of the treatment ($P < 0.01$). Clinical hypocalcaemia occurred, however, in all treated groups 8—12 d post partum, indicating an inductive effect of the 1,25-$(OH)_2D_3$ treatment on milk fever (Table 1).

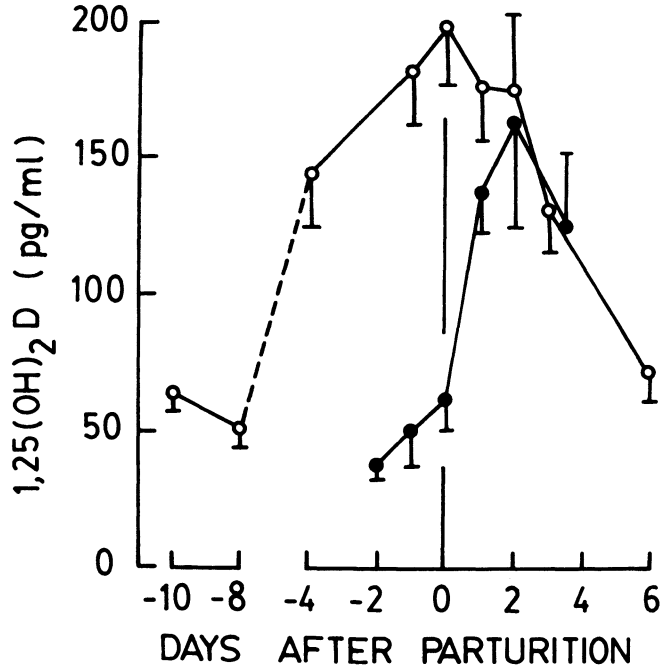

Figure 7. Plasma concentrations of 1,25-dihydroxyvitamin D (1,25-$(OH)_2D$) in 5 cows treated daily with 200 μg 1,25-$(OH)_2D_3$ from about day 5 before parturition until day 1 after parturition (○) and in 5 untreated cows (●). Averages with their standard errors.

Table 1. Summary of treatments and the number of cows contracting milk fever in each group. Days treated (± s) represent the number of days from first treatment until day 1 after parturition, both days inclusive.

	Group no.					
	1	2	3	4	5	6
1,25-$(OH)_2D_3$, (μg/d)	0	0	100	100	200	200
Days treated	—	—	8.6±4.2	6.5±2.4	6.5±2.7	7.3±2.4
$CaCO_3$, g/d	0	250	0	250	0	250
Days treated	—	5.9±2.6	—	4.8±2.6	—	6.5±3.4
Cows (no.)	11	7	5	4	6	6
Lactation no.	4.2±1.1	6.9±2.3	4.6±1.5	4.8±1.0	5.2±1.9	4.0±1.3
Milk fever (no.)	2	2	3	1	3	1

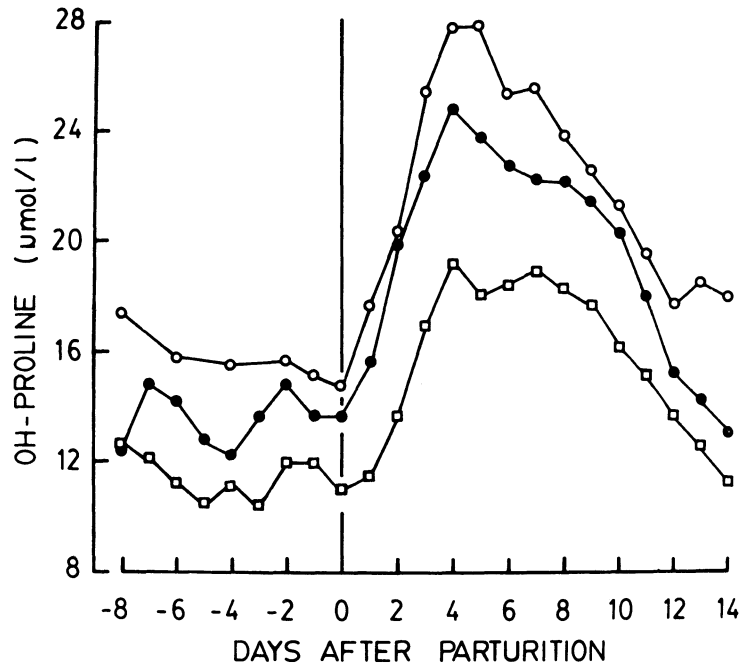

Figure 8. Average plasma hydroxyproline concentrations in cows receiving daily doses of 0, 100 or 200 μg 1,25-dihydroxyvitamin D_3 (●, ○, □) for approximately 5 d before parturition.

