Chronic Copper Toxicity in Goats: Under-diagnosed or Over-hyped?

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Learning Objectives

1. Understand the different presentations of copper toxicity in goats, and management issues that can lead to this problem.
2. Understand diagnostic approaches to chronic copper toxicity.
3. Learn how to manage copper toxicity in goats.

Introduction

Chronic copper toxicity is an insidious problem that develops slowly in flocks and herds, often without an obvious inciting cause. Animals can appear normal until a stressor (shearing, parturition, transport, handling, weather extremes, other illnesses) precipitates disease. Although hemolytic crisis is the classic presentation of copper toxicity, chronic accumulation of copper can lead to renal and liver failure in goats, sheep and camelids without obvious icterus or hemoglobinuria.[1,2,3] The author has recognized non-hemolytic copper toxicity in association with outbreaks of severe pregnancy ketosis on a sheep farm, and more recently, on a large dairy goat farm. The interrelationship between these 2 problems is speculative, but chronic hepatic accumulation of copper could hamper the liver's ability to regulate metabolism of fats and carbohydrates in the late prepartum period, thus contributing to development of ketosis. Copper dietary requirement for goats is not well understood, yet there is a trend towards increasing copper administration. It is worrisome that goat owners are eager to give copper supplements to goats whenever a hair coat issue arises, and for control of internal parasites, without knowing the copper status of their herds. Further, many trace mineral preparations formulated for goats now have high copper levels in them. These issues, combined with confusion regarding the clinical presentation of copper toxicity in goats, could result in under-diagnosis of adverse health events in herds related to excess dietary copper.

Do goats "require" more copper than sheep?

Although goats are more resistant to copper toxicity than sheep, the current belief that goats actually require more dietary copper than sheep is controversial. The recent National Research Council (NRC) publication indicated that dietary copper should range from 5-8 mg/kg in sheep, and 15-25 mg/kg in goats. [2,4] Although goats tolerate higher dietary levels of copper than sheep, the evidence cited in the 2007 NRC that indicates they require higher levels of dietary copper is insubstantial at best.[4] There is no convincing evidence that dietary copper requirements for sheep and goats are actually different.

Clinical signs

Goats can present with the classic hemolytic form of copper toxicity, or a non-hemolytic form.[1,3] Both presentations can occur in the herd simultaneously (Williamson, unpublished data). The classic presentations of copper toxicity are (1) a depressed goat (or sheep) that is "peeing red", and (2) acute death. If enough red blood cells are destroyed during a hemolytic event, the animal will present weak and anemic, but the total protein concentration remains within normal limits. The sclera might be icteric from breakdown of hemoglobin. Free hemoglobin in the plasma gives it a pink appearance. When hemoglobin-binding mechanisms are exceeded, hemoglobin filters into the urine, and discolors it red. On necropsy, the body cavity is icteric (yellow to orange color), and the kidneys have a classic "gun metal blue" (dark) appearance. Urine in the bladder is a red-to-blackish-brown color. The liver is often icteric and swollen, and the gallbladder distended with bile.[3] The non-hemolytic form of chronic copper toxicity is trickier to diagnose antemortem as well as postmortem. Chronic copper toxicity should be on the "rule out" list when goats present with liver insufficiency, particularly when accompanied by renal insufficiency.[1,4] Liver failure can present with symptoms of weight loss, icterus, anorexia, hypoglycemia, and neurologic disease (hepatoencephalopathy).

Pathophysiology

Absorption of dietary copper is dependent on the levels of copper, molybdenum and sulfur in the digestive tract. Molybdenum and sulfur complexes in the rumen bind copper, thereby preventing absorption. High dietary levels of iron, calcium, and zinc can also reduce copper availability.[2] Copper that is absorbed is stored in the liver within lysosomes. It is slowly excreted in bile, and passed out in feces. The ability to excrete copper in the bile is species-dependent.[2] Sheep are the least efficient species with regards to hepatic copper excretion. When accumulation exceeds disposal, copper can reach toxic levels, and cause hepatocellular damage. When hepatic copper is released from lysosomes (in response to stress), it spills into circulation and rapidly accumulates within red blood cells (RBC's). The intracellular RBC copper levels can increase 20 fold, but plasma copper concentration might only rise 2-3 times.[5] The copper oxidizes hemoglobin, resulting in methemoglobin and Heinz body formation. The RBC membranes are irreparably damaged, resulting in intravascular hemolysis. The free hemoglobin can cause tubular necrosis and in severe cases, renal failure.

