Role of Vitamin D in Calcium Homeostasis and Its Use in Prevention of Bovine Periparturient Paresis

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Horst RL, Goff JP, Reinhardt TA: Role of vitamin D in calcium homeostasis and its use in prevention of bovine periparturient paresis. Acta vet. scand. 2003, Suppl. 97, 35-50. — Calcium (Ca) is essential for life in higher animals. It is involved in the normal functioning of a wide variety of tissues and physiologic processes which include bone formation, muscle contraction, nerve transmission, blood clotting and as a second messenger regulating the actions of many hormones. In order for these functions to be carried out properly, blood Ca concentrations must be monitored and regulated within strict limitations. The discovery of the vitamin D endocrine system has resulted in the realization that Ca regulation in mammals and birds involves a coordinated effort between the hormones parathyroid hormone (PTH), calcitonin and the hormonally-active form of vitamin D$_3$, 1,25-dihydroxyvitamin D$_3$ [1,25(OH)$_2$D$_3$]. Failure of this system to maintain normal blood Ca concentrations at parturition is a common occurrence in ruminants leading to clinical (periparturient paresis, milk fever) and subclinical hypocalcemia. Vitamin D sterols have played a significant role in efforts to avoid parturient hypocalcemia and this report will summarize advantages and disadvantages associated with their use.

periparturient paresis; dairy cows; vitamin D; milk fever prevention.

Introduction

The demand for Ca during lactation constitutes a tremendous challenge to maternal Ca homeostasis and, in most species, the lactational drain of Ca exceeds the Ca demand for fetal skeletal formation in late gestation. For example, a lactating dairy cow in peak lactation secretes 80-100 g of Ca/d in milk. In a normal cow, the Ca content of blood is 2-3 mM, whereas that of milk is 25-30 mM and colostrum is 62-75 mM. Therefore, bovine milk and colostrum represent a 10- and 30-fold increase, respectively, in Ca concentration over that of blood. Looking at this blood to milk Ca flow a little differently we can see that a cows’ plasma Ca pool of 2-4 g would be completely depleted of Ca at least 20-30 times/d to meet the demands of peak milk production. Therefore, several adaptive changes must occur in order to deal with the lactational Ca demands. Generally, the increased need for Ca at the onset of colostrum and milk production is dealt with successfully; however, some species have difficulty maintaining normal blood Ca concentrations. For example, dairy goats and dairy cows, selected and raised for maximum milk output, can develop a metabolic disease called periparturient paresis or more commonly referred to as milk fever (Horst et al. 1994). Milk fever occurs at or near parturition, especially in high-producing dairy cattle. The onset is associated with the initia-
tion of lactation and is characterized by a rapid decline in serum Ca and phosphorus concentrations. A cow producing just 10 liters (22 lb) of colostrum (2.3 g of Ca/kg) will lose 23 g of Ca in a single milking. This is about nine times as much Ca as is present in the entire plasma Ca pool of the cow. Ca lost from the plasma pool must be replaced by increasing intestinal Ca absorption and/or bone Ca resorption. During the non-lactating period the Ca requirements are minimal (fetal and endogenous fecal Ca drain are 10 to 12 g Ca/day). Therefore, mechanisms for replenishing plasma Ca during high Ca demand are relatively inactive (Ramberg et al. 1984). At parturition, the cow must bring 30 or more g of Ca into the Ca pool each day. Thus, nearly all cows experience some degree of hypocalcemia during the first days after calving, while the intestine and bone adapt to the Ca demands of lactation. In some cows, the mammary drain of Ca causes extracellular and plasma Ca concentrations to decline to concentrations (4-5 mg/dl) that disrupt neuromuscular function, resulting in the clinical syndrome milk fever. Intravenous Ca treatments (usually 8 to 10 g Ca) are used to keep the cow alive long enough for intestinal and bone Ca transport mechanisms to adapt. If left untreated approximately 60-70% of the animals will succumb to this condition.

The reasons some species are more successful than others at maintaining normocalcemia during the onset of lactation are unclear. In this report we will discuss vitamin D metabolism and the use of vitamin D metabolites and analogues for prevention of hypocalcemia in periparturient dairy cows.

