Small ruminant toxicology and cases

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Abstract

There are numerous compounds and routes which small ruminants may access that can be detrimental to animal health and production. Many toxic compounds affect bovine, caprine and ovine in similar manners. Although these species are all ruminants, they are not identical. Due to variations among these species, the susceptibility, clinical presentation and lesions associated with toxic agents may differ. It is important to note what toxic agent species are susceptible to and how animals are affected to effectively diagnose and treat afflicted animals. The objective of this paper is to provide a brief review of some of the more common toxicities regarding caprine and ovine species. A brief review of several cases associated with the toxins covered also provides insight into situations practitioners may find themselves in.

Key words: caprine, ovine, toxicology

Introduction

Small ruminant species, especially sheep and goats, are likely to encounter similar toxic agents as cattle.[1] It is important to note that, although ruminants, sheep and goats are not miniature bovine. Sensitivity, clinical presentation, and lesions can vary greatly between bovine and small ruminants.[2,3,32] It is not uncommon that suspect poisonings cannot be definitively confirmed when samples collected from small ruminants are those which would be collected from cattle and ultimately not the optimal sample for evaluation. Understanding these differences is imperative in order to correctly diagnose intoxications through recognition of signs and collection and submission of correct samples.

Copper

Adequate nutrition is essential in all species for proper physiological function. Copper is an essential trace mineral that plays a large role in numerous enzymes and biochemical processes. Copper is vital for the oxidation and transportation of iron (ceruloplasmin and hephaestin), immune system function (super oxide dismutase), mitochondrial function (cytochrome C oxidase), and both coat color and quality (tyrosine).[34]

Although essential, excessive copper supplementation can be detrimental in sheep. Of the many livestock species, sheep are the most sensitive to copper. Excessive copper supplementation is commonly unintended. Two of the most common sources of excess include feed mis-formulations or the use of feed or feedstuffs intended for other species. Feeds intended for other species tend to have higher copper concentrations.[6] Both loose mineral and mineral blocks labeled for use in cattle may also serve as potential sources of excess copper. Many feed products that are labeled for cattle or other species often have signage specifically stating that the product should not be used for sheep. These warnings should be heeded. Mineral drenches and copper sulfate footbaths also serve as potential sources of copper.[25] Sheep grazing pastures fertilized with porcine manure are at risk of accumulating copper.[19]

Sheep and other ruminants accumulate copper over time within the liver. Animals with toxic concentrations of copper in the liver may not exhibit any outward clinical signs until a stressful event, such as transport or handling occurs, leading to a hemolytic crisis. During the stressful event, copper is released from the liver and enters the blood stream. New liver cells attempt to take in the excess copper but are soon overwhelmed. Red blood cells are then lysed and destroyed. The resulting serum has a dark brown to black appearance.[20]

Clinical signs of a hemolytic crisis include anorexia, weakness, icterus and hemoglobinuria (red to brown urine). Acute death within 24-48 hours may also be observed. On post mortem evaluation, tissues may appear icteric and the liver friable. Sheep that succumb to copper intoxication exhibit dark "gunmetal" colored kidneys.[11,36] Serum is the ideal ante mortem sample to evaluate for copper concentrations and both hepatic and renal enzymes. Serum copper concentrations do not necessarily correlate with hepatic concentrations. Both fresh and formalin fixed liver and kidney should be submitted for copper analysis and histologic evaluation. As little as 0.005 to 0.006 mg of fresh liver can be used to diagnostically evaluate hepatic copper.[4,20,29] Both hepatic and renal tissue should be evaluated for Cu for definitive diagnosis.[3] Submission of suspect feed and water should also be considered. Since copper accumulates over time, the most recent feed sample may not be representative of what was consumed during accumulation.

