

Impact of herbal calcitriol-glycoside on blood plasma calcium levels and lifetime performance in dairy cows, and the advantages of using a unique patented slow release Green bolus

Milk fever is a metabolic disturbance or production disease of dairy cows that generally occurs just before or soon after calving due to low calcium (Ca) level in the blood. It is associated with the drain of calcium within the fetus and milk during pregnancy and calving, respectively. Milk fever has both direct and indirect economic impacts in dairy industry. The most important direct economic losses due to milk fever are losses due to reduction in milk production of affected cows, loss of animals through death and culling, and the cost of treatment. In addition, the excessive drop in calcium levels around calving can lead to a long-term Ca deficiency, further threatening the economic profitability. Hence, prevention of milk fever and long-term Ca deficiency is key in dairy industry.

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Milk fever

Milk fever (also called parturient paresis or parturient hypocalcaemia) is one of the production diseases which primarily occur among older high-yielding dairy cows during the period around calving. The increased demand for calcium (Ca) at parturition due to the onset of lactation may result in a Ca deficiency situation potentially provoking the outbreak of milk fever in dairy cows. Milk fever generally occurs when Ca blood plasma concentration is lower than 8 mg/dL (i.e., 2.2 mmol/L). Such a low calcium blood plasma concentration has consequences for many nerve and muscle functions (Horst *et al.*, 1994).

Milk fever is an economically important disease due to milk secretion that can reduce the productive life of a dairy cow (Horst *et al.*, 1997). Milk fever incidence has remained steady in some countries at about ten percent (Fleischer *et al.* 2001, Rehage *et al.* 2002). Milk fever affects about six percent of dairy cows in the United States each year, according to the 1996 National Animal Health Monitoring Survey. If left untreated, about 60 to 70 % of the affected cows may die (McDowell, 2003).

There are some factors which influence incidence and severity of milk fever. These are: age (older cows are more sensitive than younger), milk yield (cows with higher yield are more predisposed than cows with lower yield) (Fleischer *et al.*, 2001; Rehage and Kaske, 2004; Taylor *et al.*, 2001), breed, body condition, length of dry period and diet composition (for more details see reviews by Horst *et al.*, 1994, 1997).

Long-term hypocalcaemia

As mentioned earlier, high yielding dairy cows suddenly experience a high demand of calcium during parturition. Calcium is necessary for the contraction of the uterine wall muscle and the milk production. The natural regulation systems in the dairy-cow cannot always cope with this sudden increase in calcium demand. As a result, calcium blood plasma levels can drop significantly.

Depending on the severity of this drop in calcium levels this can lead to a long-term Ca deficiency and thus a persistent lack of appetite, hypersensitivity, weakness and if left untreated even paralysis and mortality. Long-term hypocalcaemia has also some widespread effects that predispose to other periparturient diseases such as mastitis, ketosis, displaced abomasum and retained placenta (Curtis *et al.*, 1983; Fleischer *et al.*, 2001).

Even if no visible symptoms are observed, long-term hypocalcaemia can lead to a decrease in production and fertility and has some widespread effects that predispose to other periparturient diseases such as mastitis, ketosis, displace abomasum and retained placenta (Curtis *et al.*, 1983; Fleischer *et al.*, 2001). Even successful treatment of hypocalcaemia does not eliminate further complication associated with milk fever, which results in further economic losses.

This stresses the demand for an effective prevention: administration of calcitriol.

The role of calcitriol

Calcitriol or 1,25-dihydroxyvitamin D3 is a metabolite of vitamin D3. Unlike vitamin D3 that needs to be transformed in the liver and kidney, calcitriol works directly on the vitamin D3 receptors in the intestinal wall, bones and kidney having the following effects:

1. Intestinal wall: calcitriol is able to activate the calcium-binding proteins increasing the calcium absorption rate from the gut to the blood vessels.
2. Bones: calcitriol activates the vitamin D receptors in the bone cells increasing Ca deposition or release in of from the bones, depending on the concentration Ca in the blood plasma.
3. Kidney: calcitriol stimulates the resorption of Ca from the urinary tracts to the blood vessels (Hoenderop J. *et al.*, 2001).

Taking all the above-mentioned into account, it can be stated that calcitriol can increase the absorption and regulation rate of calcium thus maintaining an optimal calcium level in the blood plasma.

In addition, calcitriol is known to have a similar effect on the phosphor absorption and regulation, positively affecting the immune system and improving the suppression of pathogens (Yue Y., 2016 and Research performed at Ghent University, 2015).

Advantages of Calcitriol-glycoside

The binding of calcitriol to a glycoside is known to improve stability and increase bioavailability (due to better absorption through the intestinal wall). Calcitriol-glycoside can be found in dried leaves of the plant *Solanum glaucophyllum* (containing a standardized concentration).

Studies with herbal calcitriol-glycoside added to the feed of ruminants show a significant increase of calcitriol in the blood levels (Ishii J., et al. 2015). Furthermore, it was observed that a single high dose of herbal calcitriol-glycoside around calving could result in a major increase in both, calcium and phosphor blood levels.

