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Case Report

Monensin Poisoning in a Sheep Flock

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An outbreak of monensin poisoning caused severe muscular dysfunction in sheep. Fifty-eight sheep from a flock of approximately 180 died. Affected animals had dark urine, stiff gait and/or intermittent recumbency. At necropsy, animals which died acutely had pale tan striations spread throughout the cardiac muscle. Similar, but less severe changes were seen in skeletal muscles including the diaphragm. In a lamb that survived longer, the myocardium and skeletal muscles presented larger, coalescent, pale irregular areas. Histologically, muscle fibers were swollen and fragmented or had hyalinosis and loss of striation. Prominent satellite cell proliferation and mononuclear cell infiltration were evident in the muscles of chronically affected lambs. Toxicologic analysis revealed that the ration contained 334 ppm of monensin. In sheep, monensin toxicity occurs sporadically due to accidental or extra-label use. Differential diagnoses for cases of monensin toxicosis in sheep should include vitamin E and selenium deficiency, poisoning by myotoxic plants, and gossypol toxicity.

Monensin sodium is a monovalent ion-selective ionophore that assists the cell transmembrane exchange of sodium ions for protons. Feeding ionophores to ruminants increases weight gain and improves feed efficiency. The magnitude of these effects depends on several factors, including the quality of the diet and the body condition of the animal (Mollenhauer et al., 1990). The mechanisms of action of monensin on rate of gain are complex, but its consumption leads to a significant decrease in the ruminal molar proportions of acetic acid and butyric acid and an increase in the molar proportion of propionic acid. These changes reflect a shift to a fermentation that favors the production of energy (Maas et al., 2001).

In the US, monensin is approved for use in cattle to improve feed efficiency and for prevention and control of coccidiosis. With some restrictions, the drug is also approved for use in goats, chickens, turkeys and bobwhite quail (Online Green Book: Center for Veterinary Medicine, U.S. Food and Drug Administration (http://www.fda.gov/cvm/greenbook/greenbook.html). In the past, monensin was prescribed by some veterinary practitioners for inclusion in sheep feeds at 15 to 20 ppm as an aid to control coccidiosis and/or toxoplasmosis (Mathieson et al., 1990; Sip and Pritchard, 1991; Synge, 1989). However, the use of monensin in sheep is now prohibited in the United States and some other countries. Because extra-label drug use does not apply to feed additives, veterinary practitioners in the US are not allowed to write prescriptions for feed mills to incorporate the drug into sheep diets.

Monensin can be toxic when consumed at levels higher than the recommended dose. The primary target tissues are the cardiac and skeletal muscles. Susceptibility to monensin toxicity varies considerably between species, with horses being the most sensitive. In affected sheep, plasma levels of creatinine phophokinase (CPK) are increased and clinical signs may include anorexia, muscle weakness, ataxia, decreased weight gain, and eventually death (Miller et al., 1990; van Ryssen, 1991).

Monensin toxicity developed in a group of sheep in Texas during the summer of 2002. Initially, two, 5 to 6 month-old Suffolk ewe lambs that died suddenly were presented for necropsy at Texas A&M University Veterinary Medical Center (TAMU-VMC). Approximately four days before the death of the lambs, the owner had changed the diet to a cottonseed-based, grower ration. One day after the diet change, several sheep in the flock were observed to have dark urine and a stiff gait. Within five days, these clinical signs were followed by 16 deaths in a group of 18 sheep housed in a barn. In addition, 42 deaths occurred over a two-week period in a pastured flock of 160 sheep kept on the farm and supplemented with the same ration. A third ewe lamb was presented at TAMU-VMC for clinical evaluation 6 days after the feed change. This lamb was recumbent on arrival but could be induced to stand and walk a few steps before collapsing. Rectal temperature at admission was 40.2° C. The

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ewe lamb was eating and drinking. Serum CPK levels in two affected lambs were 4029 and 11396 IU/L (normal range = 8.1 to 12.9 IU/L). All lambs in the flock had been treated with one injection of Bo-Se[a] five days before the first lamb was presented for evaluation. On the day of submission to the TAMU-VMC, the third ewe lamb had been treated at the recommended doses with an antibiotic (Ceftiofur[a]) and an anti-inflammatory (Banamine[a]) by the TAMU-VMC clinical staff for suspected aspiration pneumonia. This lamb died despite treatment. Three other lambs survived to discharge.

