Copper toxicosis in a dairy goat herd

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Case Description—A closed herd of 400 mixed-breed dairy goats was examined because of a decrease in milk production and increase in mortality rate. Nine animals had died within a 1-month period.

Clinical Findings—Clinical signs were evident only in lactating goats and included anorexia and recumbency. In the most severely affected goats, signs progressed to neurologic abnormalities and death. Serum aspartate aminotransferase activity, γ-glutamyltransferase activity, and total bilirubin concentration were high in clinically affected does, but no evidence of hemolysis was found. A diagnosis of copper toxicosis was made on the basis of high liver and kidney copper concentrations and histologic evidence of hepatic necrosis. Goats were found to have been fed a mineral mix containing 3,050 ppm copper for 9 months prior to the onset of copper toxicosis. Overall, there was no consistent relationship between serum hepatic enzyme activities, serum copper concentration, and liver copper concentration.

Treatment and Outcome—Clinically affected goats were treated with penicillamine, ammonium molybdate, sodium thiosulfate, and vitamin E. Penicillamine increased urine copper excretion in treated does versus untreated control animals. An increased incidence of infectious disease was identified in the herd 9 months later. Liver vitamin E concentration was low in 10 of the 12 goats that underwent necropsy.

Clinical Relevance—Findings suggested that penicillamine may be an effective treatment for goats with copper toxicosis. Production losses months after the diagnosis was made suggested that the intoxication had a prolonged animal welfare and economic impacts. (*J Am Vet Med Assoc* 2007;231:586–589)

An investigation into possible causes of decreased milk production and increased mortality rate in a closed herd of 400 mixed-breed dairy goats was initiated following the death of 9 animals within a 1-month period. The producer reported that goats that died had developed anorexia and recumbency approximately 1 week earlier, with signs progressing to neurologic abnormalities (ie, paddling or vocalizing) before death. The herd was vaccinated against *Clostridium perfringens* types C and D and dewormed with ivermectin each year at the end of lactation. Animals were housed in dry lots and fed alfalfa hay, a custom grain mix, and a loose mineral mix in their pens. Recent changes in herd management included use of a newly formulated loose mineral mix that had been offered in all animal pens for the preceding 9 months. Sources of the alfalfa hay and custom grain mix had been unchanged during the previous 2 years.

The first doe (doe 1) examined was a 3-year-old, lactating, nonpregnant LaMancha goat that was brought to the University of California Veterinary Medical Teaching Hospital because of agalactia and anorexia of 3 days' duration. Abnormal physical examination findings included moderate dehydration, bruxism, ptyalism, obtundation, and cold extremities. Initial diagnostic testing included a CBC and serum biochemical analysis. Initial treatment included IV administration of polyionic fluids and SC administration of thiamine hydrochloride. The doe became comatose and died 3 hours after admission and was submitted to the California Animal Health and Food Safety Laboratory for necropsy and trace mineral analysis of liver and kidney specimens. Gross lesions at necropsy were restricted to the liver, which displayed a nutmeg appearance. Histologically, there was severe, acute, centrilobular and midzonal hepatic necrosis with hemorrhage. Liver copper concentration was 251 ppm (wet weight; reference range, 25 to 150 ppm), and kidney copper concentration was 44.6 ppm (wet weight; reference range, 3 to 6 ppm). A diagnosis of copper toxicosis was made.

A second doe (doe 2) that was found dead on the dairy 3 days after doe 1 died was also submitted to the California Animal Health and Food Safety Laboratory for necropsy. This was a lactating, nonpregnant Nubian goat. A diagnosis of copper toxicosis was also made in this goat on the basis of liver copper concentration (253 ppm), kidney copper concentration (109 ppm), and histologic evidence of hepatic necrosis.

Over the next 2 weeks, 3 additional lactating does (does 3, 4, and 5) were brought to the Veterinary Medical Teaching Hospital with clinical signs similar to those seen in doe 1, and a diagnosis of copper toxicosis was made in all 3. Copper concentrations measured in liver biopsy specimens from 2 of these 3 does were high (**Table 1**). Liver biopsy was not performed on doe 5 because it was moribund. In this doe, the diagnosis of copper toxicosis was made on the basis of clinical

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signs, high serum copper concentration, clinicopathologic abnormalities, and the fact that the doe was from a cohort of animals that had already been found to have copper toxicosis.

