Salinomycin toxicosis in horses

Monica Aleman, MVZ, PhD, DACVIM; K. Gary Magdesian, DVM, DACVIM, DACVECC, DACVECP; Tracy S. Peterson, DVM; Francis D. Galey, DVM, PhD, DABVT

Case Description—A 4-month-old American Paint filly was evaluated because of sudden onset of ataxia that progressed to recumbency. Five additional horses from the same and neighboring premises developed signs of poor performance, generalized weakness, ataxia, and recumbency; 2 of those horses were also evaluated. A new batch of a commercial feed supplement had been introduced to the horses’ diet on each farm within the preceding 3 days.

Clinical Findings—Other than recumbency, findings of physical and neurologic examinations of the foal were unremarkable. The other 2 horses had generalized weakness and mild ataxia, and 1 horse also had persistent tachycardia. The foal had mild leukocytosis with neutrophilia, hyperglycemia, and mildly high serum creatine kinase activity. Results of cervical radiography, CSF analysis, and assessments of heavy metals and selenium concentrations in blood and vitamin E concentration in serum were within reference limits. Feed analysis revealed high concentrations of the ionophore antimicrobial salinomycin.

Treatment and Outcome—The 5 affected horses survived, but the foal was euthanized. At necropsy, a major histopathologic finding was severe vacuolation within neurons of the dorsal root ganglia, which was compatible with ionophore toxicosis. The surviving horses developed muscle atrophy, persistent weakness, and ataxia.

Clinical Relevance—In horses, ionophore toxicosis should be considered as a differential diagnosis for acute weakness, ataxia, recumbency, or sudden death. Furthermore, ionophore toxicosis should be considered as a cause of poor performance, weakness, muscle wasting, and cardiac arrhythmias in horses. Surviving horses may have impaired athletic performance. (J Am Vet Med Assoc 2007;230:1822–1826)

A 4-month-old American Paint filly was evaluated at the VMTH of the University of California, Davis, because of sudden onset of ataxia that progressed to lateral recumbency within less than 12 hours. The foal was the youngest of 8 horses at the farm. The foal’s deworming and vaccination histories were considered adequate; ivermectin had been administered 1 month previously, but it had not received vaccines against rabies virus or West Nile virus. The diet for all horses, including the foal, consisted of alfalfa and oat hay and a commercial concentrate feed supplement. The owner recently purchased a new batch of the feed. Three horses, including the foal, were fed the newly purchased supplement for 3 days. All horses had access to an automatic water system. There was no evidence of toxic materials or plants on the property.

At the initial evaluation, the foal was recumbent and quiet but responsive and results of a physical examination were unremarkable. A neurologic examination revealed apparently normal mentation, responses to pain sensations, and anal and tail tones; no cranial nerve deficits; and intact reflexes. The foal was unable to attain sternal recumbency and made weak, unsuccessful attempts to stand. Muscle tone was considered normal, and no orthopedic abnormalities were detected.

Clinicopathologic abnormalities included mild leukocytosis (16,600 WBCs/µL; reference range, 5,400 to 14,300 WBCs/µL) with neutrophilia (12,782 neutrophils/µL; reference range, 2,260 to 8,580 neutrophils/µL), hyperglycemia (177 mg/dL; reference range, 59 to 122 mg/dL), and mildly high serum activities of creatine kinase (741 U/L; reference range, 119 to 287 U/L) and alkaline phosphatase (334 U/L; reference range, 86 to 285 U/L). The mild leukocytosis and hyperglycemia were attributed to stress-related cortisol release. The mildly high serum creatine kinase activity was attributed to recumbency. No abnormalities in the cervical portion of the vertebral column were identified radiographically. Cytologic examination of a sample of CSF revealed no abnormalities. Venipuncture was

From the Departments of Medicine and Epidemiology (Aleman, Magdesian) and Pathology, Microbiology, and Immunology (Peterson), School of Veterinary Medicine, University of California, Davis, CA 95616; and the Department of Veterinary Sciences, College of Agriculture, University of Wyoming, Laramie, WY 82070 (Galey).

Address correspondence to Dr. Aleman.
performed for assessment of trace minerals (zinc, iron, magnesium, copper, calcium, and phosphorus concentrations), serum vitamin E concentration, and whole blood selenium concentration. Results of those analyses were within reference limits. Samples of feed, water, and plants were collected from the property for examination and toxicologic analysis.

