

1969

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Recommended Citation

Buck, William B. and Sharma, Rajinder M. (1969) "Copper Toxicity in Sheep," *Iowa State University Veterinarian*: Vol. 31 : Iss. 1 , Article 1.

Available at: https://lib.dr.iastate.edu/iowastate_veterinarian/vol31/iss1/1

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Copper Toxicity in Sheep

*William B. Buck and Rajinder M. Sharma**

Introduction

During the 19th century the toxicity of copper was reported and discussed by many research workers with varied opinions. In 1897, Lemann summarized the situation by stating that the "literature on the toxicology of copper is very voluminous and is useful in clinical and forensic observations." Much of the confusion arose because of the lack of discrimination between acute and chronic poisoning, and also because of differences in solubility, toxicity of the various compounds, and the differences in susceptibility of different species. The acute and chronic toxicity of copper differ both in clinical picture and in the onset of clinical signs. Mallory (1925) seems to have been the first to report true copper poisoning in farm

animals. Hemolysis and pigmentation of the liver were characteristic lesions in experimental sheep treated with copper compounds. A similar clinical picture in sheep grazing in orchards was recognized by Beijars (1932) as chronic copper poisoning due to the use of copper in fungicidal sprays. Bisett (1932) and a detailed investigation by Broughton and Hardy (1932) established the chronic toxicity of copper in sheep.

Many reports have appeared in literature since that time and have been reviewed by many research workers, such as, Eden (1940), Boger (1959), Todd (1962), and Cock, et. al. (1966).

Etiology and Mechanism

Copper poisoning occurs mostly in meat producing breeds. It is brought about by the sudden release into the blood stream of copper which has been stored in the liver. This occurs when the hepatic storage of copper may occur as a result of: (1) high intake of copper through contaminated

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COPPER TOXICITY IN SHEEP (FIELD STUDIES)

Case No.	History	Clinical Signs	Postmortem Changes	Copper, parts/million	Source of Toxicant
3552	No. in flock: 135 No. affected: 2 No. died: 1	The animals were sick for two days before they died. The sheep showed icterus, hemoglobinemia, hemoglobinuria, and anemia.	Severe icterus of all tissues, urinary bladder contained dark colored urine (hemoglobinuria). Kidneys were swollen and had dark gun-metal colored appearance.	Liver: 183, wet weight basis.	History indicated that the sheep were kept on feed mixed with mineral supplement containing copper, but no molybdenum or sulphate.
3648	No. in flock: 80 No. affected: 6 No. died: 4	Sudden onset of symptoms, weakness, dark colored urine, jaundiced mucous membranes, hemolytic anemia and high mortality.	Icterus of all tissues, hemoglobinuria, hemoglobinemia, kidneys were chalk colored, swollen, and pulpy.	Liver: 218, wet weight basis. Complete feed: 30	The animals had been kept on complete ration containing adequate copper but insufficient molybdenum and sulphate ion resulting in an accumulation of copper.
4099	No. in flock: 2 No. affected: 2 No. died: 2 History revealed that two ram lambs were purchased from the herd of Case No. 3648 in which copper toxicity had been encountered.	Sudden onset and death within 24 hours, weakness, anemia, jaundiced mucous membranes, hemoglobinuria and hemoglobinemia.	Dark colored urine, kidneys were dark gray colored, and icterus of all tissues.	Liver No. 1, 600 Liver No. 2, 375 Kidney No. 1, 18 Kidney No. 2, 90 Urine: 7.5	The animals had been kept on complete ration containing adequate copper but insufficient molybdenum and sulphate ion resulting in copper accumulation.
4337	No. in flock: 3 No. affected: 1 No. died: 1	Ram lamb was purchased from the herd affected with copper toxicity (3648). Anorexia was noticed 4 days prior to death. Mucous membranes were pale 48 hours prior to death and urine was dark colored.	Skin and tissues were yellow, kidneys were dark and swollen, urinary bladder contained dark urine.	Liver: 260 Kidney: 28, wet weight basis.	Same as above.
4541	No. in flock: 1 No. affected: 1 No. died: 0	Weakness, hemoglobinuria and yellow mucous membranes.	The animal did not die.	Blood: 1.75	Same as above.

feed, (2) the consumption of diets containing improper levels of copper, molybdenum and sulphate, and (3) liver damage affecting the copper metabolism of the hepatocyte.

