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UNDERSTANDING COPPER METABOLISM IN SMALL RUMINANTS: TOXICITY AND DEFICIENCY RISKS

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INTRODUCTION

Copper (Cu) is an essential micromineral required by small ruminants as well as all other animals and people to help maintain normal body functions. Copper nutrition is a double-edged sword being associated with both deficiency and toxicity disease concerns, especially in small ruminants. Although all microminerals are of importance, Cu is receiving more attention as a result of the potential toxicity concerns with sheep, llamas, and alpacas while a deficiency concern with goats. There is evidence of increasing Cu content in forages, and feeding with other copper-containing supplements (pellets and mineral) may predispose animals to a greater risk for toxicity problems. Likewise, there has been an increased issue of Cu deficiency in sheep and goats resultant from low Cu availability. The objective of this presentation is to provide an overview of Cu nutrition relative to appropriate dietary supplementation practices to minimize issues of deficiency or toxicity disease.

COPPER-RELATED DISEASES

With the number of biological functions attributed to Cu, a wide range of diseases has been associated with a deficient nutrient status. A most common Cu deficiency disease that occurs in an array of animals is anemia. Classically Cu deficiency has been associated with neurologic degeneration in sheep as a result of abnormal myelin formation, with resulting disease signs of muscular weakness of the posterior legs. There have been published reports of possible association between Cu deficiency and neurologic disease and ataxia in llamas and alpacas. Other potential Cu-deficiency diseases include achromotrichia and fleece structural changes, bone development abnormalities (similar to rickets), blood vessel rupture, and heart degeneration, though these are not seen in all species. Of the small ruminant species, goats have the highest Cu requirement and are most prone to deficiency disease.

Sheep are well known to be extremely sensitive to excess dietary Cu (>10 mg/kg); however, camelids do not seem to be as keenly sensitive but are prone to toxicity. Goats are least susceptible but can become intoxicated. Copper toxicity is the result of the highly reactive nature of the Cu ion when not protectively bound to proteins in tissues or blood. Copper, like most minerals, is a strong oxidizing agent that can damage cellular membranes and proteins. In most situations Cu toxicity is a progressive disease process where excess dietary Cu accumulates in the liver until it becomes saturated. The liver is the primary mineral storage

organ of the body and contains special protein molecules capable of binding minerals and keeping them isolated from doing any damage to the surrounding tissues. Stored Cu is inefficiently excreted through bile produced in the liver and transported to the intestinal tract to be lost in fecal matter. The ability to excrete Cu is species dependent and accounts for the observed differences in sensitivity to Cu toxicity. Once the liver has become saturated with stored Cu, excess will spill out into the liver and blood, reeking oxidative havoc.

Clinical Cu toxicity in sheep is characterized by massive hemolysis with subsequent hemoglobinemia and hemoglobinuria due to oxidative damage from the Cu ion released into the bloodstream. The hemolytic crisis stage of the disease is nearly always fatal. The disease process is different in other small ruminants as the “hemolytic crisis” has not been reported or seen in field cases. The common theme in Cu toxicity cases is severe and widespread degenerative hepatic necrosis. Liver necrosis may or may not be associated with elevated hepatic enzyme activities. Affected animals have highly elevated blood (>200 µg/dL) and possibly liver (>600 µg/g dry weight) as well as elevated kidney (>100 µg/g dry weight) Cu concentrations.

Up to this point, the disease conditions discussed are classified as clinical disease syndromes. Subclinical disease is described as nonspecific consequences of a nutrient being marginally deficient or toxic. Subclinical Cu deficiency is associated with impaired immune response and greater susceptibility to disease, reduced reproductive fertility, and poor growth or lactation. Clinical disease is more readily identified, but is not nearly as prevalent as subclinical disease. With difficulties in assessing Cu status using blood concentrations, subclinical disease becomes a difficult process to diagnose.

COPPER AVAILABILITY AND METABOLISM

In the more recent NRC publications, mineral requirements have been adjusted for variable availability from dietary ingredients. It has been shown that minerals within forages are not as available for absorption as from mineral sources. Compounds, such as oxalate and phytate, in forages can bind minerals reducing their availability. Copper availability in fresh pasture is lower than from hay. When the plant is harvested, some breakdown of compounds facilitates the release of Cu making it more available. As with numerous other minerals, there are many documented interactions between minerals that can alter availability. Relative to Cu, high dietary iron (Fe), zinc (Zn), and calcium (Ca) can reduce Cu availability. Iron is high in soil, and soil consumed by grazing animals may contribute to the observed lower Cu availability from pasture.

Interactions affecting Cu availability have been well studied as a result of a unique situation in ruminant animals. Bacteria in the rumen or camelid C-1 can combine dietary molybdenum (Mo) and sulfur (S) to produce compounds termed thiomolybdates. These thiomolybdates chelate or bind Cu in the fermentation vat and prevent Cu from being absorbed in the intestine. Even if absorbed, the chelated Cu is not available for use by tissues. For any ruminant animal availability of dietary Cu will be significantly influenced by dietary Mo and S content. In this regard, often the Cu requirement is defined relative to dietary Mo as a Cu-to-Mo ratio. For sheep and camelids that are more sensitive to Cu, a suggested dietary Cu-to-Mo ratio of 6-to-

8:1 is recommended. A Cu-Mo ratio of 12:1 or greater is often associated with Cu toxicity problems. A Cu-Mo ratio less than 4:1 is associated with Cu deficiency risks. High dietary iron or zinc can further exacerbate a Cu availability issue with Mo. Also remember that iron and sulfates can be found in water sources to further add to the dietary sources.

