Minimizing Hypocalcemia During Early Lactation

Garrett R. Oetzel[1]
Department of Medical Sciences
University of Wisconsin-Madison

Abstract

There has been a recent resurgence of interest in minimizing hypocalcemia in early lactation cows. This interest has been fueled by new data from several large field studies that clearly demonstrate very detrimental effects of subclinical hypocalcemia, even when the incidence of clinical milk fever is very low. Impaired milk yield is the main economic problem associated with subclinical hypocalcemia, and the loss in milk yield begins at higher blood calcium concentrations than previously suspected. This new knowledge places even greater importance on the use of dietary means of preventing hypocalcemia (e.g., prepartum diets with low dietary cation-anion difference, low calcium, and high magnesium), as well as the strategic use of oral calcium supplements in cows after calving.

Introduction

The start of each new lactation challenges a dairy cow's ability to maintain normal blood calcium concentrations. Milk (including colostrum) is very rich in calcium, and cows must quickly shift their priorities to adjust for this sudden calcium outflow. Average blood calcium concentrations noticeably decline in second or greater lactation cows around calving, with the lowest concentrations occurring about 12 to 24 hours after calving (Kimura et al., 2006; Goff, 2008) (Figure 1).

A cow does not necessarily have to become recumbent (down) to be negatively affected by hypocalcemia. With or without obvious clinical signs, hypocalcemia has been linked to a variety of secondary problems in post-fresh cows (Goff, 2008; Oetzel, 2011). This happens because blood calcium is essential for muscle and nerve function - particularly functions that support skeletal muscle strength and gastro-intestinal motility. Problems in either of these areas can trigger a cascade of negative events that ultimately reduce dry matter intake **(DMI)**, increase metabolic diseases, and decrease milk yield (Goff, 2008).

Clinical Milk Fever vs. Subclinical Hypocalcemia

Clinical milk fever causes observable clinical signs and has been the historical focus of managing hypocalcemia. Rates of clinical milk fever appear to have substantially declined in the last 2 decades, perhaps leading to the false impression that hypocalcemia is no longer a major concern. However, recent research has shown that hypocalcemia indeed remains an extremely important metabolic disease, but now it is most apparent in its subclinical form. Trends in improving transition cow health, greater cow longevity, and even greater genetic progress toward increases milk yields suggests that hypocalcemia could become even more prevalent in the years ahead.

[1]Contact at: 2015 Linden Drive, Madison, WI 53706, (608) 265-5476, FAX: (608) 265-8020, Email: groetzel@wisc.edu.

Subclinical hypocalcemia can be defined as low blood calcium concentrations without clinical signs of milk fever. Subclinical hypocalcemia affects about 50% of second and greater lactation dairy cattle fed typical pre-fresh diets. If anions are supplemented to reduce the risk for milk fever, the percentage of hypocalcemic cows is reduced to about 15 to 25% (Oetzel, 2004).

Subclinical hypocalcemia is more costly than clinical milk fever because it affects a much higher percentage of cows in the herd (Oetzel, 2011). For example, if a 2000-cow herd has a 2% annual incidence of clinical milk fever and each case of clinical milk fever costs $300 (Guard, 1996), the loss to the dairy from clinical cases is about $12,000 per year. If the same herd has a 30% annual incidence of subclinical hypocalcemia in second and greater lactation cows (assuming they are 65% of cows in the herd) and each case costs $125 (an estimate that accounts for milk yield reduction and direct costs due to increased ketosis and displaced abomasum), then the total herd loss from subclinical hypocalcemia is about $48,750 per year. This is about 4 times greater than the cost of the clinical cases.

A recently published, large multi-site study shows that hypocalcemia around calving is most strongly associated with reduced milk yield (Chapinal et al., 2012) and increased risk for displaced abomasum (Chapinal et al., 2011). These studies also demonstrated that the cutpoint for serum total calcium is higher (about 8.5 mg/dl) than was previously assumed (see Figures 2 and 3). Another recent study (Martinez et al., 2012) defined subclinical hypocalcemia as serum total calcium below 8.59 mg/dl during any of the first 3 days in milk. Cows with subclinical hypocalcemia were at greater risk of developing fever, metritis, and ketosis. Cows with subclinical hypocalcemia in this study also had reduced pregnancy rate and longer days open.

Dietary Means of Preventing Hypocalcemia

Dietary calcium restriction

The traditional method of preventing milk fever has been to restrict calcium intake during the dry period. If extremely low calcium diets (< 20 g of daily calcium) are fed before parturition and high-calcium diets are fed after parturition, the incidence of milk fever can be drastically reduced (Green et al., 1981). Low calcium diets prior to calving apparently prevent the cow's active intestinal calcium absorption and bone calcium resorption mechanisms from becoming quiescent and unable to respond to the sudden calcium outflow that occurs at parturition. Calcium intake during the dry period is usually restricted by replacing some or all of the alfalfa in a dry cow diet with a grass hay and using additional corn silage and concentrates.

Dietary acidification

Dietary acidity or alkalinity is more important in controlling milk fever than calcium intake. The use of diets low in dietary cation-anion difference **(DCAD)** to prevent milk fever has been extensively studied and reviewed (DeGaris and Lean, 2008). A large meta-analysis (Charbonneau et al., 2006) demonstrated that reducing pre-fresh DCAD by 300 meq/kg (136 meq/lb) of diet DM (a typical approach) reduced the odds for clinical milk fever 5.1-fold, reduced urinary pH from 8.1 to 7.0, and reduced DM intake by 11.3%. It is important to implement a low DCAD strategy only in herds that already have good intakes in the pre-fresh group and can withstand an 11% intake reduction. Despite the expected decrease in pre-fresh DM intake, post-fresh intakes are improved when low DCAD diets are fed (Eppard et al., 1996; Joyce et al., 1997). Beede et al. (1991) reported 3.6% more mature equivalent **(ME)** milk when low DCAD diets are fed.

Dietary magnesium

Magnesium also plays an important role in maintaining calcium homeostasis around calving (DeGaris and Lean, 2008). A large meta-analysis (Lean et al., 2006) found that increasing dietary magnesium greatly reduced the odds for clinical milk fever. Magnesium is known to participate in calcium homeostasis via release of parathyroid hormone and the synthesis of the active form of vitamin D (1,25 dihydroxycholecalciferol). Total intakes of about 40 to 50 g of dietary Mg (about 0.30 to 0.45% of dietary DM, depending on total DM intake) have been suggested (DeGaris and Lean, 2008), although this is complicated because of the interactions between other dietary factors (DCAD, dietary calcium, and dietary phosphorus).