Further diagnostic evaluations and supportive treatments for the foal were offered to the owner, but because of finances and for humane reasons, the owner elected euthanasia. Results of assessment of brain tissue for rabies virus were negative. On necropsy, no gross lesions were identified in the musculoskeletal system, brain, or spinal cord. The notable histopathologic findings were confined to the C7 and L6 dorsal nerve root ganglia; neuron cell body vacuolation and fenestration as well as axonal vacuolar changes in the nerve roots were detected, which were suggestive of acute injury to the affected neurons (Figure 1). Analyses of heavy metals (arsenic, cadmium, copper, iron, lead, manganese, mercury, molybdenum, and zinc) and organophosphates were performed on liver and kidney tissues and ingesta. The feed was analyzed for ionophores. Results of the heavy metal analyses were within reference limits, and no organophosphates were detected. Analysis of the feed concentrate for ionophores identified salinomycin at a concentration of 130 µg/g (130 ppm).

On further questioning, the owner stated that the other 2 horses that were fed the same commercial feed developed generalized weakness and abnormal gait within 12 hours of ingestion. Weakness in one of the horses (a yearling) progressed to recumbency. Two days later, that horse was able to stand but remained weak and incoordinated. In addition, the owner’s neighbor reported that her 3 horses also had signs of poor performance and weakness and developed an abnormal gait at approximately the same time that the foal was taken for evaluation at the VMTH. Two additional bags of the commercial feed, including 1 from the neighbor, were also analyzed, and results were positive for salinomycin at concentrations of 70 and 87 µg/g (70 and 87 ppm), respectively. Two weeks later, the owner’s affected yearling was evaluated at the VMTH because of persistent weakness and abnormal gait. Results of physical and neurologic examinations confirmed the owner’s complaints. The abnormal gait was determined to be quadrilateral ataxia1 (grade 2/5). Results of a CBC, serum biochemical analyses, ECG, and echocardiography were within reference limits. One of the neighbor’s horses was transported to the VMTH for physical examination. That horse had weakness, ataxia (grade 2/5), muscle wasting, and mild tachycardia (56 beats/min; reference range, 28 to 40 beats/min) that persisted in further follow-up examinations. The owner declined further diagnostic workup. Four months later, the 3 horses affected on both farms remained weak and ataxic and had developed muscle atrophy.

Discussion

Ionophores constitute a heterogeneous group of antimicrobials that enhance membrane permeability to ions across cell membranes, affecting both ion influx and efflux.2 According to their mechanism of action, ionophores are classified into 2 major groups: mobile carriers that bind ions to form lipid-soluble complexes and channel-forming compounds.3 On the basis of the unbound electrical charge, carrier-type ionophores are classified as carboxylic (negative charge) or neutral ionophores.3 Carboxylic ionophores have been used extensively as feed additives for poultry and livestock.4 Exposure or consumption of ionophore compounds in nontarget species (including humans) and overconsumption in target species have resulted in toxicoses.4 Ionophores, when bound with appropriate cations, disrupt transmembrane ion gradients and electrical potentials that are required for normal cell function. These alterations are especially detrimental in excitable cells such as those in nervous tissue and cardiac and skeletal muscles.3

Although toxic doses of ionophores primarily affect skeletal and cardiac muscles, clinical evidence of neurologic or neuromuscular dysfunction has been identified in various species.5,6 Reported histopathologic findings in mammals and chickens include widespread swelling of peripheral nerves, primary and secondary degeneration of axons and myelin sheaths (fragmentation and loss of axons and myelin), formation of digestion chambers filled with foamy macrophages, swollen Schwann cells, collapsed axon sheaths, and Wallerian degenera-

Figure 1—Photomicrographs of a cross section (A) and longitudinal section (B) of L6 dorsal nerve root in a foal with salinomycin toxicosis. Notice the severe vacuolation within neuron cell bodies of the dorsal nerve root ganglia and nerve fiber vacuolation. H&E stain; bar = 50 µm.
tion of dorsal funiculi of the spinal cord. In most instances, histologic alterations appeared to be confined to the peripheral nervous system with no involvement of the spinal and autonomic ganglia. Noninflammatory polyneuropathies and polyradiculopathies are not frequently reported in veterinary medical literature.

The foal of this report developed noninflammatory polyradiculopathy characterized by severe neuronal vacuolation as a result of salinomycin poisoning.

