Toxicology basics: Common toxicants in bovine medicine

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Abstract

Bovine are the most commonly poisoned livestock species. Their exposure to a variety of environments ranging from dry lots to grass- or timber-laden pastures accompanied with their curious nature predispose them to numerous toxins. At times, intoxications can be difficult for practitioners to discern as the clinical presentation of intoxicated cattle can imitate signs associated with infectious agents. The objective of this paper is to provide a review of several of the most common toxicities associated with bovine medicine and to aid practitioners in recognition of potential sources, clinical signs and lesions, diagnostics and treatment related to these toxins.

Key words: bovine, toxicology

Introduction

Cattle are the most commonly poisoned livestock species due largely in part to their curious nature and eating behaviors.[4] The type and likelihood of a toxin that cattle are exposed to depends on their environment and the situation. Cattle on pasture are likely to encounter noxious vegetation or discarded batteries while cattle raised in feedlots or facilities are more likely to be afflicted by excessive concentrations of feed additives.[4,17,46] In suspect poisonings, a thorough history should collected, and even what may appear as a mundane event such as recent landscaping should be taken into consideration.[46] Toxins should always be considered, as intoxicated bovine may present in a similar manner associated with infectious agents.

Lead

Common sources of lead that cattle may come across include automobile batteries, motor oil, paint chips, and mortar from old building foundations.[4,14] Automobile batteries serves as one of the most common source of lead poisoning in cattle.[4,21] Encounters often occur during spring and summer when cattle are turned out to pastures that utilize electric fences or through placing cattle in an environment where old automobiles and junk are easily accessible.[4] Casings of batteries that have been left out during the winter crack exposing the lead plates within. Although rare, whole herd exposure may occur if a battery should find its way into the feed mixing process. In these instances, the battery is ground, and the lead plates are crushed into small fragments. Producers should be conscientious if changing vehicle batteries and where they are placed.[51] Cattle raised in environments with access to old buildings may be exposed to lead based paint.[1,14] Consumption of quantities of lead-based paint sufficient to cause intoxication may occur through the development of pica resulting in chewing wood from buildings or through the deposition of paint chips in feed bunks, especially following removal in preparation of applying a fresh coat of paint. Calves may be exposed to lead through the dams' milk as a result of deposited lead being resorbed from bone.[32]

Lead exerts its effects through a number of mechanisms. Lead binds sulfhydryl groups resulting in decreased heme synthesis as well as altered GABA transmission. Not only does lead interfere with calcium absorption, it also competes with calcium ultimately altering nerve and muscle transmission. Lead also impairs Na/K ATPase pumps.[14]

The predominant clinical signs involve the nervous system, but gastrointestinal signs may also be exhibited.[14,51] Ataxia, incoordination, bruxism, tremoring, head pressing and blindness are commonly observed in afflicted cattle.[4,34,51] Individuals may be observed to wander aimlessly throughout the premises. Intoxicated cattle may be found recumbent, unresponsive, exhibiting seizure-like activity, or simply found dead.[4]

Whole blood (2 mL) should be submitted in a purple top (EDTA) tube for antemortem evaluation.[14] Approximately 50 g of fresh liver is adequate analysis. In acute cases, kidney may also be submitted.[4] Suspect material may also be submitted for analysis. Submission of fresh and formalin fixed brain should be considered to rule out infectious or other toxicological agents. Brain alone is not sufficient to rule out lead poisoning.[4,11,21] Thiamine hydrochloride alone at 25 mg/kg subcutaneously or combination of thiamine (25 mg/kg subcutaneous) and intravenous calcium edetate (Ca-EDTA) (110 mg/kg) twice daily has been shown to lower lead in blood and tissue. The combination of Ca-EDTA and thiamine is more effective than thiamine alone.[5]

Nitrate

Nitrate is necessary for biological processes in ruminants and is found in various plant species.[30] There are numerous species that are considered nitrate accumulators including, but not limited to corn, fireweed, lambs quarter and pigweed.[15] 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.[8,53] 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. Cattle are also commonly exposed to nitrate fertilizers through supplementation of water in tanks used for fertilizer.[19,48] Exposure to nitrate in these cases usually results in high mortality even if the tank had been washed.[48]