Individual Cow Treatments for Hypocalcemia

Treatments for clinical milk fever

Clinical signs of milk fever in dairy cattle around calving may, for convenience, be divided into 3 stages. Stage I milk fever is early signs without recumbency. It may go unnoticed because it's signs are subtle and transient. Affected cattle may appear excitable, nervous, or weak. Some may shift their weight frequently and shuffle their hind feet (Oetzel, 2011).

Some cows become hypocalcemic at times other than calving and exhibit clinical signs similar to those described above for Stage I milk fever. Such non-parturient hypocalcemias are often triggered by periods of unusual stress or decreased DM intake. This condition is most commonly seen in cows in the first 2 to 10 days of lactation, cows that are in heat, cows with severe digestive upsets, or cows suffering from severe (toxic) mastitis (Oetzel, 2011).

Oral calcium supplementation is the best approach for hypocalcemic cows that are still standing, such as cows in Stage 1 hypocalcemia or who have undetected subclinical hypocalcemia (Oetzel, 2011). A cow absorbs an effective amount of calcium into her bloodstream within about 30 minutes of supplementation (Goff and Horst, 1993). Blood calcium concentrations are supported for only about 4 to 6 hours afterwards (Goff and Horst, 1993; 1994) for most forms of oral calcium supplementation.

Intravenous **(IV)** calcium is not recommended for treating cows that are still standing (Oetzel, 2011). Treatment with IV calcium rapidly increases blood calcium concentrations to extremely high and potentially dangerous levels (Goff, 1999). Extremely high blood calcium concentrations may cause fatal cardiac complications and (perhaps most importantly) shut down the cow's own ability to mobilize the calcium she needs at this critical time (Oetzel, 2011). Cows treated with IV calcium often suffer a hypocalcemic relapse 12 to 18 hours later (Curtis et al., 1978; Thilsing-Hansen et al., 2002). The problems with IV calcium treatment are illustrated in Figure 4.

Cows in Stage II milk fever are down but not flat out on their side. They exhibit moderate to severe depression, partial paralysis, and typically lie with their head turned into their flank. Stage III hypocalcemic cows are flat out on their side, completely paralyzed, typically bloated, and are severely depressed (to the point of coma). They will die within a few hours without treatment (Oetzel, 2011).

Stage II and Stage III cases of milk fever should be treated immediately with slow IV administration of 500 ml of a 23% calcium gluconate solution. This provides 10.8 g of elemental calcium, which is more than sufficient to correct the cow's entire extracellular fluid deficit of calcium (about 4 to 6 g). Giving larger doses of calcium in the IV treatment has no benefit (Doze et al., 2008). Treatment with IV calcium should be given as soon

as possible, as recumbency can quickly cause severe musculoskeletal damage.

To reduce the risk for relapse, recumbent cows that respond favorably to IV treatment need additional oral calcium supplementation once they are alert and able to swallow, followed by a second oral supplement about 12 hours later (Thilsing-Hansen et al., 2002; Oetzel, 2011).

Transient hypocalcemia can occur in cows whenever they go off feed or have periods of decreased intestinal motility (DeGaris and Lean, 2008). It can be difficult to tell which comes first - the hypocalcemia or the gastrointestinal stasis. Whatever the case, the 2 problems can positively reinforce each other. During the experimental induction of hypocalcemia (Huber et al., 1981), ruminal contractions ceased well before the onset of clinical signs of milk fever. Off-feed cows, particularly in early lactation, are very likely to benefit from prompt oral calcium supplementation.

Preventive treatments with oral calcium supplements

Because subclinical hypocalcemia is limited to the first few days after calving, individual cow supplementation with oral calcium may be practical and beneficial. A large field study recently demonstrated that strategic use of oral calcium supplements may be beneficial, even in herds with successful anionic salts programs and minimal clinical cases of milk fever (Oetzel and Miller, 2012). In this study, cows were given 2 boluses of an oral calcium bolus (Bovikalc®, Boehringer Ingelheim Vetmedica, St. Joseph, MO); one at calving and one the day after calving. A subpopulation of cows was identified that had the best response to oral bolus administration. This subpopulation encompassed about half of all second and greater lactation cows and included cows with high milk yield in the previous lactation (>105% of herd average ME milk production) and lame cows. These cows gave 6.8 lb more milk at first DHI test if they had been supplemented with 2 oral calcium boluses around calving compared to unsupplemented cows. Selecting cows based on parity (e.g., only supplementing third and greater lactation cows or only supplementing cows with low blood calcium concentrations at calving) did not identify the cows that responded the best (Oetzel and Miller, 2012). For herds with a high incidence of hypocalcemia (particularly if they are not using low DCAD diets), it may also be economically beneficial to strategically supplement all fresh cows with oral calcium.

Oral calcium supplementation can be used in a variety of situations in early lactation besides blanket prevention programs, e.g., all standing cows who have clinical signs of hypocalcemia and all down cows following successful IV treatment. Additionally, any cows in the first 2 weeks of lactation who are off feed for any reason should receive oral calcium supplementation, as they easily become hypocalcemic.

Types of oral calcium supplements

The source of calcium in an oral supplement and its physical form greatly influence calcium absorption and blood calcium responses. A series of experiments has shown that calcium chloride has the greatest ability to support blood calcium concentrations (Goff and Horst, 1993; 1994). This can be explained by its high calcium bioavailability and its ability to invoke an acidic response in the cow, which causes her to mobilize more of her own calcium stores. Providing a typical amount of elemental calcium chloride (e.g., 50 g of elemental calcium) in a small oral dose (e.g., 250 ml water) provided the best absorption (Figure 5). Administering 100 g of elemental calcium from calcium chloride in water resulted in an excessive increase in blood calcium concentrations - perhaps enough to shut down the cow's own calcium homeostatic mechanisms and to invoke a calcitonin response to protect her from hypercalcemia.

The risk of aspiration is great when thin liquids are given orally, and calcium chloride is very caustic to upper respiratory tissues. Calcium propionate is more slowly absorbed (presumably because it is not acidogenic) and must be given at higher doses of elemental calcium (usually 75 to 125 g - see Figure 6). Calcium propionate has the property of being glucogenic as well as providing supplemental calcium.

Calcium carbonate in water did not increase blood calcium concentrations at all (see Figure 7; Goff and Horst, 1993). This may be explained by its poorer bioavailability compared to calcium chloride or calcium propionate. Additionally, calcium carbonate likely invokes an alkalogenic response, which acts in a manner opposite of low DCAD diets and could impair the cow's own mobilization of calcium from bone.

