ARTICLES

Chronic copper toxicity in a dairy herd

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Abstract

The addition of excessive copper to a commercially prepared dairy ration caused chronic copper toxicity in a dairy herd. A formulation error by a feed company resulted in copper levels of 800 to 1,000 mg/kg in the "as fed concentrate," amounting to about 400–500 mg copper/kg of the whole ration. Five animals died with typical signs of acute copper toxicity, including intravascular hemolysis and methemoglobinemia. A further 39 cows died on the farm from a combination of debilitation and secondary infectious causes, and 215 were sent to slaughter because of debilitation and poor milk production. The mortality of calves born to dams that had been fed the toxic concentrate was approximately 50%.

We postulate that dairy cows, particularly pregnant cows, may be more susceptible to copper toxicity than other cattle, and suggest reexamination of the presently allowable maximum levels of copper supplementation of diets for dairy cattle.

Résumé

Toxicité chronique au cuivre dans un élevage de vaches laitières

L'addition d'une quantité excessive de cuivre à une ration alimentaire commerciale pour vaches laitières causa une toxicité chronique au cuivre dans un élevage. Une erreur de formulation effectuée par une compagnie alimentaire eut pour résultat de porter les taux de cuivre entre 800 et 1 000 mg/kg dans la ration de concentrés; la quantité de cuivre contenue dans la ration globale se totalisant à 400–500 mg/kg. Cinq animaux présentant des signes cliniques caractéristiques d'une toxicose aiguë au cuivre, incluant une hémolyse intravasculaire et de la méthémoglobinémie, sont morts. Trente-neuf autres vaches sont mortes à la ferme de causes reliées à des infections secondaires associées à un état débilitant. Deux cent quinze animaux furent envoyés à l'abattoir à cause de leur état débilitant et de leur pauvre production laitière. Le taux de mortalité des veaux nés des vaches nourries avec la ration toxique fut approximativement de 50 %. Les auteurs en conclurent que les vaches laitières gestantes semblaient être plus susceptibles à la toxicité au cuivre comparativement aux autres bovins et suggèrent qu'une réévaluation des normes maximales de cuivre présentement permises comme supplément alimentaire chez les vaches laitières soit faite.

(Traduit par Dr Thérèse Lanthier)

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Introduction

Chronic copper toxicity can result from ingestion of copper in concentrations that exceed nutritional requirements. In the first published case of copper poisoning in a dairy cow in Canada (1), the animal died five months after a spontaneous abortion. The cow had received about 100 mg of copper/kg diet, which was within the maximum allowable 100 mg/kg according to the Canadian Feed Regulations (2). Since other animals in that herd did not develop chronic copper toxicity, it may be that other hepatotoxic factors contributed to the development of copper toxicity.

In this report, we describe the events associated with chronic copper toxicity in a large dairy herd.

History

Diet: Copper deficiency has been documented in the Creston Valley, British Columbia, since the mid 1970's. Cattle in deficient herds appeared to have reduced fertility, slower growth rates, and reduced resistance to infectious diseases.

On the dairy farm in question, copper deficiency had been established by copper analyses of hepatic and renal tissues of animals of various ages since 1978. Supplementation with copper-containing mineral supplements had, therefore, been instituted.

The ration of the lactating cows on this farm consisted of alfalfa hay, alfalfa silage, corn silage, and dairy concentrate (on a dry matter basis: 50% of the ration was corn silage, 40% alfalfa silage, and 10% alfalfa hay). The roughage was fed in a concrete bunk running the length of a free-stall barn. Cows were each fed 1–2 kg barley twice daily as a top dressing in the bunk. The remainder of the concentrate was fed in the milking parlor in the form of a 16% dairy ration.

Until April of 1982, a mineral supplement containing 0.35% copper was offered free choice at stations

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throughout the free-stall area. Because serum and liver samples collected postmortem indicated some cows to be in or near a state of deficiency, it was decided that some means of force-feeding copper-containing mineral preparations should be instituted. For three months, 60 g of 0.35% copper mineral per head per day was provided as top dressing on the silage belt delivering silage from the silo to the feed belt. This method was time-consuming, and when a feed company representative suggested adding mineral to the dairy ration, the farmer was convinced that this would be the simplest way of consistently getting the minerals to the milking herd.