Prevention of excess supplementation is critical in avoiding copper intoxication in sheep. Feed and feedstuffs formulated and labeled for other species should not be provided to sheep. Feed intended for sheep should not have a copper to molybdenum ratio >10:1. Ideally, the ratio should be 6:1. Feeds possessing ratios of >20:1 provide significant risk of excessive copper accumulation.[27] Reduction of copper in the feed and administration of sodium molybdate can help in reducing further copper accumulation in affected animals.[34] Ammonium tetrathiomolybdate, a chelating agent, can be administered intravenously a total of 3 times on alternating days to decrease available copper and reduce both hepatic copper concentrations and damage.[16]

Nitrate

Nitrate is necessary for biological processes in ruminants and is found in various plant species.[23] There are numerous species that are considered nitrate accumulators including, but not limited to corn, fireweed, lambs quarter and pigweed.[13,40] Nitrate is utilized by plants during photosynthesis. Excess nitrate accumulation occurs whenever the plant undergoes stress and photosynthesis is impaired. Common causes of nitrate accumulation include drought and increased fertilizer application. Herbicide application not only increases the nitrate concentration within plants but tend to make plants more palatable.[40] Nitrate accumulates in the stalk of the plant with concentrations being highest in the lowest portion. Nitrate concentrations do not dissipate in corn stalk bales. Both sheep and goats may be exposed to nitrate fertilizers through water supplementation

or contaminated feeds.[17,31] Exposure of ruminants to nitrate fertilizers through tanks used for fertilizer, despite tanks being washed, usually results in high mortality.[37]

Nitrite, not nitrate, induces toxic effects on caprine and ovine species. Intoxication occurs when rumen microbes, metabolizing nitrate to nitrite for growth, become overwhelmed. Nitrite accumulates in the blood, oxidizes ferrous iron to the ferric form, and forms methemoglobin.[40] Methemoglobin is unable to carry oxygen, and tissues undergo anoxia.

Onset of clinical signs is rapid preceding death. Although often found dead, ruminants may be observed to exhibit signs associated with oxygen deprivation. Presentation may include weakness, ataxia, tremors and convulsions. Cyanotic mucous membranes and respiratory distress are characteristic of nitrate intoxication. Tissues and blood may have a chocolate-colored appearance due to methemoglobin formation.[10]

In ruminants, post mortem ocular fluid is the optimal sample to evaluated for nitrate.[37] Serum may be collected as an antemortem sample.[17] Submission of suspect feed and water should be considered for evaluation. While forages possessing <5,000 ppm DM nitrate are generally recognized as safe for livestock species, forages with concentrations of >10,000 ppm DM nitrate are considered lethal and should be avoided entirely.[10] Due to the acute nature of nitrate and rapid death, treatment may not be successful. Methylene blue 1% (20 mg/kg IV) and ascorbic acid (10 mg/kg IV) has been used successfully to treat goats following consumption of nitrate fertilizer.[17]

Urea/NPN

Urea is an economical source of non-protein nitrogen (NPN) in ruminants as it is incorporated into protein by ruminal microbes. Excess in the ration through misformulation or high urea content within feedstuffs can occur.[9] Urea-based fertilizers also serve as a common source of exposure in goats and sheep through contaminated water or feed. As with nitrate fertilizers, consumption of fertilizers tends to lead to high mortality.[37] Surface water sources may also pose a threat following heavy rains and run-off from fields with recently applied fertilizer. Exposure may also come in the form of fertilizer-contaminated feed from vehicles also used to haul fertilizer. Over supplementation by ration misformulation, barn-break-in, or providing high concentrations, especially mixes intended for other species, to unacclimated animals is not an uncommon occurrence. Unacclimated individuals are more susceptible to poisoning than acclimated individuals.[38]

Intoxication by urea is due largely in part to ruminal metabolism. Urease hydrolyzes urea to ammonia, and ammonia protonated to ammonium. During this process, the pH of the rumen steadily becomes more alkaline, and the production of ammonia is favored. Excess ammonia gets into the bloodstream where the liver converts it to urea that is excreted in the urine. When urea is consumed in excess, the ensuing ammonia production overwhelms the liver. Ammonia is then able to cross the blood brain barrier.[38]