A combination of calcium chloride and calcium sulfate delivered in a fat-coated bolus (Bovikalc®, Boehringer Ingelheim Vetmedica, St. Joseph, MO) resulted in more sustained improvements in blood calcium concentrations (see Figure 8) than were observed in previous studies with oral calcium chloride or calcium propionate in water (Sampson et al., 2009). This encapsulated version of calcium salts had the advantages of not having an unpleasant taste to the cow, having little to no waste of the oral formulation, no risk for aspiration pneumonia, and a more prolonged release of the oral calcium (Pehrson and Jonsson, 1991). These workers reported a 4-fold reduction in the odds for developing clinical milk fever in cows that were supplemented with 4 boluses around calving (Pehrson and Jonsson, 1991).

Timing of oral calcium supplementation relative to calving

Strategies for giving oral calcium supplements around calving should include at least 2 doses; one at calving and a second dose the next day. The expected nadir in blood calcium concentrations occurs between 12 and 24 hours after calving (Goff, 1999; Sampson et al., 2009). Giving only one oral calcium supplement around calving time leaves the cow without support when her blood calcium concentrations are naturally the lowest. It is interesting to note that the original protocols for oral calcium supplementation called for 4 doses - one about 12 hours before calving, one at calving, one 12 hours post-calving, and one 24 hours post-calving. It was very difficult to predict when at cow was in fact about 12 hours from expected calving, and many cows calved without receiving this dose (Oetzel, 1996). The dose at calving is not practically challenging to administer, and providing a dose sometime the day after calving will provide critical support around the time of nadir and can still be practical in large dairy farms where the post-fresh pen is locked up just once daily.

Subcutaneous calcium treatment

Subcutaneous calcium can be used to support blood calcium concentrations around calving but has substantial limitations (Goff, 1999). Absorption of calcium from subcutaneous administration requires adequate peripheral perfusion. It may be ineffective in cows that are severely hypocalcemic or dehydrated. Subcutaneous calcium injections are irritating and can cause tissue necrosis; administration should be limited to no more than 75 ml of a 23% calcium gluconate solution (about 1.5 g elemental calcium) per site. Calcium solutions that also contain glucose should not be given subcutaneously. Glucose is very poorly absorbed when given by this route. Abscessation and tissue sloughing may result when glucose is given subcutaneously.

The kinetics of subcutaneously administered calcium indicate that it is well-absorbed initially, but that blood concentrations fall back to baseline values in about 6 hours (see Figure 9; Goff, 1999). Thus, repeat doses would be necessary to equal the

sustained blood calcium support that is possible with oral calcium boluses.

Conclusions

Even through rates of clinical milk fever may be relatively low, subclinical hypocalcemia remains an extremely important disease problem in dairy herds. Recent research has clearly demonstrated negative effects from subclinical hypocalcemia that start whenever blood total calcium concentrations drop below about 8.5 mg/dl. Chief among the negative effects of subclinical hypocalcemia are decreased early lactation milk yield. Other detriments include increased risk for displaced abomasum, metritis, ketosis, plus impaired reproductive performance.

Strategies to prevent as much early lactation hypocalcemia as possible can be divided into dietary means and individual cow supplementation with oral calcium. Dietary measures for preventing hypocalcemia include low DCAD diets, increasing dietary magnesium, and increasing dietary magnesium. Oral supplementation strategies include strategic use of oral calcium boluses around calving, and in particular, supplementation of cows with high previous lactation milk yield and lame cows. Additional uses of oral calcium include treatment of cows with clinical milk fever and any cows with off-feed problems in early lactation.

References

Beede, D.K., D.A. Risco, G.A. Donovan, C. Wang, L.F. Archbald, and W.K. Sanchez. 1991. Nutritional management of the late pregnant dry cow with particular reference to dietary cation-anion difference and calcium supplementation. Proc. Am. Assoc. Bov. Pract. 24:51-55.

Chapinal, N., M. Carson, T.F. Duffield, M. Capel, S. Godden, M. Overton, J.E. Santos, and S.J. LeBlanc. 2011. The association of serum metabolites with clinical disease during the transition period. J. Dairy Sci. 94:4897-4903.

Chapinal, N., M.E. Carson, S.J. LeBlanc, K.E. Leslie, S. Godden, M. Capel, J.E. Santos, M.W. Overton, and T.F. Duffield. 2012. The association of serum metabolites in the transition period with milk production and early-lactation reproductive performance. J. Dairy Sci. 95:1301-1309.

Charbonneau, E., D. Pellerin, and G.R. Oetzel. 2006. Impact of lowering dietary cation-anion difference in nonlactating dairy cows: A meta-analysis. J. Dairy Sci. 89:537-548.

Curtis, R.A., J.F. Cote, M.C. McLennan, J.F. Smart, and R.C. Rowe. 1978. Relationship of methods of treatment to relapse rate and serum levels of calcium and phosphorous in parturient hypocalcaemia. Can. Vet. J. 19:155-158.

DeGaris, P.J., and I.J. Lean. 2008. Milk fever in dairy cows: A review of pathophysiology and control principles. Vet. J. 176:58-69.

Doze, J.G., R. Donders, and J.H. van der Kolk. 2008. Effects of intravenous administration of two volumes of calcium solution on plasma ionized calcium concentration and recovery from naturally occurring hypocalcemia in lactating dairy cows. Am. J. Vet. Res. 69:1346-1350.

Eppard, P.J., J.J. Veenhuizen, W.J. Cole, P.G. Comens-Keller, G.F. Hartnell, R.L. Hintz, L. Munyakazi, P.K. Olsson, R.H. Sorbet, T.C. White, C.A. Baile, R.J. Collier, J. P. Goff, and R.L. Horst. 1996. Effect of bovine somatotropin administered to periparturient dairy cows on the incidence of metabolic disease. J. Dairy Sci. 79:2170-2181.

Goff, J.P. 1999. Treatment of calcium, phosphorus, and magnesium balance disorders. Vet. Clin. North Am. Food Anim. Pract. 15:619-639.

Goff, J.P. 2008. The monitoring, prevention, and treatment of milk fever and subclinical hypocalcemia in dairy cows. Vet. J. 176:50-57.

Goff, J.P., and R.L. Horst. 1993. Oral administration of calcium salts for treatment of hypocalcemia in cattle. J. Dairy Sci. 76:101-108.

Goff, J.P., and R.L. Horst. 1994. Calcium salts for treating hypocalcemia: Carrier effects, acid- base balance, and oral versus rectal administration. J. Dairy Sci. 77:1451-1456.

Green, H.B., R.L. Horst, D.C. Beitz, and E.T. Littledike. 1981. Vitamin D metabolites in plasma of cows fed a prepartum low-calcium diet for prevention of parturient hypocalcemia. J. Dairy Sci. 64:217-226.