At necropsy, the first two ewe lambs had pulmonary edema, thoracic, pericardial and abdominal effusions, and multifocal cardiac hemorrhages. Pale tan striations were seen throughout the myocardium, especially in the interventricular septum. The endocardium of all chambers were pale gray. The livers of both lambs were swollen with rounded edges and contained several irregularly-shaped pale tan foci, indicating passive congestion of heart failure.

The third ewe lamb, that was presented for necropsy 10 days after the feed change, had severe pleural effusion that caused pulmonary atelectasis. The heart was enlarged with slight bilateral ventricular dilatation and multifocal to coalescent, pale irregular areas in the myocardium (Fig. 1). The liver had rounded edges and a mottled red and pale yellow appearance with fibrin tags attached to the surface. The caudal abdominal and rear leg muscles were reddened due to passive congestion. Various muscle groups were diffusely pale.

The most significant microscopic findings observed in the first two ewes were acute, mild, multifocal myocardial and skeletal muscle degeneration with hemorrhage. The myofibers in areas of degeneration had lost their normal striation pattern, and were multifocally swollen and deeply eosinophilic (hyaline degeneration). Fiber fragmentation and interfibrillar edema accompanied mild mononuclear cell infiltration. The liver had moderate to severe bridging periacinar congestion and necrosis (Fig. 2). The lungs were congested and edematous.

The lesions in the cardiac and skeletal muscles of the third ewe lamb were more severe and widespread. Affected areas showed a great variability in fiber diameter with swelling, hyaline degeneration, vacuolation and fiber fragmentation. Multifocal to diffuse areas of fibroplasia and mononuclear cell infiltration were present in the interfibrillar space (Fig. 3). Multinucleated regenerating cells and focal dystrophic mineralization were observed in most of the affected skeletal muscles (Fig. 4). Hepatic periacinar congestion, edema, and mild vacuolar degeneration were evident. Based on the clinical history and the macroscopic and microscopic lesions, the deaths of these sheep were attributed to severe congestive heart failure secondary to myocardial degeneration and necrosis.

Analysis of the feed provided to the sheep described in this report indicated that the ration contained 334 ppm of monensin, a concentration 16 times above the previously recommended therapeutic dose for sheep (Trower, 1998). At intakes higher than the advised level, monensin can have detrimental effects on animals (Jones, 2001; Newbold et al., 1993). Deaths due to excessive monensin intake may result from accidental inclusion of high doses of the drug in the diet or poor mixing that results in uneven distribution of the drug in the feed. Studies on the determination of monensin residues in tissues after oral administration to rabbits show that substantial levels of the drug can be found in heart, liver, brain, lung, kidney, muscle and fat as soon as 17 hours after ingestion (van Vleet and Ferrans, 1983). Experimental oral administration of 12, 16, or 24 mg of monensin/kg body weight to sheep results in signs of monensin toxicosis 24 to 36 hrs after administration (Anderson et al., 1984). Clinical signs in experimentally intoxicated sheep are similar to those observed in the outbreak reported here and consist of central nervous system depression, anorexia, diarrhea, stiffness and recumbency.

Postmortem lesions of monensin toxicity may be subtle in acute cases, but in some instances, pale streaks may be observed in skeletal muscles and myocardium. As the disease advances, the lesions become more evident (Hulland, 1993). The first two lambs presented for necropsy had been switched to a diet containing toxic levels of monensin approximately four days before their death. In these lambs, gross lesions in skeletal muscles and myocardium were mild and focal. The third lamb, necropsied 10 days after consuming the same diet, had more obvious macroscopic and histologic myocardial and skeletal muscle degenerative lesions. Despite differences in the severity and extent of muscle necrosis, all three lambs had postmortem evidence of heart failure, which is often the recognizable cause of death in cases of monensin toxicity. Histologically, the extent and severity of the muscle lesions were progressive and more severe in the lamb that survived longer. Although in the first two animals presented to TAMU-VMC the predominant change was muscle fiber degeneration with swelling and hyalinosis, the third lamb exhibited extensive interstitial fibrosis with mononuclear cell infiltration in cardiac and skeletal muscles. In the latter lamb, some degree of mineralization and focal fiber regeneration in the skeletal muscle fibers were noticeable as well.