Ionophores used as coccidiostats in poultry and as growth promotors in chickens, cattle, and pigs are monocarboxylic polyether antibiotics that are produced by saprophytic fungi, predominantly *Streptomyces* spp. These ionophores form lipid-soluble, reversible complexes with cations (K⁺, Na⁺, Ca²⁺, and Mg²⁺) to facilitate their transport across lipid membranes, resulting in a disturbance of normal ionic gradients and pH shifts. Ionophores are classified as monovalent or divalent depending on their affinity for monovalent or divalent cations. The monovalent ionophores include monensin (higher affinity for Na⁺ than K⁺), salinomycin (higher affinity for K⁺ than Na⁺), and narasin and maduramicin (both of which bind to K⁺). Lasalocid is a divalent ionophore that binds to Ca²⁺ and Mg²⁺. Ionophores that bind to K⁺ can cause loss of intracellular potassium, which results in inhibition of ATP hydrolysis in the mitochondria with subsequent decreased cell energy production and death. In addition, the increase in concentration of sodium inside the cell results in cellular water influx and mitochondrial swelling. Ionophores also cause accumulation of intracellular Ca²⁺, exceeding the ability of the mitochondria and sarcoplasmic reticulum to effectively sequester calcium; this ultimately causes cell death. Increases in intracellular calcium concentration in secretory cells or the calcium-associated release of catecholamines can induce myocardial hypercontraction and necrosis.

Overdose or use of ionophores in nontarget species can result in toxicosis. Ionophore toxicosis in horses, cattle, sheep, pigs, chickens, turkeys, dogs, cats, rabbits, rodents, and humans has been described. All animal species are susceptible to the toxic effects of ionophores, but horses and dogs are most severely affected. The recommended dose of monensin for use in cattle is lethal when administered to horses. Exercise exacerbates the toxic effects because of an increased transmembrane influx of cations. Concurrent administration of chloramphenicol, tiamulin, erythromycin, sulfonamides, triacytloleandomycin, and cardic glycosides can potentiate ionophore toxicity. In horses, salinomycin is apparently among the ionophores that have the highest toxicity, followed by monensin. As little as 40 to 50 µg of salinomycin/g (40 to 50 ppm) in feed has reportedly poisoned horses, and in 1 instance, 15 µg of salinomycin/g (15 ppm) was found in the dust from a feed bunk of a poisoned horse. Although a report of chronic ionophore poisoning stated that horses fed salinomycin develop toxic myocarditis of lesser intensity than that produced by monensin or lasalocid, toxic and lethal dosages for salinomycin were not provided. Feed containing monensin at 125 and 279 µg/g (125 and 279 ppm) is considered toxic and lethal, respectively, in horses. The reported LD₅₀ in horses for salinomycin, monensin, and lasalocid are 0.6, 2 to 3, and 15 to 21.5 mg/kg, respectively.

These dosages are considerably lower than the values in other species such as cattle, sheep, pigs, and chickens. The relative toxicities of ionophores in various species from lowest to highest are salinomycin, lasalocid, narasin, monensin, and maduramicin.

In any affected animal, the clinical course of ionophore toxicosis could be hyperacute, acute, or chronic. Extremely high doses can cause death within minutes of ingestion, but typically, clinical signs develop within a few hours to days of ingestion. Initial signs of ionophore toxicosis vary in severity and type among ionophore compounds and among species. In horses, clinical signs may include colic, lethargy, anorexia, restlessness, weakness, ataxia, stiffness, paresis, recumbency, respiratory distress, sweating, myoglobinuria, distention of the urinary bladder, and death. In addition, many affected horses develop cardiomyopathy as the primary abnormality. Epistaxis was reported in 1 affected horse. Diarrhea and frothing from the mouth in cattle and sheep with ionophore poisoning have been described. Weight loss, lethargy, poor performance, cardiac arrhythmias, edema, diarrhea, and polyuria have been developed in chronically affected horses.

Horses that survive ionophore toxicosis are at greater risk for the development of cardiac abnormalities such as atrial fibrillation, atrial and ventricular extrasystoles, intraventricular block, and chronic heart failure. Among 867 cats that were fed a contaminated commercial dry feed in the Netherlands and Switzerland, salinomycin-induced polyneuropathy (resulting in acute pelvic limbs paresis and weakness that progressed to the thoracic limbs), tetraparalysis, lack of spinal reflexes, dysphonia, dyspnea, and death were reported.