Guard, C.L. 1996. Fresh cow problems are costly; culling hurts the most. Hoard's Dairyman 141:8.

Huber, T.L., R.C. Wilson, A.J. Stattleman, and D.D. Goetsch. 1981. Effect of hypocalcemia on motility of the ruminant stomach. Am. J. Vet. Res. 42:1488-1490.

Joyce, P.W., W.K. Sanchez, and J.P. Goff. 1997. Effect of anionic salts in prepartum diets based on alfalfa. J. Dairy Sci. 80:2866-2875.

Kimura, K., T.A. Reinhardt, and J.P. Goff. 2006. Parturition and hypocalcemia blunts calcium signals in immune cells of dairy cattle. J. Dairy Sci. 89:2588-2595.

Lean, I.J., P.J. DeGaris, D.M. McNeil, and E. Block. 2006. Hypocalcemia in dairy cows: Meta-analysis and dietary cation anion difference theory revisited. J. Dairy Sci. 89:669-684.

Martinez, N., C.A. Risco, F.S. Lima, R.S. Bisinotto, L.F. Greco, E.S. Ribeiro, F. Maunsell, K. Galvao, and J.E. Santos. 2012. Evaluation of peripartal calcium status, energetic profile, and neutrophil function in dairy cows at low or high risk of developing uterine disease. J. Dairy Sci. 95:7158-7172.

Oetzel, G.R. 1996. Effect of calcium chloride gel treatment in dairy cows on incidence of periparturient diseases. J. Am. Vet. Med. Assoc. 209:958-961.

Oetzel, G.R. 2004. Monitoring and testing dairy herds for metabolic disease. Vet. Clin. North Am. Food Anim. Pract. 20:651-674.

Oetzel, G.R. 2011. Non-infectious diseases: Milk fever. Pages 239-245 in Encyclopedia of Dairy Sciences. Vol. 2. J.W. Fuquay and P.L.H. McSweeney, ed. Academic Press, San Diego.

Oetzel, G.R., and B.E. Miller. 2012. Effect of oral calcium bolus supplementation on early lactation health and milk yield in commercial dairy herds. J. Dairy Sci. 95:7051-7065.

Pehrson, B., and M. Jonsson. 1991. Prevention of milk fever by oral administration of encapsulated Ca-salts. Bov. Pract. 26:36-37.

Sampson, J.D., J.N. Spain, C. Jones, and L. Carstensen. 2009. Effects of calcium chloride and calcium sulfate in an oral bolus given as a supplement to postpartum dairy cows. Vet. Ther. 10:131-139.

Thilsing-Hansen, T., R.J. Jørgensen, and S. Østergaard. 2002. Milk fever control principles: A review. Acta Vet. Scand. 43:1-19.

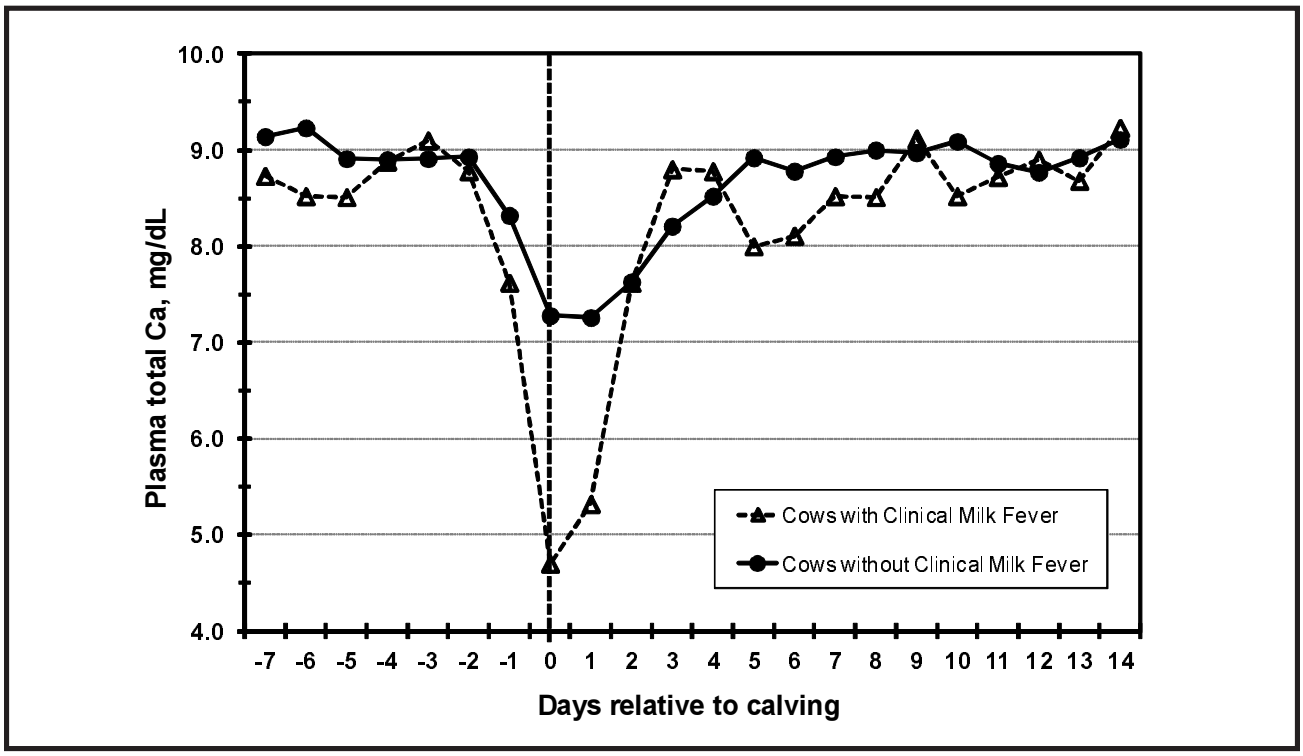

Figure 1. Plasma concentrations of total calcium before and after calving in mature Jersey cows with or without clinical milk fever (Kimura et al., 2006).