Acute death is common in urea intoxications, and clinical signs may not be observed. Onset of clinical signs observed in sheep may occur in as little as 15 minutes following ingestion and include ataxia, incoordination, muscle fasciculations, tremoring, ptyalism, anuria, bloat and convulsive seizures.[8,9] Characteristic gross and microscopic lesions are usually absent.[9] Ammonia analysis should be performed on post mortem ocular fluid and rumen content that is collected, sealed, and frozen immediately.[37] Due to the volatile nature of ammonia, diagnostic value is lost as the postmortem sample collection interval increases. Animals dead for greater than 12 hours in moderate climates have undergone too much autolysis to be diagnostically useful. This timeframe is dependent on climate of the region. Suspect feed and water samples should also be submitted for urea analysis.[38] Rumen pH can be measured in the field or through laboratory analysis. A rumen pH >8 is consistent with urea poisoning.[33]

Due to acute nature of poisoning, treatment may come too late to be effective. Treatment of urea poisoning centers around halting further formation of ammonia by inhibiting urease. Administration of cold water and acetic acid (vinegar) creates a sub optimal environment for urease to function.[33] Due to the potential of limited resources for treatment and acute nature of intoxication, individuals should be triaged as severity of signs and capacity to urinate may serve as prognostic indicators. Sheep that survived intoxication were observed to urinate frequently. Animas that retain the ability to urinate maintain a favorable prognosis. Severely affected sheep exhibiting no urination have a poor prognosis.[8]

Ionophores

The ionophores monensin (rumensin) and lasalocid (bovatec) are common feed additives in caprine and ovine production respectively to improve feed efficiency and act as coccidostats. Ionophore intoxication can be easily misdiagnosed in small ruminant species as a result of its presentation. Intoxications, although not as common as in bovine, occur through feed misformulations, misuse, barn-break-in, and delivery errors. Feed misformulations may include excess being added to the ration through incorrect additive use, equipment failure, or antibiotic synergism.[7,12]

Excessive ionophore consumption results in an increased influx of sodium into cells followed by an influx of calcium. The influx of ions creates a drastic change in pH resulting in cellular damage. This, in addition to lipid peroxidation, results in membrane damage allowing more calcium to enter. The excess calcium activates multiple enzymes that ultimately lead to muscle necrosis.[14]

The clinical signs exhibited by goats and sheep differ from cattle and may often be perceived as neurologic in nature. Onset can occur within 24 hours. Sheep may go off feed and exhibit lethargy, weakness, stiff gait, and become recumbent. Surviving individuals may have decreased muscle mass in major muscle groups. Mortality may occur for an extended period of time following consumption.[22]

Gross lesions may be difficult to discern on postmortem evaluation.[35] Sheep afflicted with salinomycin exhibited pulmonary and skeletal muscle congestion and edema. Both hydrothorax and hydropericardium have been reported to be present. Microscopically, cardiac degeneration was also observed.[35] Ascites along with pulmonary and hepatic congestion may be observed Skeletal muscle, not cardiac, is predominately affected in small ruminant species. Generalized pallor or streaking may be evident in major muscle groups including the loins and those within the forelimbs, and trunk region. Microscopically, myocyte degeneration and necrosis are observed. Fibrosis is evident in chronically affected individuals. In month-old lambs, gastrointestinal hemorrhage is reported.[22] Sections of skeletal muscle

from the aforementioned groups, along with cardiac, lung and liver, should be collected for microscopic evaluation.[22,35] Submission of suspect feed for ionophore analysis should be considered. due to the delayed onset of signs and unlikeliness of feed remining or a retained sample, the submitted feed may not be representative of the feed consumed to inflict complications. No specific treatment is available for ionophore intoxication. Animals that survive intoxication should be handled with minimal stress as mortality may persist in surviving individuals.[14]