**Results and discussion**

**Vitamin D metabolism**

Contemporary views categorize vitamin D₃ not as a vitamin but rather as a pro-steroid hormone (Figure 1). This concept is supported by the fact that in mammals vitamin D₃ is derived from a cholesterol-like precursor found in the skin. The direct action of sunlight on this precursor, 7-dehydrocholesterol, results in cleavage of the B-ring of the steroid structure that, upon thermoisomerization, yields the characteristic secosteroid. The significance of vitamin D as a pro hormone became clearer in 1967 when Morii et al. (1967) isolated a new metabolite of vitamin D₃ from rats which was as effective as vitamin D₃ in healing rickets, raising blood Ca and increasing intestinal Ca transport. This compound acted more rapidly than vitamin D₃, requiring only 8-10 hr after oral administration to initiate its response. This metabolite was identified (Blunt et al. 1968) as 25-hydroxyvitamin D₃ (25OHD₃). The liver was demonstrated to be important in the production of this most abundant circulating form of vitamin D₃ which, under normal conditions, is present at 20-50 ng/ml. Shortly following the discovery of 25OHD₃, a number of laboratories showed that this metabolite is specifically hydroxylated at the 1α-position in the kidney to yield 1,25(OH)₂D₃ (Holick et al. 1971, Lawson et al. 1971, Norman et al. 1971). This metabolite is now generally accepted as the hormonally-active form of vitamin D₃. 1,25(OH)₂D₃ circulates at ~1000-fold lower concentrations than 25OHD₃ and is generally present at 20-65 pg/ml in normal human plasma (Broadus et al. 1980).

The control of the 1α-hydroxylation process is influenced by many factors (DeLuca 1992). However, the protein hormone PTH is most active and most important in regulating the 1α-hydroxylase enzyme (DeLuca 1992). The concentration of PTH in plasma is regulated mainly by plasma calcium. As calcium concentrations in the plasma decline < 10 mg/dl, the parathyroid glands are stimulated to produce PTH. In turn, PTH stimulates the activation of 25(OH)D by up-regulating 1α-hydroxylase enzyme in the kidney to form 1,25(OH)₂D₃. If
plasma Ca is >10 mg/dl, PTH secretion is depressed, and 1,25(OH)₂D₃ synthesis is depressed. During late gestation and lactation, 1,25(OH)₂D₃ is elevated 2-3 fold in most species (Halloran et al. 1979, Kumar et al. 1979, Toverud et al. 1983) and during early lactation in the bovine can reach concentrations 10-fold normal (Horst et al. 1977). During late gestation, these elevations in 1,25(OH)₂D₃ are largely the result of enhanced renal synthesis. However, there is evidence that 1,25(OH)₂D₃ may arise from extrarenal sources (Lobaugh et al. 1993), particularly the placenta (Gray et al. 1979). During lactation, however, the elevated 1,25(OH)₂D₃ is secondary to enhanced renal biosynthesis of 1,25(OH)₂D₃ which is predominately regulated by PTH but may also be influenced by prolactin (Spanos et al. 1981, Robinson et al. 1982) and/or PTH-RP (Horiuchi et al. 1988, Rosol et al. 1988).

The simplistic picture outlined for vitamin D₃ activation is complicated by the fact that vitamin D₃ can be oxidative to a variety of metabolites. Most of these numerous metabolites

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**Figure 1. Pathways of vitamin D₃ metabolism (from Horst & Reinhardt 1997).**
have no identifiable biological function and many indeed have been isolated from animals fed abnormally high amounts of vitamin D3. Nevertheless, the evidence collected to date indicates that 25-hydroxylated vitamin D3 metabolites are preferentially metabolized at the side chain. In particular, carbon centers C23, C24, and C26 are readily susceptible to further oxidation. Figure 1 illustrates products of these oxidative pathways.