Normally, the liver metabolizes considerable copper without ill effects, provided molybdenum and/or sulfate are present. The sheep liver stores copper more readily than that of other species of animals and a copper concentration of 10–50 ppm on wet weight basis is found in the liver. When it reaches about 100 ppm or more, the animal is predisposed to characteristic hemolytic crisis which is manifested by hemoglobinemia with clinical signs of hemoglobinuria and icterus.

Additional causes of copper poisoning include:

(1) consumption of plants contaminated by copper containing herbicides, (2) copper sulphate used for the control of helminthiasis and foot rot, (3) contamination of pasture from copper mines, (4) chronic copper poisoning in sheep from the consumption of pasture plants with an unusual balance of inorganic constituents has been reported from Australia where *Trifolium subterraneum* is used extensively to raise the nitrogen level of soils. Under adverse climatic conditions associated with an early autumn break, this clover may grow abundantly. Under these conditions, the plant contains little or no molybdenum, which inhibits the uptake and storage of copper from the alimentary canal of the sheep. Sheep grazing this pasture develop high storage of copper in the liver and become predisposed to hemolytic crisis of chronic copper poisoning, (5) Another type of chronic copper poisoning of sheep, which occurs in New Zealand, is known as chronic hepatogenous poisoning. The plants, *Helitropium europeum* and *Senecio jacobaea*, cause hepatic necrosis with resulting inability to metabolize and excrete copper. (6) It has been found that sheep kept under confinement conditions are more susceptible to copper toxicity. This is supported by the findings of Bracewell (1958) who found that the typical syndrome in housed sheep receiving a small copper supplement in their

ration with no molybdenum and sulphate continued up to eleven months after copper supplement had been withdrawn.

Iowa Cases

During the investigation of several cases in Iowa we have found that confined sheep given recommended amounts of copper in mineral supplement, but with no molybdenum and sulphate, are susceptible to copper toxicity.

A number of cases of copper poisoning have been diagnosed by the Veterinary Diagnostic Laboratory during the last two to three years. Problems with copper toxicity have been more common in purebred lambs being fattened for show purposes, and ram lambs being fed for weight-gain testing.

A common history in most of the cases observed was that the animals were given a feed containing a mineral supplement with sufficient levels of copper, but no molybdenum. It has been established that copper and molybdenum influence each other in metabolism in ruminants. Feed containing even low levels of copper but no molybdenum may cause accumulation of copper in the liver until a sufficient level of copper is reached to produce toxicity. Small amounts of molybdenum and somewhat greater amounts of sulphate facilitate the metabolism of copper. After carefully going through most of the cases of copper toxicity referred to this laboratory, it has been concluded that losses in sheep are usually seen when they are kept on complete feed rations containing copper but no molybdenum.

A brief resume of five cases referred to the Iowa State Diagnostic Laboratory in 1968 is given in the following table:

Hematological Studies

Hematological studies of two sheep fed under confinement conditions, and given copper in the mineral supplement, but with no access to the pasture, showed hematological changes characteristic of copper toxicity. Two other sheep given the same amount of copper in mineral supplement but with access to the pasture did not show

any such changes because they were apparently getting molybdenum and sulphate from the forage.

The following table shows the observations recorded on the two groups of sheep:

Relationship of Copper, Molybdenum, and Sulphate

That the metabolism of copper and molybdenum are influenced by each other is evident from the effectiveness of daily

	Affected		Unaffected	
	#656 Dorset Female	#363 Suffolk Female	#225 Dorset Female	#299 Dorset Female
Copper (ppm) (Whole blood)	2.64	1.50	0.95	1.0
Hemoglobin	8.3%	7.9%	11.4%	10.7%
PCV	22.5	19.0	34.0	32.5
WBC (Corrected)	21,535	34,683	9,500	6,650
DIFFERENTIAL				
Basophils	—	—	1.0%	2.0%
Eosinophils	1.0%	1.0%	10.0%	6.0%
Stabs	—	—	1.0%	—
Segs	60.0%	78.0%	48.0%	45.0%
Monocytes	9.0%	1.0%	1.0%	2.0%
Lymphocytes	30.0%	20.0%	39.0%	45.0%
Platelets	Adequate	Adequate	Adequate	Adequate