Copper sources

When investigating a copper toxicity problem, it is important to obtain a detailed dietary history, a thorough history of any treatments over the previous 6-12 months, and if possible, a history what the pastureland was used for previously. Ask about where the hay and feed were purchased, and what fertilizers were used on the hay field and pastures. Go to the farm and look around, see how animals are being fed, look at the water source, and evaluate how the goats spend their time. Are they mainly eating pellets, or eating forage? Are they chewing on treated lumber? Are chickens pooping everywhere on the hay and in feed? Collect samples of the feed, mineral, and forage and analyze them for copper,

molybdenum and sulfur content. It is important to analyze feed and mineral at an independent laboratory because actual levels of copper can vary considerably from what is printed on a product list of ingredients. Copper levels can also be evaluated in water, and in soil samples taken from various areas. Dairy One Inc. Laboratory will evaluate feed, minerals, water and hay for various components, including copper. Good detective work can lead to inconclusive answers in some cases. Morbidity and mortality can continue after the source of the excess dietary copper is gone, since high copper levels can persist in tissues for months, even years.

The 2 primary sources of excess dietary copper are the feed and the mineral mix. Feeds formulated for goats often have copper levels as high as 30-40 ppm in them. These levels are tolerable if access to the feed is limited to a small quantity, other sources of excess copper are not being consumed, and molybdenum, sulfur and other micronutrients are in the diet at levels necessary to offset copper absorption. However, if large amounts of feed are available, such as on a free choice basis, this copper level in feed can result in chronic copper toxicity (Williamson, unpublished data 2013). Feeding horse feeds to goats is dangerous because these feeds often contain copper levels as high as 60 ppm. Most commercial mineral mixes for goats contain copper levels ranging from 1,300-1,810 ppm. Godfrey Goat Mineral has the lowest copper content (500 ppm) that I found while researching this issue. Cattle mineral mixes can have copper levels as high as 3,000 ppm. Copper toxicity in a herd of dairy goats was linked to consumption of minerals formulated for cattle.[1]

Forages are rarely the source of excess copper, but there have been instances where toxicity has been linked to pastures heavily fertilized with pig or chicken manure, as these species excrete a lot of copper in feces. Water is occasionally found to be the copper source; toxicity has been linked to use of copper pipes, copper tubs, and run off from copper roofs. Lumber treated with copper-based preservatives can be a point source of copper, also. Places where treated lumber was burned in years past can have high residual copper levels in the soil. Land currently or previously used for fruit orchards can have high copper levels in soil as a result of application of copper-based pesticides. Additionally, areas where copper-based footbaths were used can have excess copper levels in the soil. Administration of copper oxide wire particles is also a potential source of excess copper. Research has shown that administration of 1-2 grams of copper oxide wire particles (COWP) reduces *Haemonchus contortus* populations in the abomasum of sheep and goats, but researchers caution that copper toxicity is a possibility if the copper status of the herd is not known prior to administration.[6] Since the COWP boluses are available as a nonprescription item, owners can inadvertently induce toxicity through indiscriminate use. Icterus and death and can occur with within 4 days of COWP administration in goats (Joan Bowen, personal communication).

Diagnosis

Analysis of liver and kidney tissues obtained antemortem (via biopsy) or postmortem is the most reliable way to diagnose copper toxicity. It is important to

test both tissues. Although liver copper is considered to be the most valuable test, a recent report indicated that the diagnosis of copper toxicity would have been missed if kidney levels had not been determined.[3] Serum copper levels are not very reliable for diagnosis of copper toxicity, but elevated levels have been detected in dairy goats with non-hemolytic copper toxicity. [1,3]

Frozen or chilled liver and kidney samples can be sent Michigan State University Diagnostic Center for Population and Animal Health (DCPAH). Copper analysis is available on a wet weight basis on the Nutritional Panel, and on a dry weight basis on the Toxicology Panel. The normal ranges vary according to whether the tissues were analyzed on a wet verses a dry matter basis, so consult normal values for the methodology used. For instance, normal liver copper levels are 60-300 ppm on dry weight analysis, and 25-150 ppm on a wet weight analysis.