As indicated, these oxidative pathways are shared by both 25OHD3 and 1,25(OH)2D3, and their importance is still a matter of controversy. For example, there is evidence that 24,25-dihydroxyvitamin D3 [24,25(OH)2D3] may function to stimulate bone mineralization (Bordier et al. 1978, Ornoy et al. 1978), suppress parathyroid hormone secretion (Canterbury et al. 1977) and maintain embryonic development (Henry & Norman 1978). For the most part, however, these side chain modifications are generally considered to be catabolic in nature. Although these side chain oxidative pathways yield metabolites which are considered "non-functional", the presence of these compounds in circulation could pose serious problems in the analysis for 25OHD3 and 1,25(OH)2D3 (Horst et al. 1981). Further complicating the issue of understanding vitamin D activation, catabolism and metabolite analysis is the presence of vitamin D2. Vitamin D2 has been shown to contribute significantly to the overall vitamin D status in humans and other mammals consuming supplemental vitamin D2 (Hollis & Pittard 1984, Reinhardt et al. 1984, Hartwell et al. 1987). Vitamin D2 can also be metabolized in a similar fashion to produce several metabolites analogous to the vitamin D3 endocrine system, including vitamin D2's hormonally active form, 1,25-dihydroxyvitamin D2 [1,25(OH)2D2] (Jones et al. 1975). Simple inspection of the side chain, however, would imply that differences between metabolism of vitamin D2 and vitamin D3 may exist. The presence of unsaturation at carbon centers C22/C23, along with the additional methyl group at C24, would seem to preclude the existence of the same metabolic pathways for the two vitamins. Figure 2 outlines the known pathways of vitamin D2 metabolism that have been shown to date.

**Mechanism of vitamin D action**

The cellular mechanism of action of the steroid hormone 1,25(OH)2D3 is similar to that described for other steroid hormones (Figure 3). 1,25(OH)2D3 circulates in blood bound primarily to the vitamin D binding protein (DBP) (Bikle et al. 1985).

Typically, less than 5% of the hormone circulates in the free state (Bikle et al. 1984). The free form of 1,25(OH)2D3 enters the target cell and associates with the 1,25(OH)2D3 receptor (VDR). The complex is phosphorylated and combines with a nuclear accessory factor, which has been determined to be the retinoic acid X receptor (RXR), to form a VDR/RXR heterodimer (Haussler et al. 1995). The VDR/RXR heterodimer has a high affinity for a number of vitamin D response elements (VDREs) which are present in the promoter region of 1,25(OH)2D3-dependent genes. Altered expression of these genes results in target cell modification and, ultimately, in the expression of biological effects associated with the presence of vitamin D which include, but not limited to, bone remodeling, intestinal calcium and phosphorus resorption, PTH suppression and catabolism of 1,25(OH)2D3 by the 24-hydroxylase (Haussler et al. 1995). As shown in Figure 3, the present working model for the mechanism of action of 1,25(OH)2D3 suggests that natural ligand for the RXR, namely 9-cis-retinoic acid, may have a negative effect on 1,25(OH)2D3-mediated transcription by preventing the formation of the VDR/RXR heterodimer. Indeed, in well-
defined in vitro systems this does appear to be the case (Haussler et al. 1995). Recently, however, there have been cell culture (Kane et al. 1996) and in vivo (Reinhardt et al. 1999) experiments suggesting that 9-cis-retinoic acid may actually enhance the activity of 1,25(OH)$_2$D$_3$ rather than inhibit its activity. Clearly the proposed negative effect of 9-cis-RA on 1,25(OH)$_2$D$_3$-mediated events needs to be further elucidated in cell culture and in vivo systems.

Use of the vitamin D compounds for milk fever prevention

Figure 4 displays the structures of the vitamin D compounds that have been studied for use as milk fever preventatives. This section will describe some of the experimental details involved with therapeutic implementation.

Vitamin D. Shortly following the discovery of vitamin D, researchers at the Ohio State University became aware of its utility as a milk fever preventative, thus ushering in a new era.