Sulfur/sulfate

The term polioencephalomalacia (PEM) is a common term that is often tied solely to sulfur. However, PEM is a lesion describing laminar cortical necrosis in the brain as lead, water deprivation and thiamine deficiency also result in PEM.[26] The maximum concentration of sulfur in concentrated rations for small ruminants is 0.3% and 0.5% in forage diets.[7] Water may contain high concentrations of sulfate. Sulfate concentrations > 7000 ppm in water have been reported to cause death in cattle. Elevated sulfur in diets, accompanied with high sulfate water, increases the potential for intoxication. It is likely that small ruminants would be affected at concentrations such as that as well.[15]

Clinical signs are similar to those observed with lead poisoning and water deprivation. The rumen may appear gray or black in color. Fluorescence of the laminar cortical region of the brain under ultraviolet light may be present but is not definitive for sulfur associated PEM. Absence of fluorescence also does not rule out the presence of laminar cortical necrosis. Diagnosis is often made through retrospective analysis of feed and water accompanied by clinical signs and lesions consistent with intoxication. Increased dietary thiamine can help reduce clinical signs associated with sulfur induced PEM but may not completely prevent microscopic lesions in the brain.[24]

Algae

Cyanobacteria, more commonly known as blue-green (BG) algae, are organisms that have the potential to produce harmful algal blooms (HAB). Not all species of cyanobacteria produce toxins detrimental to animal health. There are numerous species with many species capable of producing multiple toxins. *Aphanizomenon*, *Oscillatoria*, *Anabaena* and *Microcystis* are some of the most common species of concern.[39]

Production of the neurotoxins anatoxin-A and guanitoxin, formerly anatoxin-A(S), is predominant in Aphanizomenon, Oscillatoria and Anabaena species. Anatoxin-A acts exerts nicotinic effects on the body. The persistent depolarization of nicotinic receptors results in tremors, rigidity, convulsions, respiratory paralysis, and death.[21] Guanitoxin is a naturally produced cholinesterase inhibitor. Clinical signs include salivation, lacrimation, urination and defecation. Tremors and convulsions may also be observed. Guanitoxin does not cross the blood brain barrier.[30] Although all species are susceptible to anatoxins, there are few reports of small ruminants afflicted by anatoxin.[39] Microcystin, produced by *Microcystis* sp., primarily affects the liver by causing massive hepatic necrosis. Clinical signs in sheep include lethargy, weakness, diarrhea, and those secondary to hepatic failure such as hemorrhage.[18] Hepatogenic photosensitivity has also been observed.[5] Death in small ruminants associated with *Microcystis* may result within 18-48 hours.[18]

Rapid evaluation of water should be performed in suspect cases to prevent further losses. Water should be submitted for microscopic evaluation and identification of cyanobacteria with toxin producing potential. Liquid chromatography mass spectrometry and ELISA testing is available.[39] Both water and rumen contents can be analyzed at select laboratories for cyanotoxin testing. Formalin fixed liver should also be submitted.[28]

No specific treatment is available regarding cyanotoxins. Treatment is supportive in nature and dependent on clinical signs. Supportive treatment may include activated charcoal, atropine, calcium, fluids and artificial respiration. Prevention of HAB may be attained through limiting nutrient runoff into water. Copper sulfate can be added to bodies of water with HAB to kill algae. Following use of copper sulfate, access to water by cattle should be restricted for a minimum of one week as toxins may be released following the destruction of algae.[39]

Copper case

Ewes within a small herd were expected to lamb in early spring. Several ewes had been lost within the period of 2 weeks. One ewe was reported to exhibit respiratory difficulty. A mineral mix designed for cattle had been provided in the feed. An automobile battery was also present with the environment. Post mortem examination revealed very icteric adipose tissue surrounding the heart and lungs. Abdominal and mesenteric fat was also icteric. The liver exhibited an orange to yellow discoloration and was friable to the touch. All other tissues, including renal, were reported to be normal in appearance. Intestines and hepatic tissue exhibited severe autolysis of the ewe. Fetal tissues were reported as unremarkable. No evidence of an infectious agent was observed in either the ewe or fetus. Heavy metal analysis was performed due to concern for both lead and Cu. Lead was not detected in the liver, but copper was detected at almost 300 ppm. Hepatic concentrations of Cu in sheep exceeding 250 ppm are consistent with toxic accumulation and potential intoxication. In this situation, the cattle mineral utilized in the diet, was the likely source of excess Cu. The characterization of the liver and widespread icterus, accompanied with the history and hepatic copper concentrations would be consistent copper intoxication and hemolytic crisis. Fresh and formalin fixed renal tissue was not available for evaluation of lesions or Cu.