The adverse effects of monensin may be direct, as a result of its effect on cell membranes, or indirect, by altering the absorption and excretion of some minerals (Ivan et al., 1992). Influx of sodium and calcium ions into cells as a result of cell membrane damage may lead to cell death. Monensin may also directly reduce mitochondrial oxidative phosphorylation in myocytes, resulting in decreased cellular respiration (van Vleet and Ferrans, 1983). Feeding monensin to sheep alters the overall digestive tract absorption and the tissue retention of minerals. The excretion of urinary magnesium is increased by 19% (Kirk et al., 1994). In the outbreak reported here, magnesium concentrations in urine of affected sheep were not determined. Increased retention of copper by the liver has been reported in sheep fed monensin in the diet (Elsasser, 1984; Ivan et al., 1992); however, in the cases reported here, copper levels in liver and kidney were within normal levels.

Common causes of muscle degeneration in sheep include vitamin E and selenium deficiency, poisoning by certain toxic plants, gossypol toxicity and monensin intoxication. Vitamin E and selenium deficiency is a cause of nutritional muscular degeneration and necrosis (white muscle disease) in ruminants. This condition is more common in growing lambs from birth to 6 weeks of age in areas where soils are deficient in selenium (Nelson, 1983). Most Texas soils are considered to have adequate selenium levels. Selenium liver levels were found to be elevated in two sheep (605 ppb and 531 ppb; normal 150 to 400 ppb) and normal in the third sheep (366 ppb) affect-

ed during the outbreak. Monensin has been shown to increase selenium levels in blood and its bioavailability in lambs (Wang et al., 1990). The increased selenium values in the livers of two of the lambs included in this report could be explained on the basis of an interaction of monensin with this mineral. Although vitamin E was added as a supplement to the feed given to the affected sheep, the concentrations of this vitamin in liver were below normal levels. This low vitamin E levels found in tissues of affected lambs are more likely the result of post-mortem degradation rather than decreased intake or absorption.

Myodegeneration-inducing plants in Texas include several species of the genus *Senna* and *Casia.* Twinleaf senna (*Senna roemeriana*) is an erect, grayish, pubescent, perennial herb of the legume family that grows in pastures and open woods on limestone soils in central and western Texas and New Mexico. The plant is toxic to cattle, goats and probably horses. Sheep are relatively resistant, but consumption of large amounts can result in poisoning and muscle degeneration (Hart et al., 2000). The presence of this plant in pastures where some of the sheep described in this report grazed was not identified by the owner, and analysis of ruminal content of the three necropsied lambs did not reveal the presence of any toxic plants. Additionally, some of the sheep had been confined to pens and had no access to feed other than the commercial ration provided; thus, toxic plants were ruled out as the cause of the muscle lesions observed in these lambs.

Gossypol is a natural toxin present in the cotton plant which protects it from insect damage. Cotton seeds and cotton byproducts are common ingredients in the rations of livestock. The feed given to the sheep described in this report contained cotton byproducts. Analysis for free gossypol levels in the liver of one affected sheep was 41.6 g/g dry weight basis. This level of gossypol is considered non-toxic (Kim et al., 1996). However, it should be remembered that tissue samples for gossypol determination should be collected within one hour of death of an animal, and either kept frozen or processed immediately to prevent gossypol degradation. Because the original cotton by-product-containing diet was removed from the lambs during their stay at TAMU-VMC, it is possible that some gossypol was metabolized by the sick lambs before death. Nevertheless, signs of gossypol poisoning in sheep frequently develop only after several weeks on diets containing high gossypol content (personal communication Dr. M.C. Calhoun, Texas Agricultural Experiment Station-San Angelo). Taken together, these studies indicate that the cause of muscle degeneration and death in these sheep was monensin poisoning. Monensin poisoning needs to be included in the differential diagnosis of myodegenerative diseases in sheep.