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of milk fever preventative measures. A variety of times and duration as well as routes of administration and quantities of the parent compound have been tried. The prophylactic regimes using vitamin D (either vitamin D₃ or vitamin D₂) requires the use of nearly toxic doses and are only effective when given within a precise time period prior to parturition. For instance, Hibbs and Pounden (1955) reported that feeding 20-30 million Units of vitamin D daily for at least 3 days prepartum, but not more than 7 days postpartum, reduced the incidence of milk fever by 80%. If treatments were extended beyond 10 days, widespread mineralization of soft tissues occurred and the incidence of milk fever was greater if vitamin D was not continued (Capen et al. 1966). Parental administration of 10 million Units 2-3 days before calving resulted in reduced incidence of milk fever. However, injection of more than 10 million Units during the last 10 days of parturition may result in clinical and pathological toxicity (Payne & Mansion 1967). A prolonged period (= 10 days) between administration of vitamin D and calving may dramatically increase the toxicity, as determined by Littledike & Horst (1980) who reported an 80% mortality in animals receiving 15-20 million Units in divided doses 30 days prepartum. This can be explained in part by the Ca demand of lactation. When relatively non-toxic doses of vitamin D (1-5 million Units) were used, they were found to be ineffective (Hibbs & Pounden 1955) or actually
increased the incidence of milk fever (Lit-tledike & Horst 1979). The availability of plasma metabolite assays provided insight into the mechanism of action of large doses of vitamin D in milk fever prevention. As discussed earlier, once in circulation the vitamin D is converted to 25OHD. Normally 25OHD circulates at 30 to 50 ng/ml in most species (Horst et al. 1981). However, when vitamin D is given in excess plasma 25OHD can be elevated to concentrations of 1000 ng/ml or greater (Clark & Potts 1977, Shepard & DeLuca 1980) while plasma 1,25(OH)_{2}D remains at or below normal concentrations (Hughes et al. 1976). When circulating at very high concentrations, 25OHD can compete effectively with 1,25(OH)_{2}D for binding to the 1,25(OH)_{2}D target tissue receptor (VDR). Therefore, during vitamin D toxicosis, 25OHD can induce actions usually attributed to 1,25(OH)_{2}D (Hughes et al. 1976). High circulating 25OHD can, therefore, explain how humans with low circulating concentrations of 1,25(OH)_{2}D can show signs of vitamin D toxicity (Hughes et al. 1976) and why anephric humans (who are incapable of producing 1,25(OH)_{2}D) can become vitamin D toxic (Counts et al. 1975).

Although it is generally accepted that 1,25(OH)_{2}D is reduced during hypervitaminosis, a notable exception to this generalization is the ruminant. Vitamin D_{3} intoxicosis initiated by giving 10-15 million IU of vitamin D_{3} IM results in significant elevations in plasma 1,25(OH)_{2}D_{3} in cattle (Reinhardt & Conrad 1980, Littledike & Horst 1982b).
contrast, pigs given the same IM dose showed a reduction in plasma 1,25(OH)\(_2\)D\(_3\), as was observed in other species (Horst & Reinhardt 1983). Therefore, elevations in plasma 1,25(OH)\(_2\)D may play a significant role in the pathogenesis of vitamin D toxicity in ruminants.

**25OHD\(_3\).** The elucidation of the vitamin D endocrine system and the availability of potent vitamin D metabolites renewed the search for a less toxic agent capable of preventing milk fever. As indicated earlier, 25-OHD is the most abundant circulating form of vitamin D in many species, including the cow. As a therapeutic agent this metabolite offered several advantages over vitamin D in that it does not have to undergo 25-hydroxylation and therefore acts more rapidly than vitamin D. This metabolite was postulated to be a prime candidate for milk fever prevention. Intramuscular administration of 4-8 mg of 25OHD\(_3\) was reported to prevent milk fever with no clinical evidence of hypervitaminosis D (Olson et al. 1973, Olson et al. 1974). Research determined that like vitamin D, 25OHD\(_3\) was less effective if parturition occurred <3 d and >10 d following treatment with 25OHD\(_3\). Frank et al. (1977) reported that 25OHD\(_3\) was effective if a 4 mg dose was given at least 3 days prepartum and repeated weekly for a maximum of three doses. Jorgensen et al. (1978) also reported that efficacy was improved in animals receiving low to normal dietary phosphorus.

