

# Post Mortem Investigation of Possible Mucosal Damages in Dairy Cows Following Four Oral Administrations at 12 Hour Intervals of a Calcium Chloride Paste Formulation

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## Introduction

It is well-known that the incidence of milk fever in dairy cows can be significantly reduced when gut absorption of approximately 50g calcium takes place 4 times with 12 hour intervals around calving.<sup>1,2,3</sup> There are several different oral calcium formulations available containing different calcium salts, e.g., chloride, propionate, formiate, oxide, and carbonate. The amount of absorbed calcium following oral administration, however, is dependent on water-solubility of the different salts.<sup>4</sup> Calcium chloride is the most readily absorbed salt. The bioavailability of calcium propionate and formiate are inferior to calcium chloride. Consequently, a higher amount of administered calcium salts like calcium propionate or formiate is needed in order to get approximately 50g calcium absorbed from the gut. Calcium oxide and calcium carbonate are not water-soluble and therefore poorly absorbed.

It is also well-known that due to its caustic effect, calcium chloride in water or watery gel causes serious mucosal damages in the pharynx, esophagus, forestomachs and abomasum.<sup>5,6</sup> Several of these products in Europe are withdrawn from the market due to the caustic effect of calcium chloride on the mucosa. A calcium chloride bolus with a protective layer of fat surrounding it is available in Scandinavia. However, serious consequences are reported following administration of the calcium bolus to calving cows with impaired or absent mobility of the digestive tract. In these cases the bolus or boli lie directly on the mucosa in either rumen or reticulum, and the caustic calcium chloride would be

in direct contact with the mucosa. A fatal case report is published in the Danish Veterinary Journal.<sup>7</sup>

A water-in-oil emulsion, where the caustic calcium chloride is dissolved in water and protected by oil, has been on the market during the past 6-7 years. The mucosal damages are minimized following administration. Maladministration into the lungs, however, has been observed due to the viscosity of the product.<sup>8</sup>

In cooperation with the Royal Danish School of Pharmacy, a calcium chloride paste formulation (BOVIVET® Calcium Paste, Jørgen Kruuse A/S) has been developed. In this paste formulation 180g calcium chloride and 6g magnesium chloride are distributed in and protected by a special two-component oil preparation and filled on to a 255ml cartridge. During the production of the paste formulation the dry materials are stuck together with the fat part of the oil which is then covered by rape seed oil.

This publication describes an investigation of possible mucosal damages of the tongue, pharynx, larynx, oesophagus, forestomachs and abomasum following oral administration of the calcium chloride paste formulation 4 times with 12 hours interval.

## Materials and methods

Three clinically healthy, non-lactating and non-pregnant Friesian cows from one dairy herd were bought and confined in a farm without other animals.

Following an acclimatization period of 7 days, 1 cartridge of calcium chloride paste formulation was administered orally to the cows four times with 12 hour

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*This manuscript was received after the program was completed and in press.*

intervals. The reaction of the cows to the administration was thoroughly observed and any abnormal reaction was registered. If any waste of paste formulation took place during the administration the amount wasted was registered.

In connection with the oral administration heparin stabilized blood samples were drawn from all 3 cows at the following time points:

Immediately before dosing, and 15, 30, 60, and 120 minutes post dosing.

Furthermore, an extra blood sample was drawn 240 minutes post first and third dosing.

The plasma samples were analyzed for total calcium on VetTest® 8008 (Idexx Labs, Inc.). In a Danish study VetTest® 8008 is described as user-friendly for dry chemical analyses in veterinary practice.<sup>9</sup> Duplicate analyses of all samples were performed.

Approximately 12 hours after the last administration the cows were slaughtered at a local abattoir.

The tongue, pharynx, larynx, oesophagus, rumen, reticulum, omasum, oesophageal groove, and abomasum were removed and inspected. All changes were photographed.

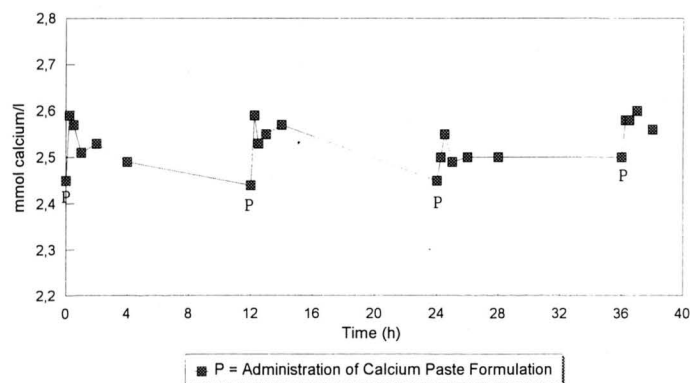
All handling and registrations were done by experienced large animal veterinarians.

## Results

Administration of the paste formulation was uneventful. The cows hardly resisted the administration which lasted on average 30-40 seconds. In few cases, a small amount of paste (5-10 ml) fell out when the cartridge was withdrawn after the administration.

Increased salivation for approximately 1 minute was observed in almost all cows following administration, and one cow showed increased tear production immediately after dosing.

The average plasma concentrations of total calcium (mmol/l) for the three cows are given in figure 1.



**Figure 1.** Calcium Conc. after 4 x Calcium Adm.

The clinical findings at post mortem are shown in table 1.

**Table 1.** Macroscopic changes of the cranial part of the digestive tract of three dairy cows 12 hours post 4th administration of a calcium chloride paste formulation.