Higher average plasma Ca concentrations in the $CaCO_3$ supplemented, 1,25-$(OH)_2D_3$ treated groups than in unsupplemented groups on days 8—12 (Figs. 2 and 3) were paralleled by a tendency to higher milk fever frequencies in the unsupplemented groups (Table 1).

DISCUSSION

Treatment with 1,25-$(OH)_2D_3$ before parturition resulted in plasma 1,25-$(OH)_2D$ concentrations of 100—200 pg/ml on day —2 to 0. Similar plasma levels were observed after parturition in untreated animals, in agreement with findings in the literature (*Horst et al.* 1977, *Green et al.* 1981, *Hove & Kristiansen* 1982). The treatments given thus appeared to mimic the changes which normally occur in plasma 1,25-$(OH)_2D$ at parturition a few days before calving actually took place. Plasma concentrations of 1,25-$(OH)_2D$ were generally lower than those reported

following injections of 1,25-$(OH)_2D_3$ and 1-$(OH)D_3$, but consistent with observations from cows treated orally (*Hove et al.* 1983).

The observed effects of 1,25-$(OH)_2D_3$ on plasma mineral levels before and around parturition may largely be attributed to a stimulation of intestinal calcium and phosphorous absorption, since we have previously shown a dose-related stimulation of radiocalcium absorption in goats following oral treatment with 1,25-$(OH)_2D_3$ (*Hove* 1984b). Daily oral doses of 5 μg 1,25-$(OH)_2D_3$ resulted in a 2—3 fold increase in radiocalcium absorption, when given for 5 d to non-lactating goats.

Although systemic concentrations of 1,25-$(OH)_2D$ remained within the physiological range during treatment, there were several cases of hypocalcaemia and hyperphosphataemia before parturition. This suggests a local effect of the orally administered 1,25-$(OH)_2D_3$ on intestinal cells during absorption of the metabolite. The normal 1,25-$(OH)_2D$ and hydroxyproline concentrations in plasma before parturition exclude a major effect of 1,25-$(OH)_2D_3$ on bone mobilization. This is in agreement with reports of constant or decreased plasma hydroxyproline levels after vitamin D metabolite treatment in lactating and non-lactating cows (*Bjorklund et al.* 1976, *Hove et al.* 1983). The parallel plasma hydroxyproline curves after parturition in both 1,25-$(OH)_2D_3$ treated and untreated cows (Fig. 8) suggest that plasma hydroxyproline is a poor indicator of bone mobilization in the periparturient cow. The doubling of plasma concentrations of hydroxyproline was probably instead due to involution of the reproductive organs, which proceed rapidly during the first weeks post partum.

Plasma minerals and prevention of milk fever

A milk fever frequency at parturition of only 5 % in the 1,25-$(OH)_2D_3$ treated cows showed that oral treatment with 1,25-$(OH)_2D_3$ significantly reduced milk fever at this time. Daily doses of 1,25-$(OH)_2D_3$ thus appeared much better than the single dose treatment used previously (*Hove & Kristiansen* 1982), and in line with the best results from trials using injections of 1-$(OH)D_3$ (*Wittwer & Ford* 1978, *Mazor et al.* 1980, *McMurray et al.* 1980). Plasma analyses further indicated that all cows which remained healthy had Ca values above 1.95 mmol/l on day 0—1 (Fig. 4), the time when plasma Ca reached a minimum in untreated animals.