**1,25-Dihydroxyvitamin D\(_3\).** The use of 25OHD\(_3\) as a milk fever preventative did not receive much research beyond the 1970's because the active form of vitamin D\(_3\), 1,25(OH)\(_2\)D\(_3\), had been isolated and identified during this period. This metabolite had several distinct advantages over vitamin D and 25OHD in that it required no further metabolism to become active, resulting in a more rapid onset of action. The discovery of this metabolite prompted several reports regarding its efficacy for milk fever prevention. Experiments by Gast et al. (1979) suggested intramuscular injections of 1,25(OH)\(_2\)D\(_3\) resulted in an increase in serum Ca within 12 hr of administration. They also determined that 400 µg of 1,25(OH)\(_2\)D\(_3\) beginning 5 days before parturition and repeated every 5 days was successful at preventing milk fever with no signs of hypervitaminosis D. Similar findings were reported by Hoffsis et al. (1979) who suggested an initial 600 µg dose at least 24 hr prepartum followed by 270 µg every 2-3 days until calving prevented milk fever, and again these treatments resulted in no clinical evidence of toxicity. Hove & Kristiansen (1982, 1984) demonstrated the efficacy of oral administration of 1,25(OH)\(_2\)D\(_3\) in a fatty acid matrix. They found that 100-200 µg/day orally beginning 5 days before predicted calving and fed until 1 day postpartum was effective at preventing hypocalcemia at parturition and was more efficacious than a single oral dose of 500 µg given 1-3 days prepartum.

**24,25-Dihydroxyvitamin D\(_3\).** In their studies with 24,25(OH)\(_2\)D\(_3\), Barton et al. (1984) noticed a dramatic increase in the milk fever incidence when pharmacologic doses (4 mg) of this metabolite were given parenterally 7 days before predicted calving date. Fifty percent of the animals receiving the metabolite developed milk fever verses 7% of the controls, suggesting that 24,25(OH)\(_2\)D\(_3\) somehow induces milk fever. Research conducted by Cornell (Smith et al. 1982) found a negative correlation between 24,25(OH)\(_2\)D\(_3\) and Ca concentration in paretic cows. Horst et al. (1979), however, found only slight elevations in plasma 24,25(OH)\(_2\)D\(_3\) precalving in cows developing milk fever and no differences were observed between paretic and non-paretic animals at parturition. Barton's observation suggests that pharmacologic concentrations of 24,25(OH)\(_2\)D\(_3\) may influence responsiveness.
of target tissues to Ca regulation hormones. 24,25(OH)2D3 has been shown to antagonize 1,25(OH)2D3 actions in bone cells (Kriajev & Edelstein 1994). However, there has been no compelling evidence to date to suggest that 24,25(OH)2D3 plays a significant role in the etiology of milk fever under physiologic conditions.

1α-Hydroxyvitamin D3. 1α-hydroxyvitamin D3 is an analogue of 1,25(OH)2D3 which was discovered during the development of a synthetic process for production of 1,25(OH)2D3. To become active, 1α-hydroxyvitamin D3 must be metabolized in the liver to 1,25(OH)2D3. The process of 25-hydroxylation is relatively unregulated; therefore, 1α-hydroxyvitamin D3 has almost equal biological activity to 1,25(OH)2D3. In addition, this compound was relatively inexpensive and easier to produce compared to 1,25(OH)2D3 and therefore more available for experimentation. These advantages made it one of the more popular vitamin D analogues to be tested for milk fever prevention. Sansom and co-workers (1976a, 1976b) had the first reports on the use of 1α-hydroxyvitamin D as a preventative for milk fever. These initial reports were followed by several investigations from Israel (Sachs et al. 1977, Bar et al. 1980, Sachs et al. 1983, Bar et al. 1985), Europe (Davies et al. 1978, Wittwer & Ford 1978, McMurray et al. 1980, Wittwer & Ford 1980, Mansion et al. 1981, Vagg et al. 1981, Barlet & Davicco 1992) and the United States (Marquardt et al. 1974, Gast et al. 1977, Hodnett et al. 1992) describing several dosage regimes. As with the other attempts to use compounds in the vitamin D family, predicting calving date was a problem; i.e. animals calving <1 day or >5-7 days after treatment were not protected. This problem was somewhat overcome by use of multiple injections (Vagg et al. 1981) or induction of parturition (McMurray et al. 1980, Sachs et al. 1983) to occur within the protective range.