Salinomycin-induced clinicopathologic abnormalities may include RBC fragility, electrolyte disturbances, and high serum activities of creatine kinase and its isoenzymes that develop within 24 hours of ingestion, in addition to high serum activities of aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase 1 and 2. Myoglobinuria has been detected in ionophore-poisoned horses, pigs, and humans. High serum creatine kinase activity and myoglobinuria were detectable for approximately 40 and 35 days, respectively, in a human after a single exposure of inhaled and ingested salinomycin. The definitive diagnosis of ionophore toxicosis is achieved via detection of ionophores in feed, stomach contents (minimum sample of 100 g), or tissue samples. Ionophores are rapidly metabolized by the liver. The liver is the primary site of ionophore storage, but the compounds may also be present in other tissues such as the heart, skeletal muscle, and stomach. However, accumulation of the ionophores in tissues is low, and often they are undetectable in intoxicated animals.

Pathologic findings that are typically identified at necropsy in animals with ionophore toxicosis involve the myocardium and skeletal muscles. However, lesions may be minimal or absent in many cases. Histopathologic findings include cardiac and skeletal myodegeneration and myonecrosis. Monophasic (1-stage) or polyphasic (multiple-stage) myopathic alterations may
develop in animals that have consumed ionophores on 1 occasion or long term, respectively. In cases of sudden or peracute death, there may be no apparent macroscopic lesions. Vacuolation, swollen mitochondria, lipid vesicles, hypereosinophilia, pyknosis, mineralization, and loss of fiber striation of the skeletal and cardiac myocytes may be detected histologically in affected animals. Sarcoplasmic vacuolation may be reversible, but at high doses of ionophores, muscle necrosis supervenes. Cardiac myocytes do not regenerate and fibrosis develops, predisposing the affected animal to congestive heart failure. In horses with monensin toxicosis, cardiac muscle abnormalities primarily develop, whereas skeletal muscle lesions are more frequently detected in monensin-poisoned sheep, swine, and dogs. Horses with monensin toxicosis typically develop signs acutely; however, delayed cardiomyopathies have been reported. * Petechial hemorrhages in muscle, heart, lungs, gastrointestinal tract, and spleen have also been detected in horses following ingestion of monensin. Pleural and peritoneal effusion and pulmonary edema have been described in cattle with monensin toxicosis. Severe vacuolation in cultures of neuronal cells derived from the brains of chicken embryos, similar to those detected in nervous tissue from the foal of this report, has been induced by exposure to monensin. Severe polyneuropathy of peripheral nerves characterized by primary axonal degeneration (swelling, fragmentation, and loss) and secondary degeneration of the myelin sheath were identified in cats with salinomycin toxicosis. Wallerian degeneration in the dorsal funiculi of the spinal cord in cats has also been reported.

To date, there is no antidote or specific treatment for ionophore toxicosis. However, amelioration and delay of onset of clinical signs in pigs and cattle were achieved via administration of vitamin E and selenium, which act to stabilize cell membranes and prevent lipid peroxidation-mediated cell injury. Gastric lavage and the administration of activated charcoal may reduce the amount of toxic material available for absorption from the gastrointestinal tract, especially in cases of recent ionophore ingestion. Supportive care should be provided for all affected animals; those that survive but have persistent signs including cardiomyopathy should be rested because exercise may result in sudden death. The prognosis for animals with ionophore toxicosis varies. In instances of consumption of contaminated feed, prognosis is dependent on the concentration of ionophore in the feed, amount consumed per kilogram of body weight, and duration of consumption. Typically, prognosis is considered guarded to poor for affected horses. Because the horses with toxicosis in this report were fed in groups, it was not possible to estimate the amount of consumed supplement per horse. Salinomycin toxicosis in horses has been reported in England, South Africa, and Germany but not in the United States. Monensin toxicosis in horses has been reported in the United States, Germany, Brazil, and Mozambique. The morbidity rate among all those cases was 100%, and the mortality rate was high, ranging from 60% to 100%. Clinical, clinicopathologic, and ECG assessments in surviving animals could be used as prognostic indicators for future athletic performance.

The history; clinical signs; and clinicopathologic, histologic, and toxicologic findings in the foal of this report were consistent with ionophore toxicosis. It is possible that the older horses consumed less salinomycin per kilogram of body weight and their clinical signs were therefore not as profound. As highlighted in this report, it is important to avoid feeding ionophore compounds to nontarget species such as horses. Horses are particularly susceptible to the effects of ionophores (morbidity and mortality rates are high among affected animals), especially to those of salinomycin. Ionophore toxicosis should be considered as a differential diagnosis in horses fed a commercial feed that have signs of acute weakness or ataxia, become recumbent, or suddenly die and in horses with poor performance, weakness, muscle wasting, and cardiac arrhythmias. It is also important to advise owners that surviving horses may have impaired athletic performance for an indefinite period.

References


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