Green bolus™: slowly releasing calcitriol-glycoside

Considering calcitriol-glycoside as an effective substance to prevent hypocalcaemia, it was of the highest importance for Emma Nutrition to search for the most convenient and easiest way of administration. As displayed in Figure 1 and 2, Emma Nutrition developed a slowly disintegrating bolus should only be administered once (approximately 1-2 days before calving).

Figure 1: Single dose green bolus that could slowly release calcitriol-glycoside.



Figure 2: Impact of gastro-intestinal residence time (days) on bolus weight (g).

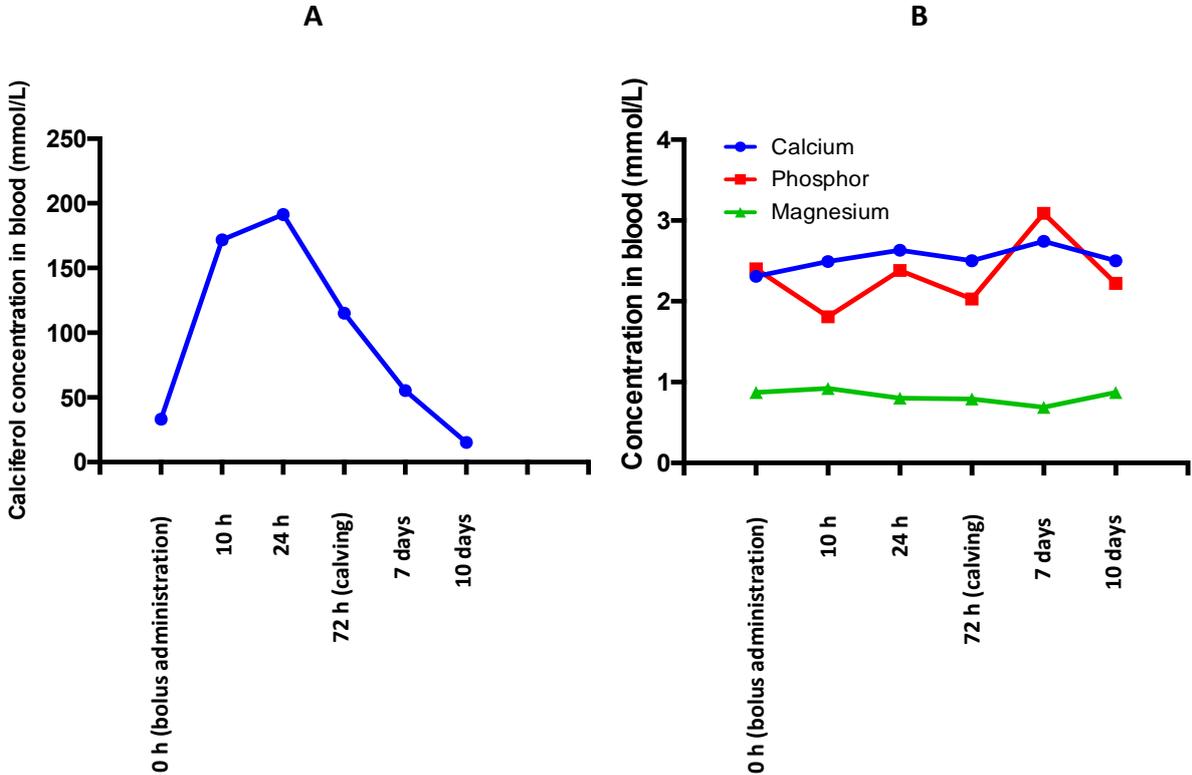


As listed in Table 1 and displayed in Figure 3, this unique patented formula allows farmers to easily increase calcitriol blood concentration already 8-10 hours after oral administration. Furthermore, it was found that calcium concentration in blood could be kept above 2.2 mmol/L (i.e., 8.8 mg/dL which is the recommended minimum calcium blood plasma concentration to prevent milk fever and long-term hypocalcaemia). Therefore, one might assume that hypocalcaemia could still be countered even in case the Green Bolus™ is administered just before or after calving. Finally, it was observed that the administration of Green Bolus™ could positively affect phosphor levels. As a result of the excellent *in vivo* performance, the Green Bolus™ of Emma Nutrition has been officially recognized in 2020 as a highly effective diet food for the prevention of long-term hypocalcaemia and milk fever.

Table 1: Impact of Green Bolus™ administration on calcium concentration in blood of Holstein-Friesian cattle.

Calcium concentration in blood (mmol/L)			
	Cow	T0 (when applying bolus)	T1 (24 hours after calving)
Control	1	2.33	2.13
	2	1.93	1.83
			(2.93 24 hours after Green bolus™)
Green Bolus™	3	1.87	2.47
	4	1.98	2.16
	5	1.96	2.16
	6	2.51	2.16
	7	2.10	2.21
	8	2.20	2.25
	9	2.24	2.33

Figure 3: Impact of Green bolus administration on (A) cholecalciferol; (B) calcium, phosphor and magnesium levels.



Conclusion

Emma nutrition successfully developed a single dose calcitriol glycoside bolus (Green Bolus™) that is officially recognized as a diet food to prevent dairy cows from hypocalcaemie and milk fever, resulting in a higher economic yield.