24F-1,25-dihydroxyvitamin D [24F-1,25(OH)2D3]. 24F-1,25(OH)2D3 is an analogue of 1,25(OH)2D3 containing a fluoro group in the 24R position. Presence of the fluoro group in this position blocks 24-hydroxylation which is the first step in deactivation of 1,25(OH)2D3. Therefore, 24F-1,25(OH)2D3 is ~1.5 times more potent and acts over a longer period of time than 1,25(OH)2D3. Two reports have been published using this active analogue of 1,25(OH)2D3 for milk fever prevention (Goff et al. 1988, Goff & Horst 1990). Injections of 100 μg and 150 μg at 7 days before calving and repeated every 7 days resulted in significant decline in milk fever incidence. Goff & Horst (1990) also reported the success of a sustained release implant of 24F-1,25(OH)2D3. The implant allowed for continuous release of small amounts of the analogue, thus minimizing the potential for tissue residues and short-term elevations in plasma analogue and metabolite concentrations associated with intramuscular injections of vitamin D compounds. The implants reduced the incidence of milk fever from 80% in control animals to 9% in the treated group. The combination of a longer acting analogue and the sustained release technology circumvented many of the problems regarding dose timing.

Calcinogetic plants. Plants in which vitamin D sterols have been found belong largely to the family of Solanaceae. Solanum glaucophyllum, a.k.a. Solanum malacoxylon, appears to be the species with the most abundant vitamin D activity, although others (Cestrum diurum, Trisetum flavescens) with less activity have been identified (Boland 1986). S. glaucophyllum has been extensively studied and a comprehensive review of the research has been published (Puche & Bingley 1995). S. glaucophyllum is widely distributed in the province of Buenos Aires in Argentina and in Brazil and causes the development of a calcinoctic disease in cattle called "Enteque Seco" (Worker Acta vet. scand. Suppl. 97, 2003)
& Corrillo 1967). The prevalence of this disease in South America prompted investigations into the factor(s) responsible for this disease. Early experiments suggested that the plant contains a water-soluble material, which stimulated Ca metabolism much like vitamin D₃ (O'Donnel & Smith 1973, Uribe et al. 1974). Later investigations identified the active principle as a 1,25-dihydroxyvitamin D₃-glycoside which explained its water-soluble characteristics and biological activity (Wasserman et al. 1976). Vitamin D sterols other than 1,25(OH)₂D₃ have also been shown to be present in the S. glaucophyllum (Esparza et al. 1982). These include 25OHD₃ and vitamin D₃; however, they are much less abundant and are less important than 1,25(OH)₂D₃ with regards to the biological activity associated with this plant. Although disease associated with this plant has been described only in ruminants there is a substantial evidence suggesting that the plant and/or plant extracts are also active in monogastrics (Canas et al. 1977, Napoli et al. 1977, Peterlik & Wasserman 1978). The calcinogenic activity of S. glaucophyllum was initially thought to reside only in the leaves; however, recent results suggest that there is substantial activity in the berries, stems and roots (Weissenberg et al. 1988). Estimates from bioassays suggest that the dried leaves of S. glaucophyllum can contain as much as 100 µg of 1,25(OH)₂D₃ activity/g dried material (Boland 1986). Many of the aforementioned compounds which have been used in milk fever preventative scheme are also popular in human medicine, making them less attractive for agricultural development. The naturally occurring 1,25(OH)₂D₃-glycoside found in S. glaucophyllum offers a potentially cheap viable alternative to the more expensive synthetic forms.

In order to become active the glycoside must be cleaved to liberate the 1,25(OH)₂D₃. Rumen microbes are very efficient at this process (de Boland et al. 1979). The first experiment utilizing S. glaucophyllum for milk fever prevention was reported by Roux et al. 1979. They found that feeding S. glaucophyllum significantly improved the Ca status of periparturient cows. They observed no significant negative effects of feeding S. glaucophyllum on milk production and feed consumption during the periparturient period. They did, however, observe that concentrations of Ca, phosphorus and magnesium were significantly higher during the first milking in the animals fed S. glaucophyllum. They also observed that plasma Ca concentrations in the newborn calves of treated cows were higher than those born to control animals. In later studies (Kunz & Hähnichen 1980, McMurray et al. 1983, Dirksen & Fricker 1986) similar results were observed with regards to preventing hypocalcemia at calving. Dirkson & Fricker (1986) concluded that 7.5-9 g/day was a safe effective dose for milk fever prevention. Kunz & Hähnichen (1980) performed extensive pathological studies on animals receiving 10-20 g/day of S. glaucophyllum for 5-6 days. Animals were slaughtered 19-31 days following the last dose of material. They observed mild microscopic calcification in those animals receiving 10 g/day for 5-6 days and more extensive lesions in animals fed the 20 g/day dose.