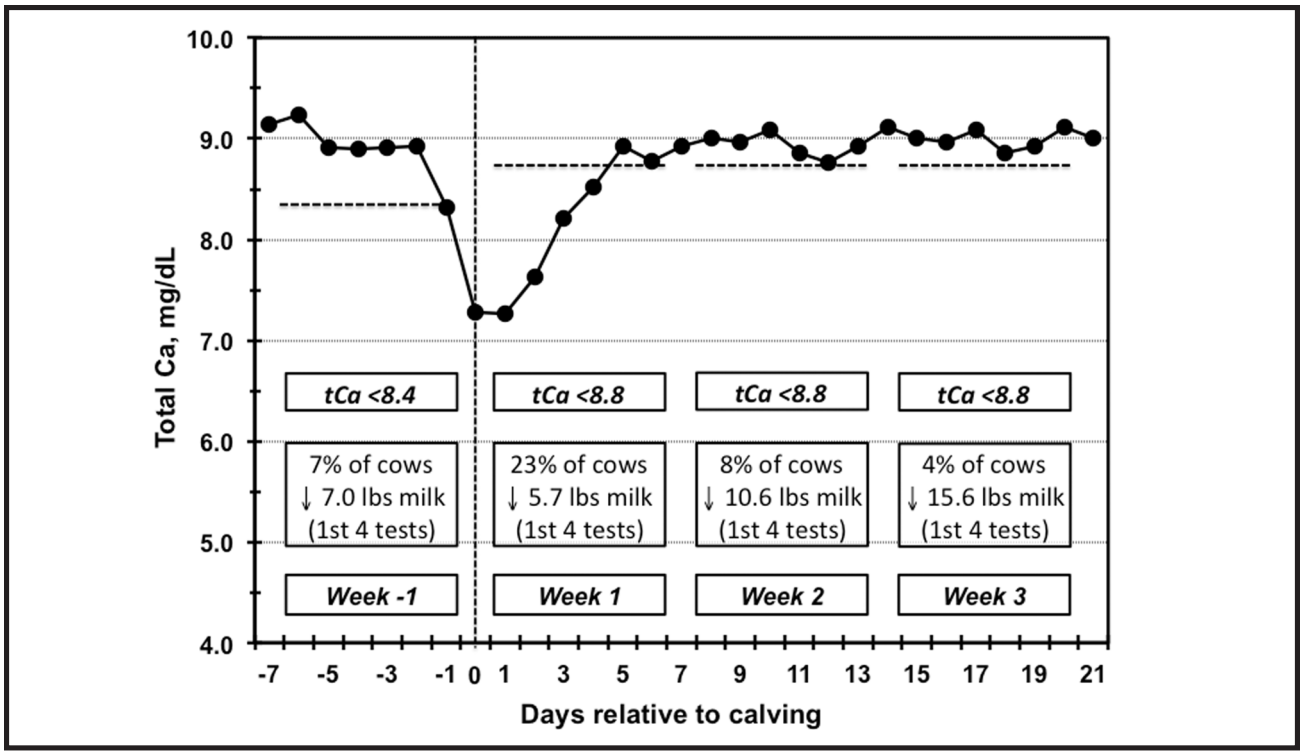

Figure 2. Effect of serum total calcium (tCa) on milk yield for the first 4 DHI tests after calving. Different cutpoints were derived for serum samples collected on weeks -1, 1, 2, and 3 after calving. Data are from 2,365 cows in 55 Holstein herds in Canada and the US (Chapinal et al., 2012).

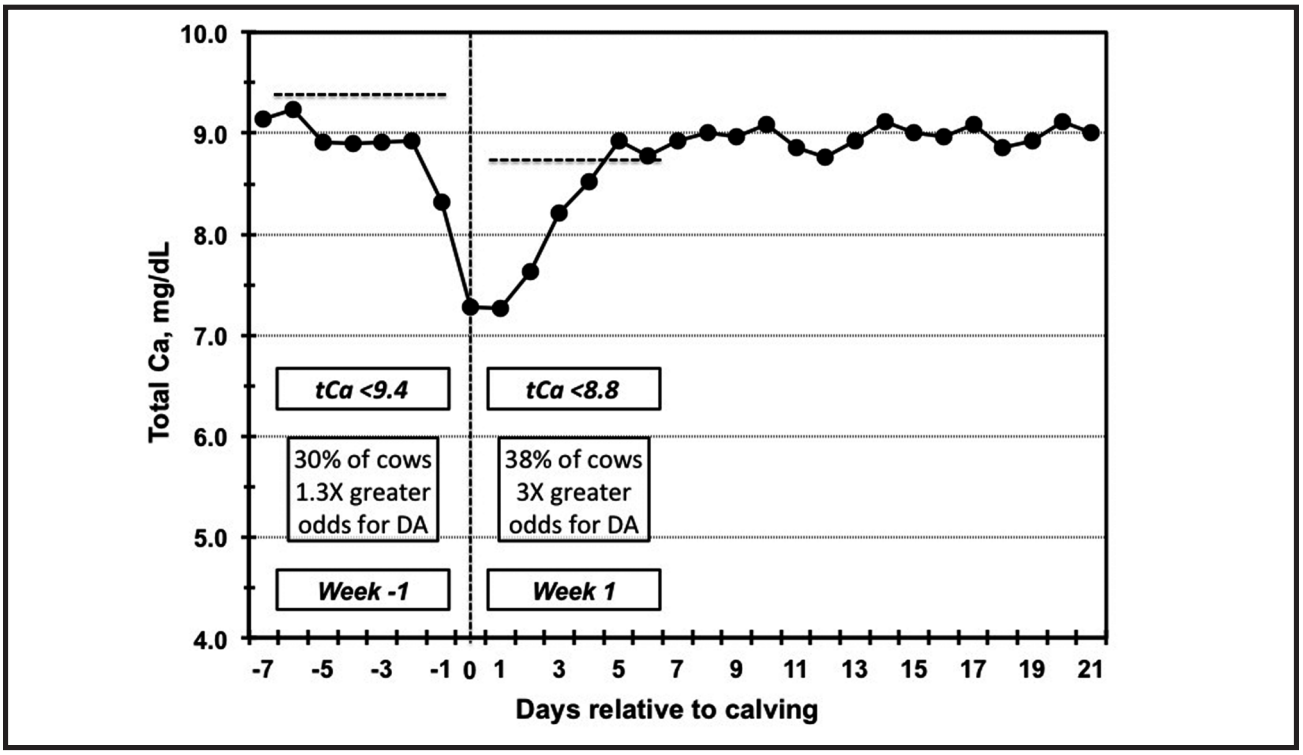

Figure 3. Effect of serum total calcium (tCa) on the odds for displaced abomasum (DA) after calving. Different cutpoints were derived for serum samples collected on weeks -1, 1, 2, and 3 after calving. Data are from 2,365 cows in 55 Holstein herds in Canada and the US (Chapinal et al., 2011).