Urea cases

In the month of August, 5 adult sheep were found dead in the morning on pasture. A pile of fertilizer was identified the subsequent day following evaluation of the environment. Aqueous fluid from 2 individuals were submitted frozen and evaluated for ammonia. Ocular ammonia concentrations of both sheep exceeded 200 ppm. Ocular ammonia concentrations >20 ppm are consistent with poisoning. Careful evaluation of the environment prior to turning out is an important consideration to prevent such poisonings. Another incident of urea poisoning involved the undiluted supplementation of a urea NPN mineral premix to a herd of goats. Soon after provision of the premix, multiple individuals died acutely. Further evaluation of the supplement revealed that it was a mixture designed for cattle in which the label specifically indicated that the product not be provided to sheep or goats.

Ionophore case

New feed was delivered to a herd of 200 Boer goats. The herd was comprised of both mature does and 1-3-month-old kids. Feeders were noted to contain larger amounts of feed than usual with animals displaying more interest in consuming the straw bedding. The feed was removed and replaced, with goats vigorously consuming the replacement feed. The following day, a doe exhibited weakness characterized by recumbency and inability to rise. Thiamine, penicillin and dexamethasone were administered with no effect, and the doe displayed respiratory distress prior to death. A day later, a single buck kid was found dead, and 3 does were observed exhibiting clinical signs of hind limb weakness, thrashing and panting. Death occurred soon after in all individuals. Several does were noted to have dark brown urine. Multiple goats, tissues and feed samples were submitted for evaluation. Grossly, congested lungs and hydrothorax was noted on one doe while the lungs of 2 other individuals were dark and firm. Microscopically, 3/6 goats exhibited severe skeletal myodegeneration and necrosis characterized by fragmented sarcoplasm, loss of cross striations and hypereosinophilc myocytes. Mineralization and necrotic debris replaced normal tissue. No myocardial lesions were observed. Two of the 6 were found to have suppurative bronchopneumonia while no remarkable lesions were observed on the remaining induvial. Monensin was detected in the replacement feed at 349 g/ton. The expected concentration of monensin in the feed was 20 g/ton. An inquiry into the misformulation revealed that the feed truck had not been flushed out prior to delivery of the replacement feed. Prior to delivery of the replacement feed, the preceding load of feed contained monensin pellets (400 g/ton). The pellets were delivered with the replacement feed and resided in the bottom of the bin. The clinical history, presentation of the goats, lesions and detection of monensin at excessive levels in the feed was consistent with an ionophore intoxication. The small number affected is likely due to the limited amount of monensin pellets instead of an entire misformulated ration. Skeletal muscle breakdown likely resulted in myoglobinuria giving the urine a dark color. This case is an example of inadvertent and incorrect administration of a feed additive as a result of lack of flushing feed equipment. It also exemplifies the difference in presentation and lesions between bovine and caprine ionophore intoxication.

Conclusion

The toxins covered in this paper are by no means all-inclusive as there are many other toxins that may be encountered by small ruminants. Sheep and goats may be exposed to different toxins through a variety of ways. Clinical presentation of individuals aids in deriving a list of differentials, and toxins should always be considered. Recognition of sources, clinical signs and lesions associated with toxins in small ruminant species can greatly aid practitioners in differentiating toxic and infectious etiologies. The understanding that some intoxications in small ruminants present differently than that in bovine is critical in proper sample collection and diagnosis.

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