Hospitalized does were treated with polyionic fluids as needed. Penicillamine[a] (50 mg/kg [23 mg/lb], PO, q 24 h), ammonium molybdate (300 mg, PO, q 24 h), and sodium thiosulfate (300 mg, PO, q 24 h) were administered as chelation therapy, and vitamin E (2,000 U, PO, q 24 h) was administered to reverse copper-induced oxidation. Thiamine hydrochloride (10 mg/kg [4.5 mg/lb], q 12 h) was administered SC because the does were anorectic. Ceftiofur sodium (2 mg/kg [0.9 mg/lb], IV, q 12 h) was administered prophylactically because of the risk of bacterial hepatitis and septicemia.

None of the does treated at the Veterinary Medical Teaching Hospital (ie, does 1, 3, 4, and 5) had evidence of hemolysis (icterus, anemia, or hemolyzed plasma) at the time of initial examination, and urine was grossly normal in the doe in which toxicosis was confirmed at necropsy. However, in the does that were treated, serum aspartate aminotransferase activity, γ-glutamyltransferase activity, and total bilirubin concentration were consistently high (Table 1), although there was no clear association between the magnitude of the increases in these analytes and the serum or liver copper concentration.

To identify possible sources of copper exposure in the herd, copper content of samples of hay (12 ppm), water (< 50 ppb), grain (34 ppm), and mineral mix (3,050 ppm) was analyzed. According to the National Research Council,[1] the recommended total dietary intake of copper for a lactating dairy doe weighing 70 kg (154 lb) is 61 mg/d. Assuming total dry matter intake of 2.5% of body weight, daily grain intake of 0.91 kg (2 lb [31 mg of copper]), and daily hay intake of 0.84 kg (1.85 lb [10 mg of copper]), then a doe would have been able to ingest only 6 g of the mineral mix (20 mg of copper) before exceeding this daily requirement. The nutritionist working for the mineral mix manufacturer had instructed the dairy owner to withdraw the mineral mix from the pens at the time doe 1 was examined at the Veterinary Medical Teaching Hospital because of safety concerns related to the product, which was labeled for administration to beef cattle on pasture. Previously, a local distributor for the mineral mix had recommended this product to the owner of the goat dairy.

To this point, the only animals with clinical signs of copper toxicosis had been lactating does. To determine whether other animals in the herd were affected, liver biopsy specimens were obtained from 22 juvenile does and submitted for mineral analysis. In addition, serum copper concentration and serum sorbitol dehydrogenase and γ-glutamyltransferase activities were measured. For liver biopsy, the does were sedated with diazepam (10 mg, IV) and hair was clipped on the right side of the thorax. The liver was identified with a 5-MHz curvilinear probe in the right 9th to 11th intercostal space. The skin was prepared aseptically and infiltrated with 1.5 mL of 2% lidocaine. A stab incision was made through the skin with a scalpel blade, and a 16-gauge biopsy needle[b] was used to collect liver samples. At least 2 samples were collected from each doe, and samples were pooled for mineral analysis. The skin incision was closed with a single staple. Animals were treated at the time of biopsy and for 48 hours thereafter with penicillin G procaine (20,000 U/kg [9,090 U/lb], SC, q 12 h). No complications were observed in any of these animals. Samples were delivered frozen to the California Animal Health and Food Safety Laboratory for trace mineral analysis.

Analysis of the liver biopsy specimens revealed that 7 of the 22 juvenile does had liver copper concentrations higher than the upper reference limit and 9 had serum copper concentrations higher than the upper reference limit (**Table 2**). Three does (does 10, 13, and 14) had high serum and liver copper concentrations. One doe (doe 7) had a high serum sorbitol dehydrogenase activity, and 4 does (does 6, 7, 10, and 16) had high se-

Table 1—Selected hematologic and biochemical test results for 4 lactating goats with clinical copper toxicosis.

Variable	Reference range	Doe No. 1	3	4	5
Serum copper (ppm)	0.8–1.2	4.52	7.6	1.91	3.04
Liver copper (ppm)	25–150	251	195	327	ND
RBC count (× 10^6/μL)	11–21	28.5	18.4	18.39	11.36
Hemoglobin (g/dL)	8–12	16.9	14.3	12.7	8.6
Hct (%)	23–36	54.6	50	43.3	28.0
MCV (fL)	15–25	19.2	27.2	23.5	24.6
MCH (pg)	5–8	5.9	7.8	6.9	7.6
Plasma protein (g/dL)	6.0–7.5	7.5	7.9	7.4	7.6
AST (U/L)	58–196	17,546	8,715	3,333	498
GGT (U/L)	34–65	492	925	622	322
SDH (U/L)	2–57	1	7	1,517	78
Bilirubin (mg/dL)	0.0–0.1	1.5	4.8	1.7	4.7
Creatinine (mg/dL)	0.7–1.0	2.6	3.6	1.3	0.8
Urea nitrogen (mg/dL)	19–31	54	30	64	23

ND = Not determined. MCV = Mean corpuscular volume. MCH = Mean corpuscular hemoglobin. AST = Aspartate aminotransferase. GGT = γ-Glutamyltransferase. SDH = Sorbitol dehydrogenase.