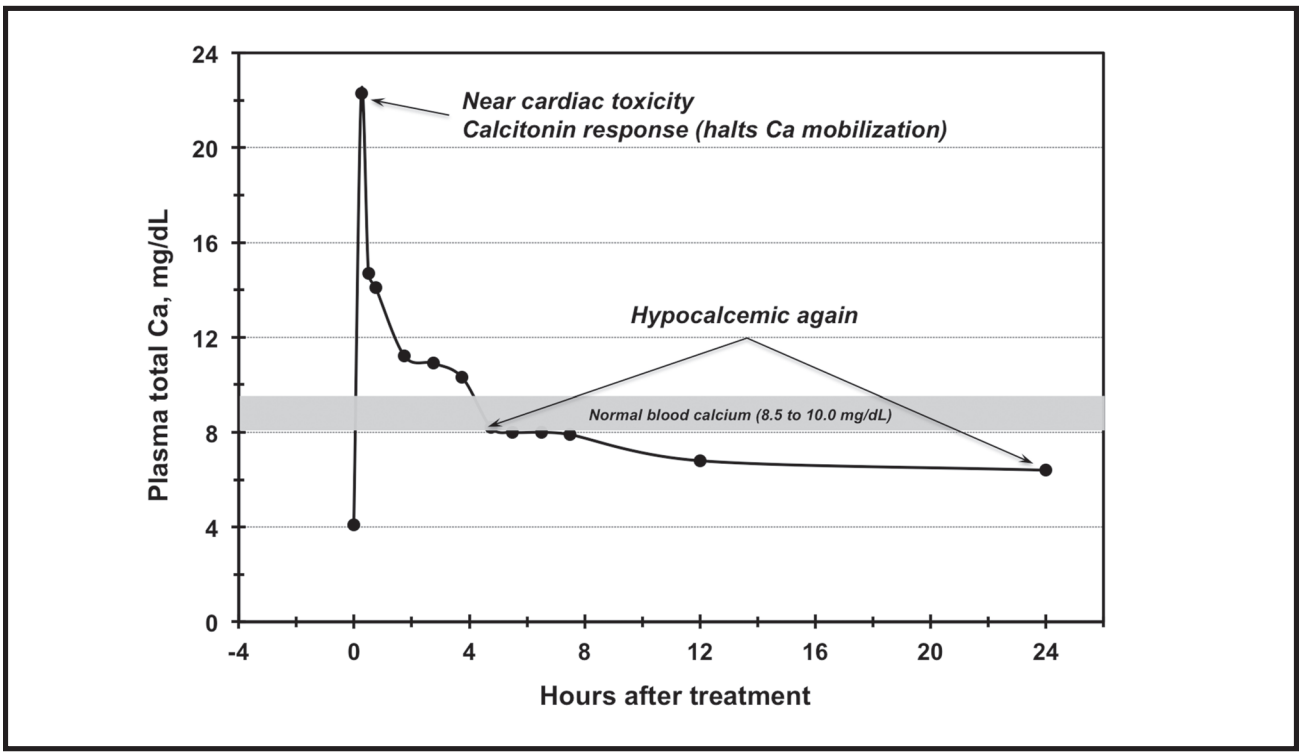

Figure 4. Effect of IV calcium treatment with 10.5 g of elemental calcium on serum total calcium concentrations in a mature Jersey cow with clinical milk fever (Goff, 1999).

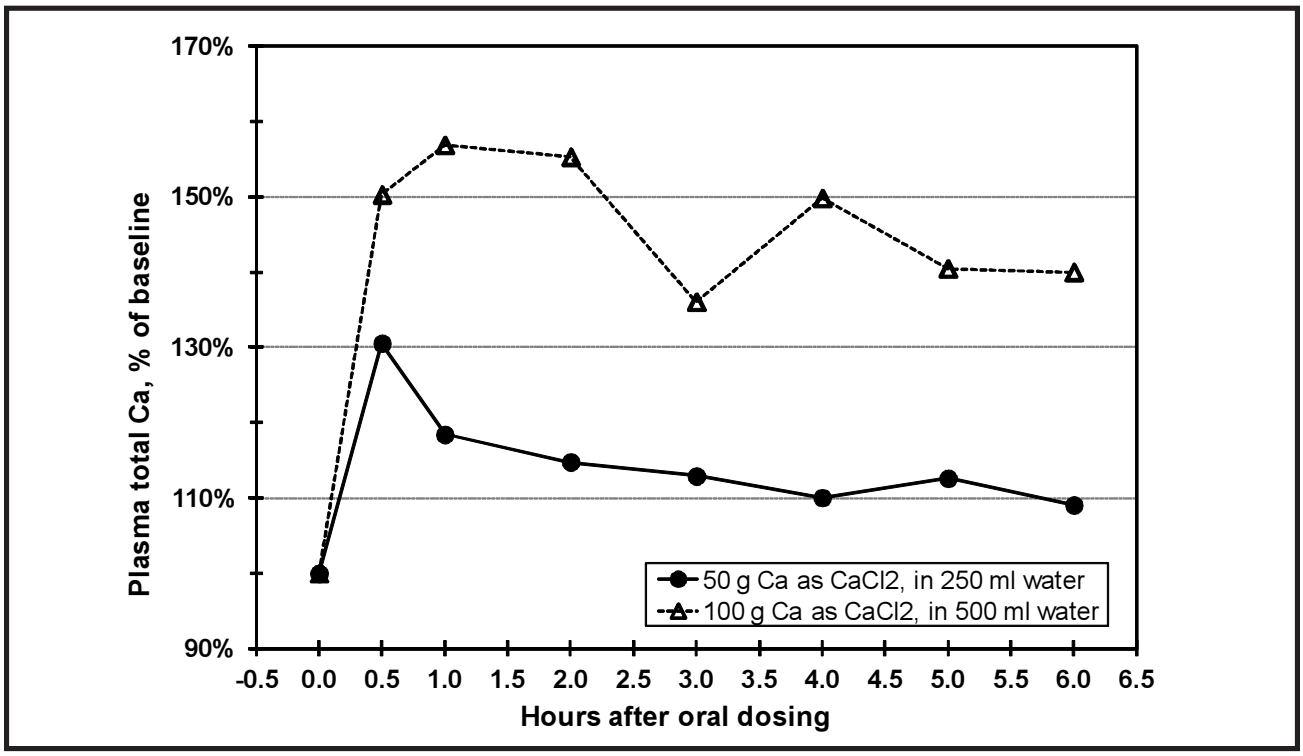

Figure 5. Effect of 2 different doses of oral calcium chloride on plasma total calcium concentrations, expressed as percent of baseline values (Goff and Horst, 1993).