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Sources and Manufacturers

[a] Schering-Plough, Kenilworth, NJ

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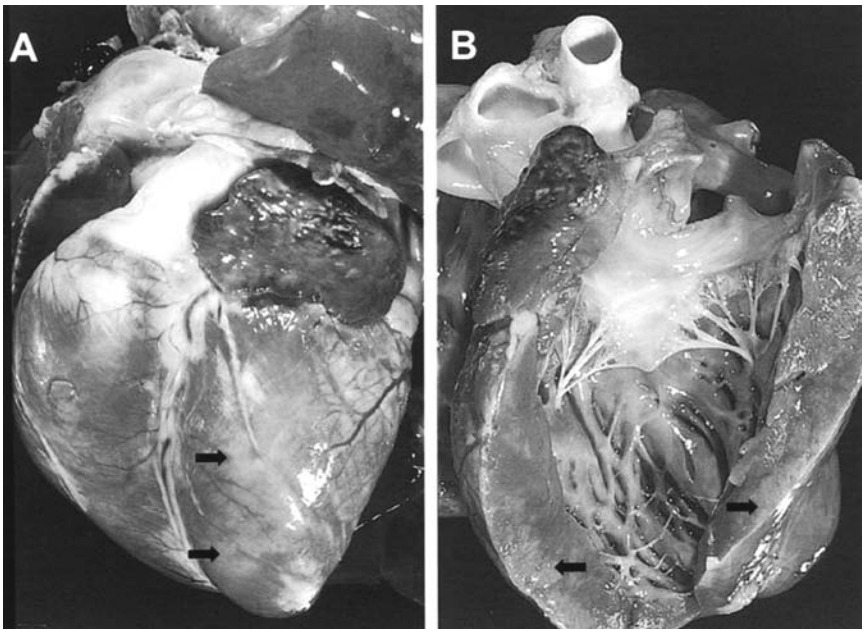

Figure 1. Heart photograph (**A**) of a sheep affected with chronic monensin poisoning, showing pale irregular areas of degeneration (arrows) in the myocardium. Cut surface (**B**) of left ventricle displaying subepicardial myodegeneration.

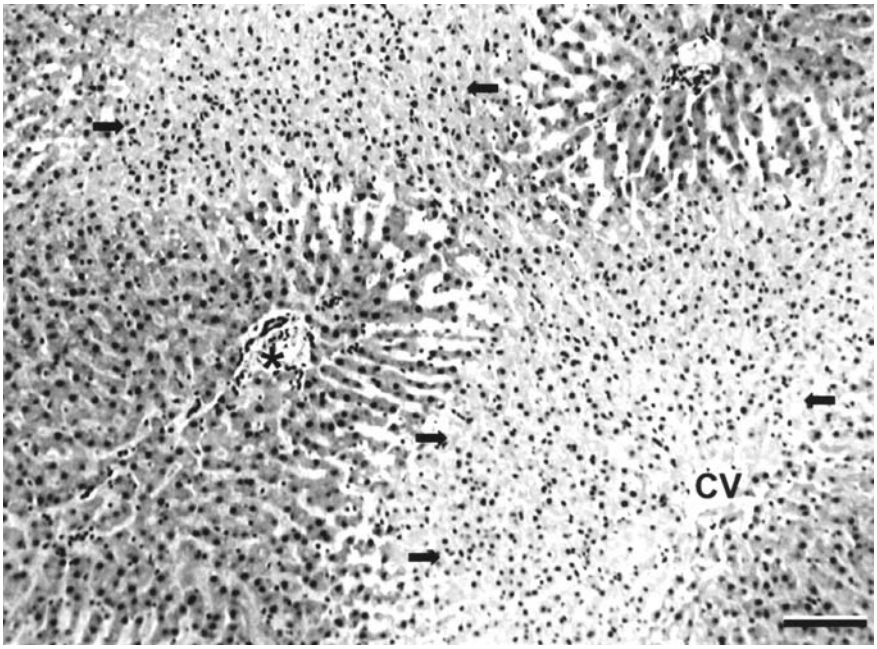

Figure 2. Microphotograph of liver from sheep affected with acute monensin poisoning, showing severe, bridging, periacinar necrosis (arrows). CV = central vein; * = portal area. (H&E stain, Bar = 50 m).