Table 2—Age and selected biochemical values for 13 juvenile goats with subclinical copper toxicosis.

Variable	Reference range	Doe No. 6	7	8	9	10	11	12	13	14	15	16	17	18
Age (mon)	NA	12	12	12	12	12	12	12	9	9	9	9	9	9
Serum copper (ppm)	0.80–1.20	1.49	1.63	1.07	1.25	1.38	1.02	1.05	1.28	1.21	1.43	1.40	1.14	1.24
Liver copper (ppm)	25–150	51	117	260	77	159	177	155	223	280	113	148	195	108
GGT (U/L)	34–65	93	90	60	44	66	39	60	47	38	41	67	39	58
SDH (U/L)	2–57	18	60	39	24	22	41	31	40	28	22	20	24	41

NA = Not applicable.
See Table 1 for remainder of key.

rum γ-glutamyltransferase activities. Of the 4 does with high serum γ-glutamyltransferase activities, only 1 (doe 10) had a high liver copper concentration, although all 4 had high serum copper concentrations. One doe (doe 7) with high serum γ-glutamyltransferase activity and high serum copper concentration had a liver copper concentration within reference limits. Conversely, a doe (doe 14) with hepatic enzyme activities within reference limits had a slightly high serum copper concentration but also had the highest liver copper concentration observed. Overall, there was no consistent relationship between serum hepatic enzyme activities, serum copper concentration, and liver copper concentration in the juvenile does.

All lactating goats (n = 205) in the herd were treated with penicillamine (50 mg/kg, PO, q 24 h) for 7 days. The dosage was modified from published recommendations for the treatment of sheep[2] to accommodate the extensive labor requirement involved. The effectiveness of chelation therapy was assessed by comparing urine copper concentrations in 2 goats receiving penicillamine with concentrations in 2 age- and sex-matched control goats that were not being treated. After administration of 5 doses of penicillamine, urine copper concentrations in the treated goats were 3.54 and 3.23 ppm, whereas urine copper concentrations in the control goats were less than the limit of detection for the assay method used (ie, < 0.05 ppm).

To our knowledge, there are no published meat or milk withdrawal times following penicillamine treatment in lactating goats. After consultation with the California Department of Food and Agriculture, the dairy was banned from selling milk for 21 days after the last treatment with penicillamine.

It has previously been recommended that small ruminants with copper intoxication be provided supplements containing molybdenum or sulfur[2,3] because these elements mix with ingested copper in the rumen, forming insoluble, acid-stable copper tetrathiomolybdenate complexes, thus limiting absorption of ingested copper. The addition of molybdenum and sulfur to the diet also increases the concentrations of these minerals in the enterohepatic circulation, providing a means to bind copper being released from liver stores.[4] Finally, biliary and fecal copper concentrations are substantially increased in ruminants receiving diets with a high molybdenum concentration.[4,5] For these reasons, all animals in the herd were treated with ammonium molybdate (300 mg, PO, q 24 h) and sodium thiosulfate (300 mg, PO, q 24 h) for 3 weeks. Additionally, all goats were administered vitamin E (2,000 U, PO, q 24 h) for 3 weeks to mitigate possible copper-induced oxidative damage. The dosage of vitamin E was extrapolated from dosages recommended for horses with conditions such as degenerative myeloencephalopathy, protozoal myelitis, and cervical vertebral malformation in which oxidative damage may be a concern.[6] This dosage was more than 4 times the published recommended daily requirement of 448 U/d for an 80-kg (176-lb) lactating doe.[1]

Four months later, 2 of the adult does (does 4 and 5) with clinical copper toxicosis and 2 of the juvenile does with subclinical toxicosis (does 13 and 14) were reevaluated at the Veterinary Medical Teaching Hospital. Both of the does with clinical toxicosis had recovered. One of the juvenile does (doe 13) had sentimental value to the dairy owner and had been treated with penicillamine PO for 5 days after results of mineral analysis of a liver biopsy specimen were obtained. This was the only juvenile goat treated with penicillamine. In all 4 goats, serum γ-glutamyltransferase, sorbitol dehydrogenase, and aspartate aminotransferase activities and serum bilirubin concentration were within reference limits. Liver copper concentration was within reference limits in the 3 does that had been treated with penicillamine but was still high in the doe (doe 14) that had not been treated (201 ppm).