The mechanism in which nitrate exerts its effects on cattle is through nitrite.[8] 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, resulting in methemoglobin.[53] Methemoglobin is unable to carry oxygen, and tissues undergo anoxia.[8]

Clinical signs are not often observed due to acute death in animals.[19] Cattle are often found dead. Ataxia and tremors may be observed. Cyanotic mucous membranes and respiratory distress are characteristic of nitrate intoxication. Tissues and blood may have a chocolate-colored appearance due to methemoglobin formation.[8]

Post mortem ocular fluid is the optimal sample to evaluated for nitrate. Serum may be collected as an antemortem sample. Submission of suspect feed and water should be considered for evaluation.[48] Forage possessing >5,000 ppm DM nitrate should not be given to gestating cattle whereas forage >10,000 ppm DM nitrate is considered lethal and should be avoided entirely.8 Intravenous administration of methylene blue 1% (20 mg/kg) has been used to treat acutely poisoned cattle.[19]

Urea/NPN

Urea is an economical source of non-protein nitrogen (NPN) in ruminants as it is incorporated into protein by ruminal microbes.[26,37] The most common sources of intoxication in cattle stem from excessive supplementation through feed misformulations, barn-break-in, careless placement of fertilizers, or through consumption of feeds or water contaminated with urea-based fertilizers.[9,44,48] Like nitrate fertilizers, water administered in tanks used for urea fertilizers tends to lead to high mortality.[48] 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.[44] The LD50 of urea in acclimated cattle is 1 g/kg whereas in unacclimated cattle it is 0.5 g/kg.49

Intoxication by urea is due largely in part to ruminal metabolism. Urease hydrolyzes urea to ammonia, and ammonia protonated to ammonium.[9] 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 producing neurologic signs.[49]

As with nitrate poisonings, death is acute, and clinical signs may not be observed as onset is rapid. Clinical signs may include ataxia, incoordination, polyuria, salivation, and seizures. Prostration of the forelimbs may also be observed. Gross and microscopic lesions are usually absent, but bloat is commonly reported.[9,48] Post mortem ocular fluid and rumen content should be collected, sealed, and frozen immediately.[48] 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 time frame is dependent on climate of the region. Suspect feed and water samples should also be submitted for urea analysis.[49] Rumen pH can be measured in the field or through laboratory analysis. A rumen pH >8 is consistent with urea poisoning.[44]

Rapid onset and death may preclude successful treatment. Treatment of urea poisoning is focused on halting further formation of ammonia by inhibiting urease. Administration of up to 40 liters of cold water and 2-8 liters of acetic acid (vinegar) creates a sub optimal environment for urease to function.[44] Due to the potential of limited resources for treatment and acute nature of intoxication, cattle should be triaged. Ruminants exhibiting clinical signs with the ability to urinate were observed to maintain a favorable prognosis. Severely affected individuals exhibiting no urination were observed to have a poor prognosis.[6]

Ionophores

Ionophores such as monensin (rumensin) and lasalocid (bovatec) are common feed additives used in cattle production to improve feed efficiency while also acting as coccidostats.[26] Ionophore intoxication may be one of the most mis-diagnosed complications in bovine medicine. Although clinical signs may be non-specific, presentation often occurs in a predictive manner.[7] Intoxications are commonly encountered 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.[17]

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 result in membrane damage allowing more calcium to enter. The excess calcium activates multiple enzymes that ultimately lead to muscle necrosis.[29]

Clinical signs exhibited by cattle are non-specific and may be perceived as something else. Onset of clinical signs are typically delayed 2-5 days post consumption. Initially, cattle may be observed to go off feed and have loose stools. Individuals may become weak and depressed while exhibited respiratory difficulty.[43] Subcutaneous edema, pica and jugular pulse may be observed.[17] On postmortem evaluation, cardiac tissue may exhibit pallor while skeletal muscle may exhibit pale streaking.[7,43] Both hydrothorax and ascites along with pulmonary and hepatic congestion may be observed. Multiple sections of heart, particularly the left papillary muscle, should be submitted for histologic evaluation. Lungs, liver, and skeletal muscle of major muscle groups should also be submitted. Microscopically, myocardial necrosis is evident. Lesions may be absent in cattle that die acutely. 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. Surviving animals may recover but may later die during a stressful event as a result of cardiac insufficiency due to potentially permanent cardiac lesions.[17]