FEEDING RECOMMENDATIONS

Given the described dietary interactions with Cu, one needs to account for these other minerals in the total diet, including water sources. The challenge here is remembering dietary Cu is contributed by every ingredient fed, to some extent. This is where many people become confused. Daily Cu requirement on a dietary concentration basis is between 5 and 15 ppm for the range of small ruminant species. Each feed ingredient contributes to the overall total dietary Cu content, but only to the proportion of the total diet the individual feed represents. Additionally, each feed ingredient may contain some amount of the antagonistic elements. Molybdenum and many times sulfur content of feeds are not included in routine analysis reports and must be specifically requested at an additional charge.

In the typical small ruminant diet there are essentially three feed ingredients: forage, concentrate, and mineral. Due to forage composing the greatest proportion of the diet, it will provide the largest amount of dietary Cu even though it usually has the lowest Cu content. Mineral sources are highly variable, ranging from a low of 30 ppm Cu upward to more than 1,500 ppm Cu. With many small ruminant owners purchasing forage, there are some concerns about sources and impact on Cu status. I have had some case situations where Cu toxicity was induced by excessively high forage Cu content (>20 ppm). There is concern for increasing forage Cu content as a result of widespread copper sulfate use in footbaths for dairy cattle. Many small ruminant owners purchase hay from dairy farms and may be at risk. East of the Mississippi River, forage Cu content averages between 9 and 12 ppm DM, while westward it is much lower averaging between 4 and 8 ppm DM. Forage Mo seems to be hit and miss, though it is sporadically high in regions associated with mining activities. Typical forage Mo is less than 1 ppm DM, whereas it can be as high as 20 ppm or more. The majority of Cu availability problems I have diagnosed in sheep and goat herds is when forage Mo is >3 ppm. The forage Cu-Mo ratio sets the stage for Cu availability in the diet and dictates the need or lack thereof for additional Cu from the supplements.

In one given herd, we have been battling issues of lamb and kid stillbirths and weakness over a period of years. Liver Cu concentrations from affected lambs and kids showed very low values (<10 µg/g DW). Forage Mo typically was between 4.5 and 6 ppm. We developed a feeding program using these forages that contained 43 ppm Cu for sheep! The balance of total dietary Cu-Mo was 8:1 in this diet given the high Mo content. Reproductive performance following this dietary change resulted in high lamb and kid survival and health. Most recently this flock had devastating losses to its lamb and kid crops. It was found that the alfalfa hay being fed to the ewes and does contained 22 ppm Mo! We have since recorrected the diet to account for this higher Mo content in balancing the diet. In a goat herd, problems with doe fertility and stillborn/weak kids were observed in different years. Forage analysis showed Cu between 6 and 9 ppm and Mo between 2.25 and 3.5 ppm (Cu-Mo ratios <3:1 in diet). This herd had a free choice mineral containing 1,500 ppm Cu, but it was not consistently fed. In

reviewing purchasing records, the owner tightly correlated doe and kid issues with years where the mineral was not fed. Affected kids had low (<9 ppm DW) hepatic Cu content. My experience to this point has found poor lamb or kid survival, increased stillbirths, and poor ewe/doe reproduction in the face of marginal to low dietary Cu.

Given these dietary examples, it is imperative that all potential sources of Cu be accounted for in the diet to ensure adequate, but not excessive, Cu is consumed. As previously described, dietary Mo is an important factor to address in assessing dietary Cu status. If testing feed ingredients for Cu content, one should also have Mo and S content determined. In feeding appropriately for Cu, one should first evaluate forage Cu content then match pellet and mineral supplement accordingly. If your hay has a Cu content greater than 15 ppm, then you may need to feed a grain with lower Cu content and a low Cu mineral. It must be remembered that high dietary Cu intake does not guarantee that a toxicity event will occur. Most reported toxicity cases in goats and camelids are associated with dietary Cu content exceeding 25 ppm and a high (>12:1) Cu-to-Mo ratio.

MONITORING COPPER STATUS

With concerns for disease related to either Cu deficiency or toxicity, methods to assess Cu status are of interest. Copper can be directly determined in serum, plasma, or liver samples. Serum or plasma Cu concentrations are most easily obtained and determined, though interpretation relative to dietary status is confounded. Only very low (<0.1 µg/mL) or very high (>5 µg/mL) blood Cu concentrations are diagnostic. Values within the normal reference range (0.3 to 0.8 µg/mL) could also be associated with marginally deficient or excessive dietary Cu intake. Liver Cu concentration is considered the best measure of dietary Cu status, but requires an invasive liver biopsy to obtain a sample. If an animal dies from unknown causes, a sample of liver and kidney should be obtained to determine Cu concentration. Liver Cu concentrations below 25 ppm (dry weight basis) or above 500 ppm (dry weight basis) are suggestive of deficiency or toxicity, respectively. Kidney Cu content is very diagnostic for toxicity with values >100 µg/gm dry weight. At this point, serum Cu concentration should be used as a screening tool to assess Cu status. This measure should be evaluated in conjunction with dietary Cu and Mo content.

Suggested Reading

NRC. Mineral Tolerances of Domestic Animals, 2nd rev. ed., National Academy Press: Washington, DC, 2005.
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Suttle NF. The Mineral Nutrition of Livestock, 4 ed., CABI Publishers: Wallingford, MA, 2010.