Apparently, an error occurred in either the calculation or the interpretation of the mixing instructions by the feed mill. In any case, from April to June of 1982, 5 kg of copper sulphate was added to two tonnes of dairy ration (equal to 328 mg of copper per kg), and from June 1982 to October 1983, 10 kg of copper sulphate were added per two tonnes (equal to 656 mg of copper per kg). Assuming a 50:50 dairy concentrate:roughage ratio, then at least 328 mg of copper/kg would have been available, in the total diet, for the dairy cows. In fact, three different analyses of the concentrate in November 1983, revealed 794, 803, and 1,001 mg of copper/kg. Eventually, a mixing error was admitted by the feed company in an out-of-court settlement of the dairy farmer's claim for restitution.

Clinical observations and laboratory findings

By August of 1982, four months after supplementation with high-level copper had started, it became obvious that there was a problem with the herd. Cows were losing weight and had poor hair coats. Many cows had developed dark-green to black diarrhea. Several cows were affected more than others, losing appetite, falling dramatically in milk production and eating only enough to stay alive. Total herd milk production declined from an average of 22.9 L/cow in the months from March to August 1982, to 19.9 L/cow in September and 17.3 L/cow in October 1982. Thus, 125 milking cows had maintained production over 3,250 L (required to maintain quota during the previous six months), but during October 1982, daily production averaged only 2,800 L.

Routine feed analyses were performed on forages, and protein and energy supply were found to be adequate. The silage looked and smelled good and was free of nitrites and low in nitrates. Analyses of the silage and prepared concentrate for mycotoxins were negative. The molybdenum concentration in the feed was 0.7 mg/kg, which was considered to be within normal limits.

Persistent diarrhea was noticed in several cows during this time. Therefore, serum samples from a number of cows were sent for complement fixation tests to rule out the possibility of Johne's disease. Since one sample tested "questionable," the entire herd was bled and 207 samples were tested along with 15 randomly selected fecal samples. All samples were negative for Johne's disease. At the same time, serum samples were taken from the 25 most severely affected cows to be evaluated for trace minerals. Eleven cows were determined to be copper deficient, and nine were determined to be borderline deficient for copper. One animal was found to be selenium deficient.

Compounding the problems of the cow herd was a persistent problem in newborn calves. Calves that appeared strong at birth became gaunt and weak within 12 hours. Many calves developed diarrhea, meningitis, navel infections, or other common diseases of newborn calves, and responded poorly to treatment. In fact, 75 of 153 calves (49%) born in 1982 died.

In October 1982, serum samples from 14 cows were submitted for trace mineral analysis. Three of these sera were determined to be marginally deficient in copper. The highest copper level measured was 0.95 mg/kg. Levels considered to be adequate are between 0.7 and 1.3 mg/kg (3).

In June of 1983, two cows developed signs of acute toxicity within 24 hours. Both cows were typical examples of the diseased cows that were now frequently observed in the herd; both developed severe diarrhea, were weak, depressed, and barely able to stand. The mucous membranes of both cows were a muddy brown color, and urine collected had a brown-maroon color; blood samples were very similar in color. The rectal temperatures of the two cows were 37.5°C and 37.8°C.

Suspecting that the apparent methemoglobinemia was due to nitrate poisoning, both cows were treated with methylene blue. In addition, steroids, antibiotics, fluids, and electrolytes were administered as supportive treatment. Blood and urine samples were sent for laboratory examination. High levels of methemoglobin (39%) and severe intravascular hemolysis were present.

When the first cow died, fresh and formalinized tissues were submitted to a laboratory. Histological diagnoses were acute hepatic necrosis, severe bile duct hyperplasia and hepatic fibrosis, and hemoglobinemic nephrosis. The etiological diagnosis was "suspect toxicity." Toxicological analyses were done on the fresh tissue, but no copper analysis was performed. When the second cow died, she was buried without a postmortem examination.