Sodium ion intoxication / water deprivation

Water is the single most important nutrient of any species. Water deprivation/sodium ion intoxication is a common cause of hypernatremia in bovine and arises when out of water events occur followed by uninhibited access to water.[40] Intoxication also largely depends on sodium intake. Potential situations that may result in such instances include frozen waterers, broken lines, incorrect milk replacer formulations, or unpalatable water.[31,40] Acute illness characterized by high morbidity and mortality often results.[33]

During an extended period without water, sodium accumulates in neurons. This excess of sodium within the cells leads to decrease in glycolysis resulting in impairment of the sodium-potassium ATPase pump. Movement of sodium out of the brain is diminished. When animals are reintroduced to water with unlimited access, water follows the concentration gradient into neural cells resulting in cerebral edema. Onset of clinical signs in cattle may occur within hours and are akin to signs observed in lead poisoning. Anorexia, diarrhea and abnormal gait may also be observed.[31,40] Animals are centrally unaware, and opisthotonos may be observed. Gross lesions are typically absent upon postmortem examination.

A single homogenized hemisphere of both fresh and fixed brain should be submitted respectively.[40] Laminar cortical necrosis, necrotic neurons, and perivascular edema may be observed microscopically.[33,35] Sodium analysis may be conducted on fresh brain. Normal bovine brain sodium concentrations reside between 600-1600 ppm. Brain sodium concentrations >2,000 ppm are consistent with water deprivation.[23,33] Sodium analysis of brains from cattle that have undergone treatment may be of little value as brain sodium concentrations are likely to have returned to normal.

During a suspected deprivation case, the availability of water and functionality of equipment should be ascertained. Inquisition of water consumption, even if water is available, is vital. This is especially true in the event that anything has been added to the water that may have made the water unpalatable. Water sourced from freshly dug wells should be evaluated for salinity and sulfate. Evidence of consumption of excessive amounts of sodium should also be considered.[41] Slow intermittent reintroduction to water following an out of water event is encouraged.

Yew

Plants of the genus Taxus such as Japanese (T. cuspidate) and English yew (T. baccata) serve as ornamental shrubs that are commonly found throughout North America as decorative pieces in yards and surrounding facilities.[36,46] All parts of the plant, with exception of the aril, are toxic.[50] Exposures in cattle commonly occur as the result of feeding clippings by individuals that are unaware of the plant's toxic nature.[46] It is not uncommon for cattle to encounter yew in the environment. Evaluation of the environment for yew, especially if new or unfamiliar, prior to turning cattle out, is recommended.[46]

Yew contains taxine alkaloids that act as calcium channel antagonists resulting in conduction blocks within the heart.[50] Death is acute, occurring within hours, and cattle that consume yew are often found dead with no observed or reported signs. Clinical signs that have been reported include respiratory distress and collapse.[46] A thorough post mortem evaluation of the gastrointestinal tract should be performed to identify leaves or stems. The waxy bayonet shaped leaves are identifiable in the rumen and esophagus. Plant fragments may also be present in the oral cavity. Presence of any yew within the GI tract is diagnostic for yew poisoning.[36] Rumen contents may be submitted to select laboratories for taxine alkaloid analysis.[47] Pulmonary edema and pleural effusion along with myocardial degeneration and fibrosis have been observed microscopically in bovine.[3,45]

No antidote is available to treat yew poisoning, so prevention practices are critical. Clippings and plants should not be accessible to cattle. Taxine is stable in the plant even through drying. Plant material should be disposed of or incinerated. Mortality in cattle is expected within 24 hours but can also be observed days later following exposure.[3] Client education is critical in preventing poisonings as many do not realize that yew is toxic.