Five months after copper toxicosis was initially diagnosed, the herd had an outbreak of infectious disease, with 4% of the herd dying over a 3-month period. Pleuropneumonia, mastitis, and caseous lymphadenitis accounted for the death of 15 animals, 13 of which were lactating does. Liver vitamin E concentration was low in 10 of the 12 goats that underwent necropsy (mean, 1.1 ppm; reference range, > 3 ppm). To increase vitamin E consumption, the grain mix was reformulated with twice the previous vitamin E content.

Discussion

Goats are reportedly less susceptible to copper intoxication than sheep.[7] Thus, although there is an abundance of clinical data for sheep, there are relatively few published reports[8,9] of copper toxicosis in goats. The present report highlights several key aspects of naturally occurring copper toxicosis in goats. The most striking finding was absence of hemolysis in any of the clinically affected does. This contrasts with the disease process in sheep, in which hemolysis often marks the transition between subclinical (copper accumulation phase) and clinical disease.[2] A previous report[8] of copper toxicosis in Nubian goats reported decreases in PCV and RBC count; however, actual values were not included in that report.

For clinically normal goats described in the present report, serum hepatic enzyme activities and serum copper concentrations were insensitive markers of liver copper concentrations. These results were in agreement with findings in a recent report[10] involving cattle, in which no significant associations were found between serum copper concentration, liver copper concentration, and serum γ-glutamyltransferase activity. In that report,[10] serum aspartate aminotransferase activities were significantly correlated with liver copper concentrations; however, activities were generally within reference limits and, therefore, would not typically have caused any concerns. Mineral analysis of liver biopsy specimens remains the definitive method for diagnosing copper toxicosis antemortem.

Oral administration of penicillamine has been found to increase urinary copper excretion 10- to 20-fold in sheep.[11-13] To our knowledge, there are no published reports of the efficacy of this drug in the treatment of copper toxicosis in goats. However, goats described in the present report that were treated with penicillamine had substantially higher urine copper concentrations than did untreated control animals. Furthermore, fol-

low-up liver copper concentrations measured 4 months after penicillamine treatment suggested that penicillamine was more efficacious at decreasing liver copper concentration than was treatment with ammonium molybdate and sodium thiosulfate. On the other hand, although penicillamine administration may be useful in clinically ill or pet goats, the substantial expense of this drug (approx $165 for a 50-kg [110-lb] doe) means that it may not be cost effective for treatment of subclinically affected goats in a production setting. Lactating goats described in the present report were treated with penicillamine for 2 reasons. First, there was a geographic lack of replacement milking does should more animals in the herd die. Second, costs associated with the penicillamine treatment were not paid by the dairy owner. In other circumstances, removal of the copper source and treatment with agents such as molybdenum and sulfur, while less than optimal, may provide a practical solution for some herds.

At the time copper toxicosis was first diagnosed, there was little information available on possible long-term sequelae. Continued monitoring of the herd has suggested that the intoxication had a prolonged animal welfare and economic impact. Specifically, the increased incidence of infectious disease and low vitamin E concentrations observed months later were associated with continued animal losses totaling approximately 123 animals. The low hepatic vitamin E concentrations were unexpected because all goats in the herd had been receiving supplemental vitamin E in their diet. Furthermore, testing of does that died of acute copper toxicosis, before dietary supplementation with vitamin E was begun, revealed normal liver vitamin E concentrations (mean, 4.5 ppm; n = 3). We hypothesize that copper accumulation in does that died months later of respiratory or mammary gland infection had created an ongoing oxidative crisis in these goats, such that they may have become secondarily immunocompromised. Vitamin E has been found to augment several aspects of the immune response, including neutrophil function and macrophage cytokine production in ruminants.[14]

Clinical disease was limited to lactating does in the present report, even though similar liver copper concentrations were detected in juvenile animals. We can only speculate that the increased demands of lactation precipitated clinical signs of toxicosis. This agrees with findings in sheep, in which additional physiologic stress superimposed on excessive liver copper concentrations results in the sudden release of copper stores and fulminant disease.[1,2] These results offer insight for future herd-based risk assessment and management for goat herds with excessive copper exposure.

a. Cuprimine, Merck & Co, Whitehouse Station, NJ.
b. Bard Biopty, Bard Access Systems, Salt Lake City, Utah.

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