There were no further deaths until October of 1983. Herd average production was below 18 L/cow early in October 1983, and the number of cows necessary to maintain the milk quota had increased from the 1981 average of 126 cows to 174. Artificial insemination conception rates declined from 62% in 1982 to 52% in 1982 and 1983 (not included in the figures for 1982 were three cows that were culled for failure to become pregnant and 15 animals that died; not included in the 1983 figure were nine cows culled for not being pregnant and 12 that died).

On October 21, 1983 three cows experienced signs similar to the previously acutely ill cows. Two of these cows died within 24 and 48 hours. Necropsies were performed and findings similar to those described above were recorded. The third cow staggered around for weeks, surviving through vigorous oral electrolyte and propylene glycol therapy. She slowly started eating, but was shipped for slaughter after four

months. Histological findings were similar to the previous submission. This time, however, trace mineral analysis was performed, and copper levels in the liver were found to be in the toxic range (381 mg/kg, wet weight). The molybdenum level (0.35 mg/kg) was within the normal range. Nitrate and nitrite concentrations in rumen contents were within the normal range.

As an immediate follow-up, 23 of the most severely affected cows were bled and serum samples were submitted for trace mineral analysis. All copper levels were found to be in the normal range. A complete feed analysis was performed on all ingredients in order to rule out nitrates, nitrites and mycotoxins (aflatoxin, ochratoxins, zearalenone, sterigmatocystin, citrinin, patulin, T-2 toxin, diacetoxyscirpenol, penitrem A, penicillic acid, and deoxynivalenol), but all were negative. The dairy ration was found to contain about 920 mg of copper/kg. Immediately upon receipt of the diagnosis and further analyses of the dairy ration, feeding of the copper-supplemented dairy concentrate was terminated.

The milk production of all cows, with the exception of newly introduced heifers, continued to be poor, with many cows eating only enough to stay alive and producing accordingly. Average milk produced per cow had reached a low of 15.8 L at the end of October 1983, and newly calved cows were not able to produce normally. Retained placentas and metritis were often observed after parturition, and ketosis and disinterest in eating were common features. Many cows that came from the drylot looked emaciated at a time when they should have been ready to start producing.

Four months after the removal of supplemental copper from the ration, milk production was still not improving (production average was just over 16 L/cow) and the general health of the herd was considered to be poor. In order to evaluate the potential future performance of the herd, it was decided to obtain liver biopsies from a random selection of cows. Biopsies from 18 animals were taken in January 1984 and analyzed for copper and examined histologically. Wet weight copper values of these liver samples ranged from 51-313 mg/kg ($\bar{x} \pm SE = 126 \pm 17.6$ mg/kg). Histological observations were graded by assigning observations to the following categories: (a) vacuolation of hepatocytes; (b) swelling of cells or nuclei; (c) necrosis of hepatocytes; (d) bile duct (ductule) proliferation; and (e) hepatic fibrosis, particularly around bile ducts. These criteria were chosen according to the variables used by Ishmael *et al* (4) in a study of ovine copper toxicity, since they appeared to be more differentiated than those earlier published for calves by Weiss and Baur (5). Findings associated with categories (a) to (c) were considered not specific enough to allow for an etiological diagnosis. However, various degrees of bile duct proliferation and hepatic fibrosis were observed in all cases but one, at various degrees of severity, and were interpreted to be associated with copper toxicity. It was not possible to correlate the analytical findings with the histological findings; for example, whereas one animal with the highest level of hepatic copper contents (313 mg/kg, wet weight) had very prominent bile duct proliferation and extreme fibrosis with pseudolobulation, another animal with 306 mg/kg had only irregularly sized nuclei and small foci of necrosis.

A full year after withdrawal of the high levels of copper, the cows that had been exposed to copper showed little improvement in either milk production or body condition. Cows and heifers that were newly introduced performed well, however, and were in good condition on the same feed and management conditions. Even with the addition of cows that were producing well, average daily production for the calendar year of 1984 was only 17.9 L/cow. During any month of that year, one could walk through the herd and pick out the affected cows, which could be described as emaciated. Cows that died were necropsied; diagnoses included primary copper toxicity, recurrence of traumatic reticulitis, pyelonephritis, acute mastitis, and metritis. For virtually every etiological diagnosis, the histological description included hepatic lesions consistent with copper toxicity.