Sulfur/sulfate

The term polioencephalomalacia (PEM) is a common term that is often tied solely to sulfur (S). However, PEM is a lesion describing laminar cortical necrosis in the brain. Lead, water deprivation and thiamine deficiency also result in PEM.[18,33] Cattle rations that include distillers grains (DDGs) and molasses contain sulfur. The maximum amount of S in a diets containing >0.4% or >0.3% sulfur DM have been associated with the development of PEM in dairy and beef cattle respectively.[26] Water may contain high concentrations of sulfate. Sulfate concentrations > 7000 ppm in water have been reported to cause death in cattle.[18]

Cattle exhibit clinical signs similar to those observed with lead poisoning and water deprivation. Signs include head pressing, convulsions and death.[12] The rumen may appear gray or black in color.[16] Flattened gyri may be observed grossly.[27] 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.[22] Diagnosis is often made through retrospective analysis of feed and water accompanied by clinical signs and lesions consistent with intoxication. Further exposure to the source should be prevented and administration of thiamine may be considered.[28]

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 capable of producing multiple toxins. Aphanizomenon, Oscillatoria, Anabaena and Microcystis are some of the most common species of concern.[52]

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.[25] 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.[39] Guanitoxin has not been reported in cattle suggesting a decreased susceptibility.[52] Microcystin, produced by Microcystis sp., primarily affects the liver by causing hepatocellular necrosis.[38] Livers may be large darkened and friable.[52] Clinical signs include GI atony, diarrhea, weakness and those secondary to hepatic failure such as decreased coagulation capabilities. Cattle may also exhibit weakness and recumbency.[38]

Rapid evaluation of water should be performed in suspect cases to prevent further losses.[10] Water should be submitted for microscopic evaluation and identification of cyanobacteria with toxin producing potential. Liquid chromatography mass spectrometry and ELISA testing is available.[52] Both water and rumen contents can be analyzed at select laboratories for cyanotoxin testing. Formalin-fixed liver should also be submitted.[38]

No specific treatment is available. Treatment is supportive in nature and dependent on clinical signs and 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.[52]

Cyanide

Cyanide or prussic acid can be found in over 3,000 plant species.[20] Forages of most concern regarding cattle include Sorghum sp. (milo, sudan grass and johnson grass).[13] Young plants possess the potential for cyanide.[42] As with nitrate, excessive cyanide accumulation may occur during periods of stress. Poisoning may occur following administration of feedstuffs outside of normal forages such as apricot seeds.[20]

Cyanogenic glycosides (CGs) and the enzymes that convert them to hydrogen cyanide (HCN) are found in separated compartments within the plant. Damage to the plant through mastication, cutting or freezing destroys the barriers separating CGs and enzymes. Ruminants also possess ruminal enzymes that are able to convert CGs to HCN making them particularly susceptible. Cyanide inhibits the electron transport chain resulting the in the inability for oxygen to be utilized leading to anoxia and death.[42]

The onset of clinical signs tends to be rapid and within several minutes. Cattle exhibit tremoring, collapse, seizures, respiratory distress and death. Mucous membranes may appear hyperemic while blood may have a cherry red coloration, but coloration of blood and tissues alone is not definitive in diagnosing cyanide poisoning.[13] The rumen may exert an almond-like odor. Whole blood, liver, rumen content and the suspect feed stuff should be submitted for cyanide analysis. Samples should be collected, sealed and frozen immediately. Rapid plant identification through submission of digital images may aid in the identification of potential CG producing plants.[24] Adminstration of hydroxycobalamin alone may be able treat poisonings. Hydroxycobalamin forms cyanocobalamin that is excreted in the urine. The combination of either hydroxycobalamin or sodium nitrite immediately followed by sodium thiosulfate may be considered as a treatment. Sodium nitrite results in methemoglobin formation. Methemoglobin has a high affinity for cyanide. Sodium thiosulfate draws the cyanide off methemoglobin where it forms thiocyanate that is excreted in the urine. Repeated administration should be used with cause so as not to induce a nitrite intoxication.[2] Due to acute onset of signs, prevention is key. Forage with high cyanide potential should be left to rest for a minimum of 72 hours to allow for volatilization of cyanide before being fed to cattle.

Conclusion

Cattle can encounter toxins in a variety of ways. Other common toxins associated with bovine medicine include ergot, selenium, copper and numerus toxic plants. The presentation of clinical signs among toxins can be similar as seen with lead, water deprivation/sodium ion intoxication, and sulfur associated polioencephalomalacia. Recognition of both clinical signs and potential sources of intoxications aids greatly in diagnosis as sample collection is critical for definitive diagnosis. Due to either acute morbidity and mortality associated with many of the aforementioned agents along with limited treatment options, preventing exposure to toxins is paramount to bovine health.

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