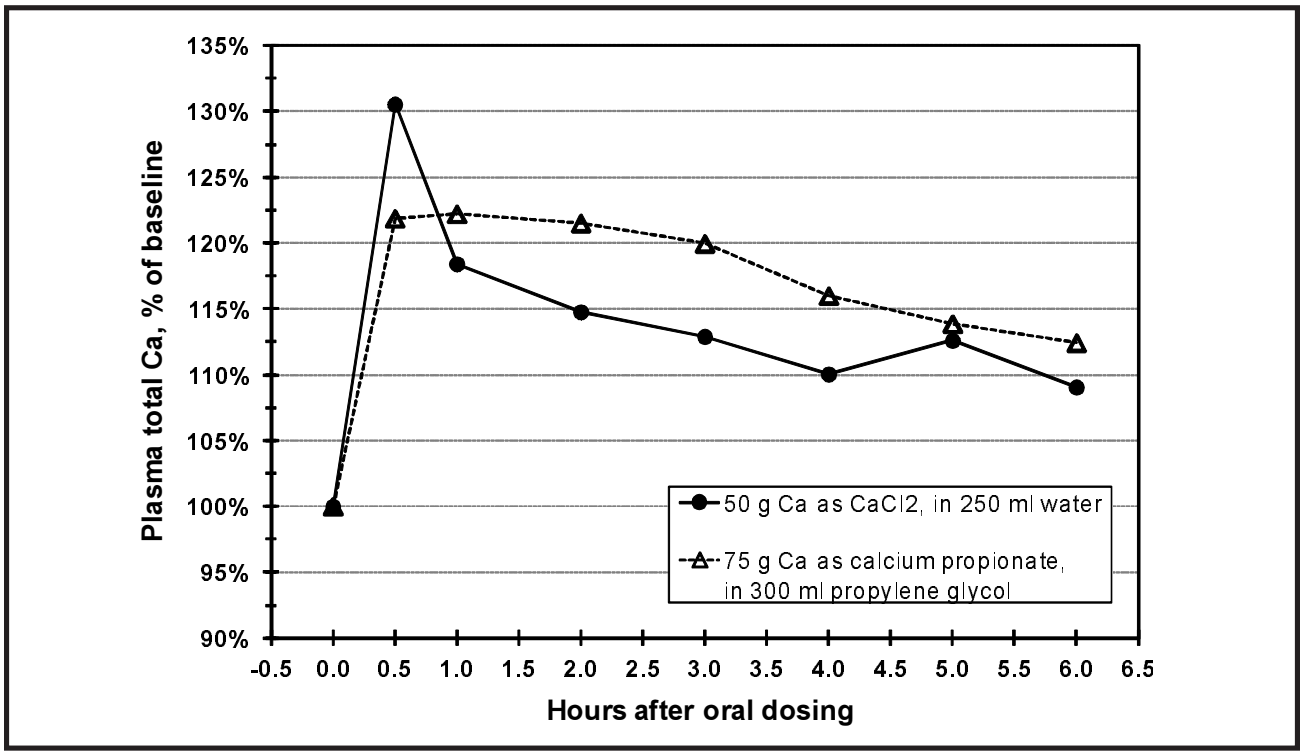

Figure 6. Effect of oral calcium chloride and oral calcium propionate on plasma total calcium concentrations, expressed as percent of baseline value (Goff and Horst, 1993; 1994).

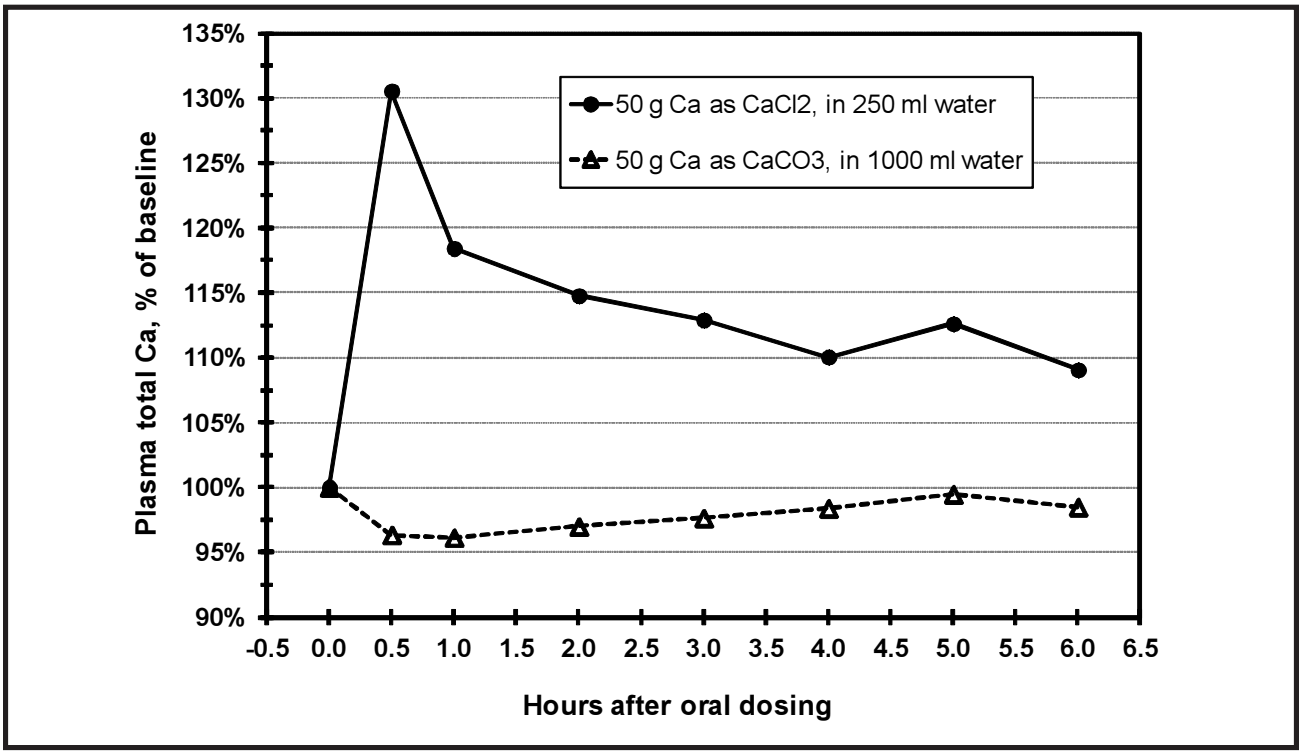

Figure 7. Effect of oral calcium chloride and oral calcium carbonate on plasma total calcium concentrations, expressed as percent of baseline values (Goff and Horst, 1993).