In September of 1984, almost a year after removal of copper supplementation, 30 cows were shipped to slaughter and liver and kidney samples were submitted for analytical and histological examination. Toxic levels of copper were not detected, and the molybdenum levels were within the normal range. The histological examination employed the same criteria as described above for the biopsies. Lesions strongly suggestive of copper toxicity (i.e. bile duct proliferation, hepatic fibrosis) were found in 6 of 30 animals; lesions suggestive of copper toxicity were diagnosed in 15 of 30 animals, and no significant findings were observed in 9 of the 30 animals.

Discussion

Interestingly, very little has been published about the occurrence of copper toxicity in the bovine species (1,3,5–7). However, the increasing attention now being paid to trace mineral deficiencies in dairy rations and the presence of copper in mineral supplements, concentrate premixes, and liquid feeds, makes it likely that copper toxicity will be seen more frequently in the future. Dairy practitioners and nutritionists should consider a number of noteworthy points that emerge from this case:

1) The insidious nature of chronic copper toxicity, i.e. the low morbidity, the mild chronic signs, and the "unthriftiness" of the animals, makes clinical diagnosis extremely difficult.
2) A diagnosis of (chronic) copper toxicity can easily be overlooked by diagnosticians unless liver copper levels are routinely examined and liver tissue is examined histologically.
3) In comparison to sheep (3,4,7), cattle appear to be resistant to copper toxicity and it may require a considerable length of time for typical clinical and pathological features to emerge.
4) During the period of excessive supplementation of copper, body defense mechanisms may be impaired, and the mortality rate of cows and calves afflicted with infectious conditions might be much higher than usual.

5) There is probably considerable variation in the individual ability to absorb and concentrate copper in cows fed the same ration, and the classical signs of copper toxicity, such as the hemolytic crisis and methemoglobinemia, can occur quite some time after exposure has occurred.
6) Serum levels of copper are a very poor indicator of the copper-loading of the liver (3,7,8). In our case, cows that were considered, on serum evaluation, to be in the low normal and deficiency range, were found, on liver biopsy and postmortem, to be at or near a toxic state.
7) Postmortem findings, such as hepatocellular necrosis, biliary proliferation and peribiliary/periacinar fibrosis, are not necessarily indicative of copper poisoning because aflatoxicosis, or other hepatotoxic injury, must be considered and excluded by further laboratory analyses. In fact, high levels of copper in the liver can occur subsequent to hepatic damage, leading to secondary copper accumulation (3,7).

Since this particular event occurred, we have been made aware of other instances of copper toxicity in dairy cows in which the copper supplementation was within the recommended (2) range of 20 to 100 mg/kg, although often little was known about the molybdenum status in the diet. If molybdenum was low, such levels of copper may become toxic because the ratio of copper to molybdenum is critical. A cursory review of such events indicates that only about 10% of the animals in a dairy herd may be affected. However, most, if not all, animals succumbing to copper toxicosis were at the end of pregnancy or had given birth a few days prior to the hemolytic crisis.

Such empiric observations indicate that a certain percentage of dairy cows might be particularly susceptible to accumulation of copper in the liver, a process that might be related to pregnancy. It is documented that high levels of estrogens increase absorption of copper from the intestine, and can accelerate hepatic synthesis of ceruloplasmin, a copper-binding protein (9). Estrogen levels in cows increase slowly during early pregnancy, but rise sharply near parturition (10). In fact, it has been speculated that increased copper in serum may be a factor in toxemia of pregnancy. The frequently cited "general stress factors" such as a fall in the plane of nutrition, stress due to transport, etc. (8), which can precipitate an acute hemolytic crisis even months after exposure, would apply here as well.

Circumstances outlined herein suggest that it might be prudent to examine the potential long-term effects of copper-supplementation of the diet of animals which do not die from an acute hemolytic crisis, and to re-examine the appropriateness of the presently allowable level of 100 mg of copper/kg in dairy rations (2). Although copper certainly can promote growth and performance in many animals, the possibility of copper toxicity appears to exist in a certain percentage of dairy cattle, particularly pregnant cows.

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