	Cow A	Cow B	Cow C
<b>Oral cavity</b>	n.a.d.*	n.a.d.	n.a.d.
<b>Tongue</b>	n.a.d.	n.a.d.	scar at back of tongue
<b>Pharynx</b>	n.a.d.	n.a.d.	n.a.d.
<b>Larynx</b>	n.a.d.	n.a.d.	n.a.d.
<b>Oesophagus</b>	n.a.d.	n.a.d.	n.a.d.
<b>Rumen</b>	n.a.d.	n.a.d.	n.a.d.
<b>Reticulum</b>	n.a.d.	hyperaemia at the tip of the papillae	n.a.d.
<b>Oesophageal groove</b>	n.a.d.	slight hyperaemia	hyperaemia
<b>Omasum</b>	n.a.d.	n.a.d.	n.a.d.
<b>Abomasum</b>	small area with hyperaemia and oedema close to pylorus (not related to calcium chloride administration)	n.a.d.	n.a.d.

\*n.a.d.= no abnormalities detected

## Discussion

The uneventful administration of the paste formulation is a good sign of protection of the caustic calcium chloride. The wasted amount of paste formulation at the end of dosing is negligible and does not influence the effect of the preventive program.

Increased salivation is a known phenomenon following administration of calcium chloride formulations.

It appears from figure 1 that an increased absorption of calcium is registered immediately after each administration of the calcium paste formulation. This increased absorption of calcium takes place at two locations of the gut. Firstly, an instant peak absorption from the esophageal groove and abomasum within 15 minutes post administration and secondly, a slightly increased absorption of calcium across the small intestinal wall 1-2 hours later.

For this study non-lactating and non-pregnant cows were used. The normal homeostasis of calcium in non-calving cows is well functioning. Consequently, excessive amount of calcium given orally might only temporarily disturb the cow's own ability to regulate calcium absorption. The effect of calcium dosing on the absorption of calcium in calving cows with suppressed calcium regulation is expected to last longer.

It can be seen in table 1 that the damaging effect on the mucosa is almost eliminated for this special formulation. A few hyperaemic area only in the mucosa of

the forestomachs are observed, i.e., at the tip of the papillae in the reticulum of one cow, and in the oesophageal groove of two cows. One cow was without any calcium chloride related changes at all.

The observed slight changes do not affect the cow and will heal in no time. Other observations registered are all occasional findings at slaughter and not related to this investigation.

The rapid peak concentration of plasma calcium around 15 minutes after dosing suggests that the calcium paste formulation passes by the rumen and is introduced directly into the oesophageal groove and abomasum.

### Conclusion

This study has demonstrated that oral dosing of 1 cartridge of a newly developed calcium chloride paste formulation given 4 times with 12 hour intervals to 3 non-lactating and non-pregnant Frisian cows did not cause any resistance to the administration. Only a few small amounts of paste formulation were lost when the cartridges were withdrawn from the mouth after administration.

One cartridge of calcium paste formulation contains 180g calcium chloride and 6g magnesium chloride.

An increased concentration of calcium in plasma was seen within 15 minutes after each administration and this increase lasted for several hours.

The damaging effect of calcium chloride following administration of this newly developed paste formulation was reduced to slight hyperaemia at the tip of the papillae in the reticulum and in the oesophageal groove. These changes, however, are negligible. They do not disturb the well being of the cow and the changes heal instantly.

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NADA #141-063, Approved by FDA.

**PRODUCT  
INFORMATION**

**Nuflor®**  
(FLORFENICOL)

**Injectable Solution 300 mg/mL**

**For Intramuscular Use in Cattle Only.**

**CAUTION:** Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**DESCRIPTION:** NUFLOOR is a solution of the synthetic antibiotic florfenicol. Each milliliter of sterile NUFLOOR Injectable Solution contains 300 mg of florfenicol, 250 mg n-methyl-2-pyrrolidone, 150 mg propylene glycol, and polyethylene glycol q.s.

**INDICATIONS:** NUFLOOR Injectable Solution is indicated for treatment of bovine respiratory disease (BRD), associated with *Pasteurella haemolytica*, *Pasteurella multocida*, and *Haemophilus somnus*.

**RESIDUE WARNINGS:** Animals intended for human consumption must not be slaughtered within 28 days of the last treatment. Do not use in female dairy cattle 20 months of age or older. Use of florfenicol in this class of cattle may cause milk residues. Do not use in veal calves, calves under one (1) month of age, or calves being fed an all-milk diet. Use in these classes of calves may cause violative tissue residues to remain beyond the withdrawal time.

**WARNINGS: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.** This product contains materials that can be irritating to skin and eyes. Avoid direct contact with skin, eyes, and clothes. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. Consult a physician if irritation persists. Accidental injection of this product may cause local irritation. Consult a physician immediately. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information.

For customer service, adverse effects reporting, and/or a copy of the MSDS, call 1-800-932-0473.

**CAUTION:** Not for use in cattle of breeding age. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck are likely to be more severe.

**ADVERSE EFFECTS:** Inappetence, decreased water consumption, or diarrhea may occur transiently following treatment.

**DOSAGE AND ADMINISTRATION:** NUFLOOR Injectable Solution should be administered by **intramuscular** injection to cattle at a dose of 20 mg/kg body weight (3 mL/100 lbs). A second dose should be administered 48 hours later. Do not inject more than 10 mL at each site. **The injection should be given only in the neck musculature.**

**NOTE:** Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck are likely to be more severe.

Clinical improvement should be evident in most treated subjects within 24 hours of the first injection. If a positive response is not noted within 24 hours of the second injection, the diagnosis should be re-evaluated.

**STORAGE CONDITIONS:** Store between 2°-30°C (36°-86°F). Refrigeration is not required. The solution is light yellow to straw colored. Color does not affect potency.

**HOW SUPPLIED:** NUFLOOR Injectable Solution is packaged in 100 mL (NDC 0061-1116-04), 250 mL (NDC 0061-1116-05), and 500 mL (NDC 0061-1116-06) glass sterile multiple-dose vials.

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