Classic copper toxicity signs (hemolytic anemia, icterus) often prompt a pathologist to submit postmortem liver and kidney samples for mineral analysis. However, the practitioner might have to insist on submission of liver and kidney samples for copper analysis in cases lacking these obvious signs. As a general rule, it is a good idea to monitor liver and kidney mineral levels in small ruminants that die from unknown causes, if for no other reason than to evaluate nutritional adequacy. It is particularly important to measure minerals such as copper when signs of liver and kidney damage are evident, otherwise non-hemolytic cases of chronic copper toxicity will go unrecognized.

CASE EXAMPLE: 5 year-old "dry" Nubian doe with a history of aggression towards people and animals. No evidence of icterus was noted antemortem or postmortem. On necropsy, the liver was grossly swollen, and histopathology revealed moderate hepatic degeneration with multi-nucleation, cytomegaly, cell necrosis and multifocal bridging fibrosis. The pathologist commented that changes were indicative of chronic exposure to a hepatotoxic substance. Rhodanine red staining of the liver revealed red-orange granular material (copper) in hepatocytes. Hepatic copper levels were 1,899 ppm (normal 60-300 ug/g dry basis). Clinical signs were attributed to hepatoencephalopathy secondary to copper-induced liver failure.

Hepatocellular injury and bile duct occlusion is associated with copper toxicity, so measurement of serum liver enzymes is clinically useful.[5] A report in a sheep flock with copper toxicity indicated that serum aspartate aminotransferase (AST) concentration was helpful for detecting liver damage associated with chronic copper toxicity, and for monitoring recovery during treatment.[7] Elevated liver enzymes have been noted in clinically affected goats as well, and levels returned to normal in does that received penicillamine therapy.[1] However, a consistent relationship between liver enzyme and liver copper levels was not found.[1]

Management

Goats with clinical copper toxicity have a guarded prognosis as a result of liver and kidney damage. The rest of the herd is at risk, as subclinical involvement is common.[1] It is important to eliminate the source of the excess copper in the diet,

and to hasten the elimination of tissue copper. If the mineral mix is the source, a sheep trace mineral (no added copper) can be substituted. If the feed comprises a significant part of the diet, and it contains 20 ppm copper (or more), with minimal molybdenum levels, then reduction of the copper level and addition of molybdenum (to achieve a ratio of approximately 6:1 to 10:1) is indicated. The ration also needs to contain sufficient levels of sulfur, calcium, iron and zinc. Vitamin E levels can be increased in feed to reduce oxidative stress in tissues.[1]

Chelation therapy

Chelation therapy reduces tissue copper levels, but it is important to warn owners that results vary among animals, and the consequences of copper toxicity can continue for 5 months or more.[1,7] Chelation protocols vary among sources. [1,5,7]

Fecal excretion of copper is enhanced through oral administration of sodium molybdate (100-300 mg) and sodium thiosulfate (300-1,000 mg) daily for 3-4 weeks. Molybdenum can be purchased from feed companies since it is added to rations, and sodium thiosulfate is available from Spectrum Chemicals.

Penicillamine (Cuprimine, 250 mg capsules,) given orally at 50 mg/kg per day for 7 days, is the treatment of choice for valuable animals.[1] Penicillamine induces profound cupuresis by liberating protein bound copper from tissues.[7] The main drawback to this treatment is the expense. It would cost approximately 900 dollars to treat a 60 kg doe at today's prices. Withdrawal data for goats has not been established. Meat withdrawal is 21 days in sheep, and a milk withholding of 21 days after the last treatment was used in a dairy goatherd.[1,5]

Conclusion

With the current trend towards supplementing goats with copper for various ailments, and the ambiguity regarding dietary copper requirements, it is likely that copper toxicity issues will increase in goats. Practitioners need to be mindful of the various presentations of copper toxicity in goats, and know how to investigate the role dietary copper might be playing in herd health issues.

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