Vitamin D treatments and early lactation hypocalcemia

One of the potential problems utilizing the vitamin D family of compounds is the development of hypocalcemia and clinical signs of milk fever 10-14 days postpartum. In most of the experiment describing this problem, treatment with the vitamin D compounds was stopped at the day of parturition (Littledike & Horst 1982a, Hove & Kristiansen 1984, Goff et al. 1988). Postpartum 1,25(OH)₂D₃ concentrations in animals receiving prepartum treatments with vitamin D compounds suggested
Figure 5. The relationship between postpartum Ca nadir and plasma 1,25(OH)₂D₃ in control animals and those animals receiving treatment with vitamin D compounds.

that animals were unable to synthesize 1,25-(OH)₂D₃ in response to hypocalcemia (Littledike & Horst 1982a, Goff et al. 1988). Figure 5 plots the relationship between postpartum Ca nadir and plasma 1,25(OH)₂D₃ in control animals and those animals receiving treatment with vitamin D compounds. In control animals, there was a clear negative correlation between plasma Ca and plasma 1,25(OH)₂D₃; however, in treated animal’s plasma 1,25(OH)₂D₃ did not increase appropriately in response to hypocalcemia.

The animals in the latter group became dependent on exogenous 1,25(OH)₂D₃ to reverse their hypocalcemia. This apparent drug dependency problem is a significant problem in the use of vitamin D compounds for milk fever prevention. Goff & Horst (1990) overcame this problem by using slow release im-plants or phased withdraw of the compound to avoid problems associated with acute drug withdraw. Hove & Kristiansen (1984) also achieved some success by adding additional Ca to the postpartum ration.

Future considerations for the use of vitamin D metabolites in milk fever prevention

The utility of vitamin D sterols for use in milk fever prevention has been demonstrated. There is no question that the active metabolites and analogues work and have advantages over the parent compounds vitamin D₂ and vitamin D₃ because of their shorter half-life and reduced toxicity. However, they are prohibitively expensive (because they are also used in human medicine) and they have detrimental side effects, such as down-regulating kidney 1α-hydroxylase (Littledike et al. 1986).
Down-regulation of the kidney 1α-hydroxylase is a result from decreased sensitivity of the kidney to PTH, as demonstrated by Goff et al. (1988). They demonstrated abnormal production of 1,25(OH)₂D₃ in hypocalcemic animals treated with vitamin D analogues in the presence of a normal parathyroid response. Active metabolites and analogues stimulate intestinal Ca absorption having little, if any, effect on bone calcium resorption in normal animals (Goff et al. 1988). Up-regulating calcium absorption while having no effect on bone resorption and down regulating kidney 1α-hydroxylase will not likely be an effective milk fever preventative method. The most effective treatment would seem to involve a combination of enhanced bone resorption and increased intestinal Ca absorption similar to that observed with Ca-restricted diets (Green et al. 1981). Exogenous treatment with vitamin D compounds alone will not accomplish both tasks simultaneously in normal animals. As suggested earlier with 24F-1,25(OH)₂D₃, development of slow release forms for parenteral or oral administration would perhaps offer some advantages in avoiding side effects associated with abrupt withdrawal of treatment. Combinations of vitamin D compounds with dietary manipulations may also prove useful. For example, diets high in chloride and/or sulfur induce a metabolic acidosis, which also stimulates both intestinal Ca absorption and bone Ca resorption (Vagg & Payne 1970). These diets have been used successfully in milk fever prevention (Goff et al. 1991, Beede 1992, Oetzel 1993, Goff & Horst 1998). Horst et al. (2001) published preliminary observations suggesting that a combination of anionic diets along with S. glaucophylhum significantly reduced the incidence of subclinical hypocalcemia in dairy cows.

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