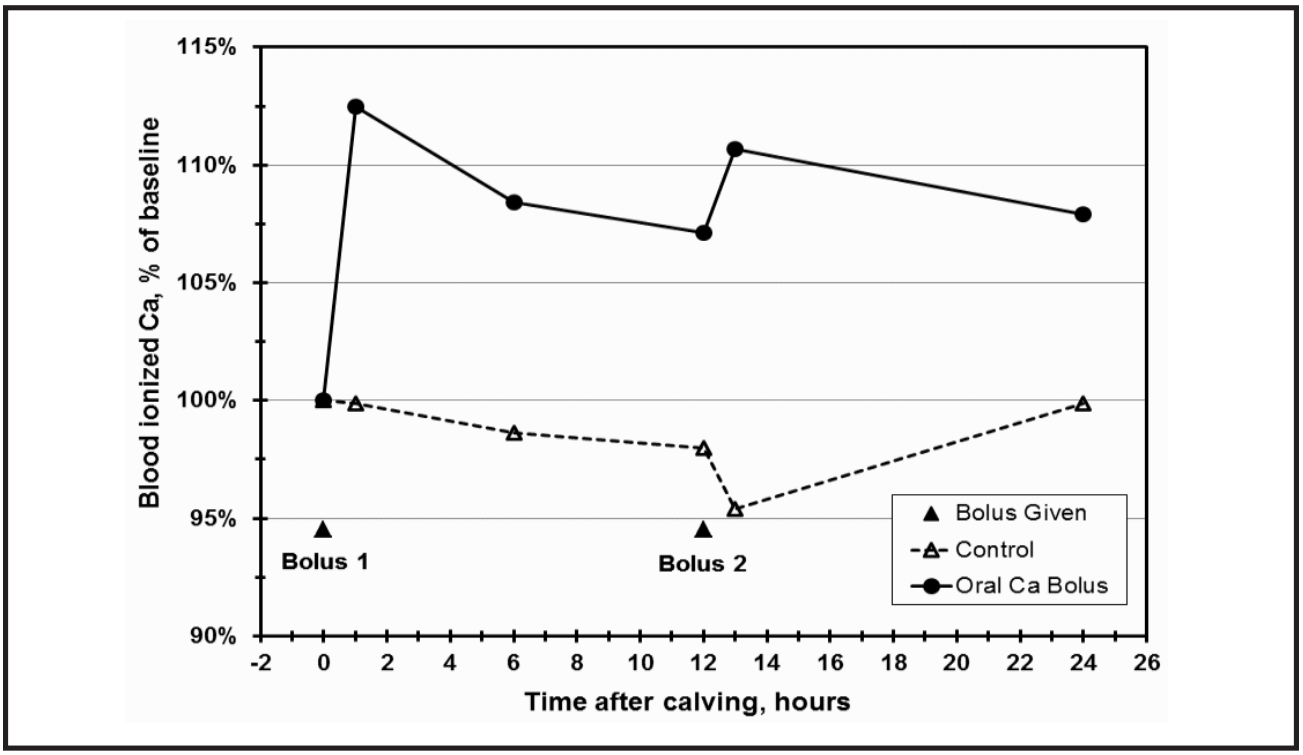

Figure 8. Effect of administration of 2 Bovikalc® boluses on blood ionized calcium concentrations (expressed as percent of baseline) at calving and 12 hours later. Experimental animals were Holstein cows (n=20) with hypocalcemia at calving (Sampson et al., 2009).

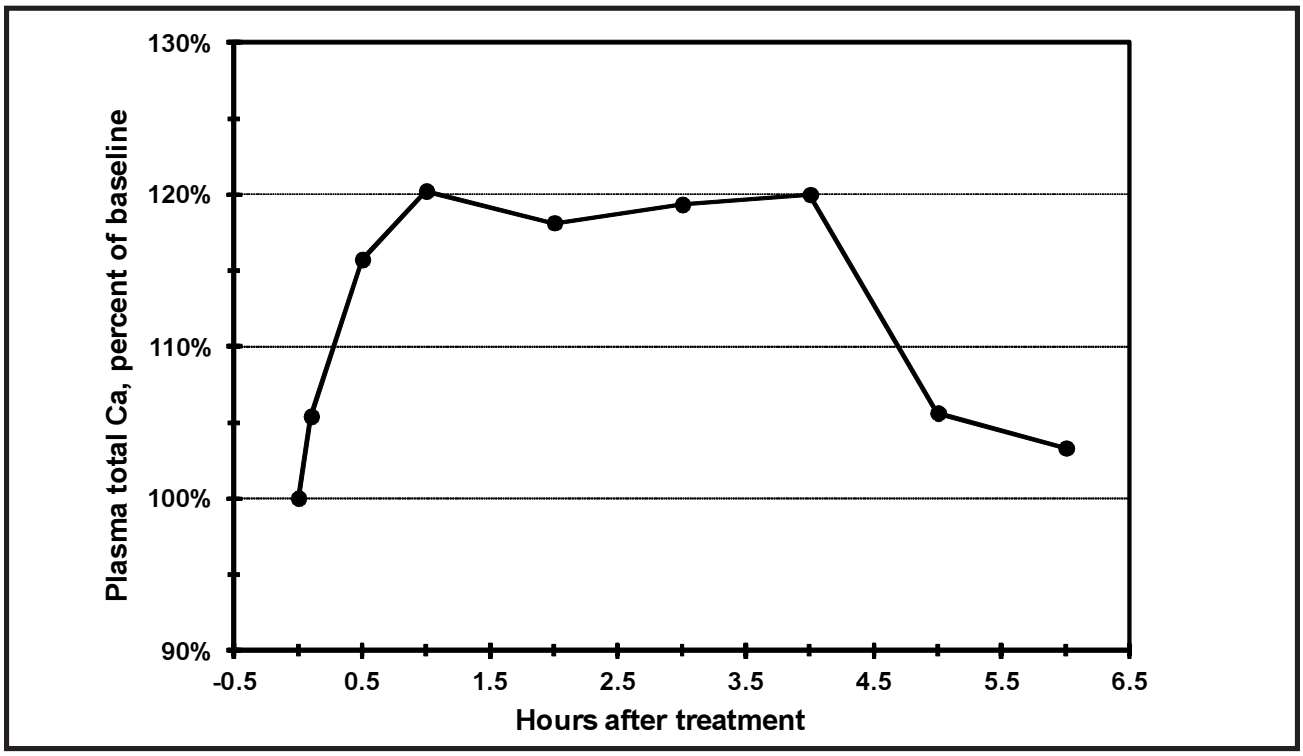

Figure 9. Effect of subcutaneous administration of 500 ml of 23% calcium gluconate on plasma total calcium, expressed as percent of baseline. The 500 ml solution was divided into 10 different sites (Goff, 1999).