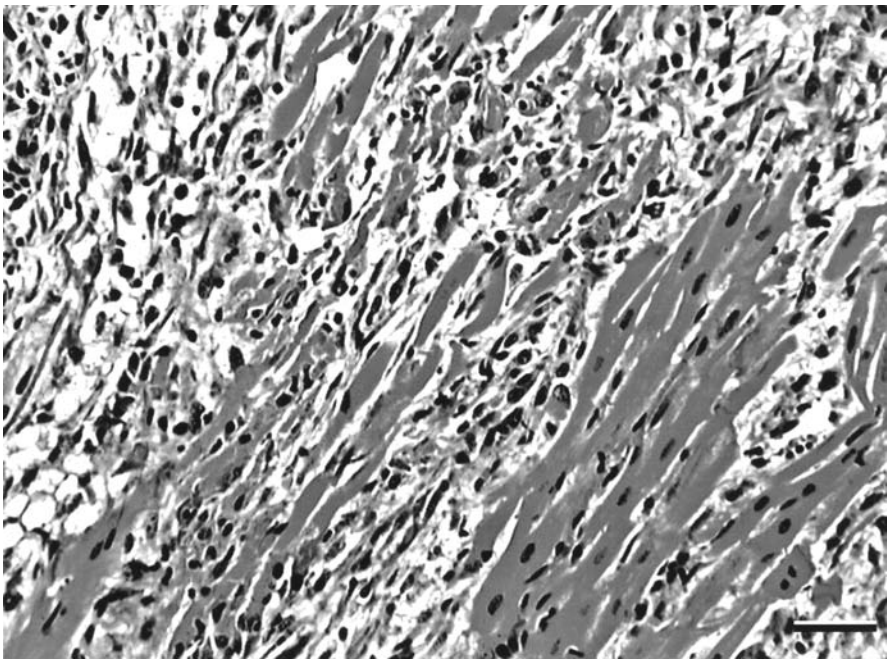

Figure 3. Microphotograph of heart from sheep affected with chronic monensin poisoning, showing muscle fiber hyalinosis, and severe interstitial fibrosis with mononuclear cell infiltration. (H&E stain, Bar = 50 m).

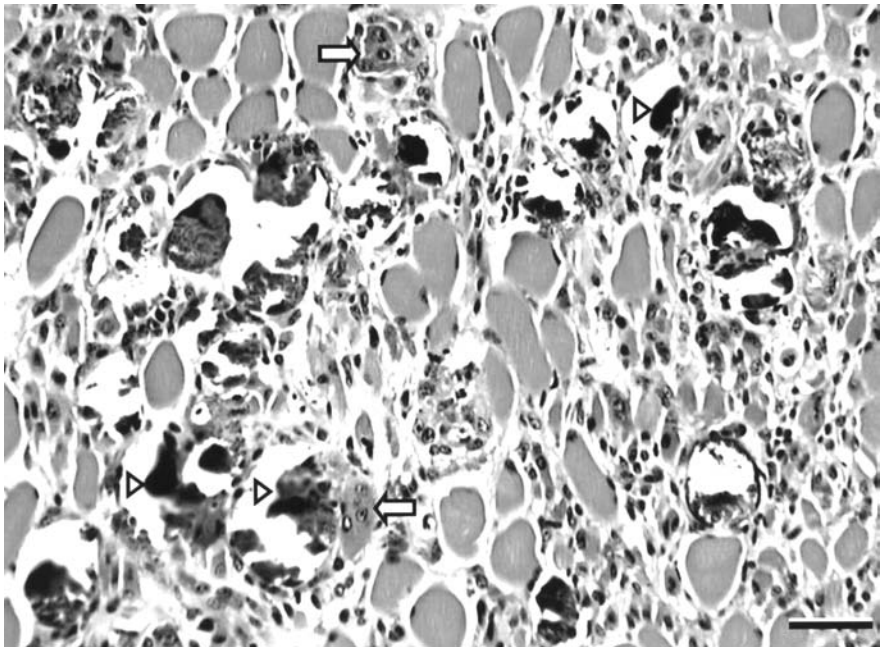

Figure 4. Microphotograph of skeletal muscle from sheep affected with chronic monensin poisoning, showing severe interstitial cell proliferation, myofiber regeneration (**arrow**) and mineralization (**arrow head**). (H&E stain, Bar = 50 m).