A dramatic rebound of plasma Ca concentrations with several cases of clinical milk fever occurred, however, on days 8—12 in the 1,25-$(OH)_2D_3$ treated cows. A similar tendency to reductions in plasma Ca some 10 d after parturition were noted also after single treatments with 1,25-$(OH)_2D_3$ (*Hove & Kristiansen* 1982) and by *McMurray et al.* (1980, 1983) following 1-$(OH)D_3$ treatment or feeding of single doses of leaves of the calcinogenic plant Solanum malacoxylon. It is remarkable that other studies have not reported difficulties with the Ca homeostasis of the cow in this period, despite the many studies published on the use of vitamin D metabolites for milk fever prevention. An explanation may be that blood sampling in most milk fever trials is discontinued about a week after calving. The high incidence of hypocalcaemia and clinical paresis of this trial suggested that 1,25-$(OH)_2D_3$ treatment could have been responsible. Closer examination of the untreated cows showed a tendency to spontaneous hypocalcaemia in several of the animals 8—12 d post partum (Fig. 1). Similar plasma Ca changes were found in about 50 % of older cows (*Hove*, unpublished). A possible explanation of this apparently impaired Ca-homeostasis is that adaptations triggered by parturition, predominantly in intestinal Ca absorption, last about a week. There is supporting evidence for this explanation in the fact that a single dose of 1,25-$(OH)_2D_3$ stimulates absorption for at least 6 d in the goat, but returns to control levels 12 d after treatment (*Hove* 1984b). In the present experiment treated cows were exposed to a longer period of elevated plasma 1,25-$(OH)_2D$ levels than the control animals, and it is possible that the cows became severity hypocalcaemic because of the known action of 1,25-$(OH)_2D_3$ in suppressing renal 1α-hydroxylase. Alternatively the period of hypercalcaemia before parturition may have affected the homeostatic responses required to cope with the demands of lactation. Further experimentation is required to clarify this.

The effect of 1,25-$(OH)_2D_3$ on plasma Ca was dose related, 200 μg/d giving the most pronounced hypercalcamia. Interestingly the treated cows showed a drop in Ca and P on day 0—1 indicating that the stimulated intestinal absorption could not completely balance the increased demands at the onset of lactation. This drop in plasma Ca could be secondary to a transient reduction in intestinal activity at parturition, since normal or

elevated plasma Ca levels were maintained for the following first few days of lactation in treated cows.

Side effects of 1,25-$(OH)_2D_3$ treatment

Treatment with vitamin D or its metabolites carries a risk of toxic side effects. The hypercalcaemia observed in the present experiment was considerably milder than that reported in 1-$(OH)D_3$ intoxicated cows or calves (*Bjorklund et al.* 1976, *Mullen et al.* 1979). No impairment of appetite was noticed in the present experiment, while this was prominent both in the studies just referred to an in a study where 1—25 μg 1-$(OH)D_3$ was injected per kg body weight (*Sansom et al.* 1976). 1,25-$(OH)_2D_3$ is apparently less potent than 1-$(OH)D_3$ in stimulating Ca absorption in ruminants (*Hove* 1984b). The relatively low doses of 1,25-$(OH)_2D_3$ (200—400 ng/kg used in the present experiment can probably explain the absence of symptoms of vitamin D toxicity.

An inverse relationship between plasma Ca and Mg has been reported repeatedly both around parturition and following treatment with vitamin D and its metabolites. The hypomagnesaemia seen during vitamin D metabolite treatment may be mediated by an effect of the hypercalcaemia on renal Mg transport (*Hove et al.* 1983, *Halse* 1984). Hypomagnesaemia may impair Ca homeostasis at parturition by reducing bone mineral mobilization (*Contreras et al.* 1982). In the present study all cows received Mg supplements, and nearly identical plasma Mg values were observed in the periparturient period in treated and untreated animals. This is in agreement with results obtained in 1-$(OH)D_3$ treated cows (*McMurray et al.* 1980). Plasma Mg should, however, be cautiously monitored, since oral, 1,25-$(OH)_2D_3$ treatment may have clinically important effects on plasma Mg under differing feeding conditions.

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SAMMENDRAG

Melkefeberprofylakse ved oral tilførsel av 1,25-dihydroxyvitamin D_3.

Virkningene av daglige orale doser av 1,25-dihydroksyvitamin D_3 (1,25-$(OH)_2D_3$) på innhold av mineraler i plasma og på forekomst av melkefeber ble studert hos 39 eldre kyr. Tre dose-nivåer av 1,25-$(OH)_2D_3$ (0, 100 og 200 μg/d) ble sammenlignet hos dyr med og uten tilskudd av 100 g Ca/d (250 g $CaCO_3$). Behandling ble gitt fra dag 5 før forventet kalving (dag —5) til dagen etter kalving (Kalving = dag 0).

Gjennomsnittlig plasma Ca nivå var normalt eller forhøyet under behandlingen og gjennom kalvingsperioden fram til dag 3—5. I kalvingsperioden fikk 1 av 21 behandlede og 4 av 18 ubehandlede dyr melkefeber. Mens ubehandlede raskt normaliserte plasma Ca etter kalving utviklet samtlige behandlede dyr hypokalsemi og hypofosfatemi som kulminerte dag 8—11 med 7 tilfeller av melkefeber. Tilførsel av ekstra $CaCO_3$ reduserte, men kunne ikke forhindre utvikling av hypokalsemi.

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