Severe anisocytosis, moderate poikilocytosis and immature red blood cells were present in peripheral blood of the affected sheep. Basophilic stippling and polychromasia were prominent in the red cells. The plasma was severely hemolyzed. These lesions indicate a typical bone marrow response to the hemolytic anemia caused by copper poisoning. The plasma of the unaffected animals was clear and there was no detectable abnormality in the red blood cells.

Chemistry of Blood and Tissues

One of the important features of chronic copper poisoning in sheep is that blood copper concentration remains within normal range during the period of accumulation of copper and increases very markedly and abruptly 24–48 hours before clinical signs appear (Barden and Robertson, 1962; Todd and Thompson, 1962).

Normal levels of copper in the blood range from 0.75 to 1.35 ppm, but at the onset of the hemolytic crisis concentrations may be much higher (Beck, 1955).

doses of copper in controlling the profuse scouring of teart, caused by the high concentration of molybdenum in the pastures (Ferguson, et al., 1943). Dick and Bull (1945) and Cunningham and Davis (1950), provide definite evidence that dietary molybdenum will affect the storage of copper in sheep and cattle. When dietary copper is low or around normal (5–20 ppm), an increase in molybdenum intake reduces the copper already stored in the liver and the amount of copper deposited there from the food.

With forage containing normal copper content (8–11 ppm), molybdenum toxicity may occur in sheep if the forage contains 10–12 ppm or more of molybdenum. The copper and molybdenum are also related to the sulphate ion. When the dietary copper level falls much below normal or the sulphate level is high, molybdenum intake as low as 1–2 ppm may prove toxic. Molybdenum toxicity is effectively controlled by increasing the copper level in the diet by 5 ppm above normal. Cook, et al. (1966), reported that molybdenum toxicity was successfully controlled in Hereford

steers by the administration of copper glycinate.

The presence of sufficient sulphate in the forage will permit molybdenum excretion and enable the molybdenum present to exert its full effect on copper elimination. Dick (1955) reported that the factor in alfalfa which suppressed molybdenum in the circulation was inorganic sulphate. Inorganic sulphate, together with molybdenum, prevented copper storage in the liver.

Prevention, Treatment and Control

Administration of small amounts of molybdenum, 50–500 mg of ammonium molybdate per day, and 0.3–1 gram of thio-sulphate daily for three weeks, is recommended for the prevention of copper toxicity. Molybdenumized superphosphate (4 oz. molybdenum per acre) is valuable to increase the molybdenum content of pasture and reduce the retention of copper. Molybdenumized licks or mineral mixture (190 pounds salt, 140 pounds finely ground gypsum, and one pound sodium molybdate) can be used alternately.

According to Paragraph 121–101, Code of Federal Regulations, copper is officially recognized as a suitable mineral ingredient in animal feeds. Molybdenum is not yet recognized as a safe and necessary additive to the diet of animals. This means that animal feeds may contain added copper but no molybdenum. Complete feeds fed to sheep and cattle may, therefore, contain mineral mixtures which in effect increase the copper content without providing the molybdenum necessary for metabolism of the excessive copper. Our investigations of field cases of copper poisoning in sheep revealed that losses have occurred because no molybdenum was incorporated into the complete feed to which copper had been added. Also, the added copper has been in the form of a carbonate or oxide, rather than a sulphate, the former being more toxic.

It is our opinion that the federal regulations need be amended to recognize molybdenum as a safe and necessary additive in conjunction with added copper in animal feeds.

Summary

Copper toxicity in sheep may result from an imbalance of copper, molybdenum and sulphate in the diet. This was found to be the cause of losses in sheep on confinement feeding in Iowa. Complete feeds containing added copper at levels of 30–35 ppm but no added molybdenum caused storage of excess copper in the liver, resulting in hemolytic crisis and death.

It is recommended that the federal FDA regulations be amended to recognize molybdenum as a safe and necessary additive in conjunction with added copper in animal feeds.

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