Ivermectin toxicosis in three adult horses

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Case Description—Three adult Quarter Horses were evaluated for acute, progressive neurologic signs 18 hours after oral administration of 1 dose of 1.87% ivermectin paste.

Clinical Findings—Clinical signs included depression, forelimb and hind limb ataxia, drooping of the superior and inferior lips, and muscle fasciculations. Bilateral mydriasis, decreased pupillary light reflexes, and absent menace reflexes were evident. Clinical signs progressed in severity for 36 hours after administration of the ivermectin.

Treatment and Outcome—All horses were treated supportively with IV administration of fluids and anti-inflammatory medications. Two horses survived with no apparent long-term sequelae. One horse was euthanized, and a high concentration of ivermectin was detected in its brain tissue at postmortem examination. Analysis of the ivermectin concentration in the paste product revealed that the concentration was approximately that indicated on the packaging.

Clinical Relevance—Ivermectin toxicosis is an uncommonly reported condition in equids that should be considered when acute neurologic impairment develops after ivermectin administration. Recovery is possible with supportive care and time. (J Am Vet Med Assoc 2009;235:558–562)

A 7-year-old 450-kg (990-lb) Quarter Horse mare (horse 1) was admitted to a veterinary hospital for evaluation of acute neurologic impairments. The horse was 1 of 5 adult Quarter Horses owned by 1 individual and, similar to the other horses, was strictly confined to a stall and denied access to pasture or paddock. All 5 horses were fed identical diets of Bermuda coastal grass hay plus commercial sweet feed (12% protein).

Five horses were fed identical diets of Bermuda coastal grass hay plus commercial sweet feed (12% protein). Vaccinations of all horses were current and included those against West Nile virus, equine herpes virus, and western, eastern, and Venezuelan equine encephalitis viruses. The horses were on a parasite control program consisting of a commercial paste product administered orally every 6 to 8 weeks. Three of the 5 horses had received 1 tube each of a commercially available dewormer containing 1.87% (120 mg) ivermectin. The tubes were the last in a box of 12 tubes, and the other tubes had been administered to the horses in prior treatments. Approximately 18 hours after administering the ivermectin paste, the owner noticed signs of depression, profuse salivation, and ataxia in all 4 limbs of horse 1 and the other 2 horses that received the same dewormer. When admitted to the hospital, horse 1 had hyper-salivation, forelimb and hind limb ataxia, hypersensitiv-ity to touch and sound, and bilateral mydriasis. Physical examination revealed tachycardia (54 beats/min; reference range, 26 to 50 beats/min), but respiratory rate and rectal temperature were unremarkable. Oral mucous membranes were pale and slightly tacky. An IV catheter was placed in a jugular vein, and lactated Ringer’s solution (60 mL/kg/d [27.3 mL/lb/d] for a total of 10 L) was administered. The mare was treated with flunixin meglumine (1.1 mg/kg [0.5 mg/lb], IV), dexamethasone (0.2 mg/kg [0.09 mg/lb], IV), detomidine hydrochloride (0.022 mg/kg [0.01 mg/lb], IV), and diazepam (0.022 mg/kg, IV). Clinical signs continued to progress in severity over the next 5 hours, and the mare began to head press, tremble, and have diffuse muscle fasciculations throughout the shoulder and gluteal regions. It eventually became recumbent and unable to rise. The mare appeared blind and had signs of extreme agitation such that it was unsafe to approach and treat. A decision was made to euthanize the mare on the basis of progressive neurologic deterioration and safety concerns for those providing veterinary care.

A necropsy was performed at the Texas Veterinary Medical Diagnostic Laboratory by a board-certified pathologist. Gross necropsy findings included congestion in the right lung lobe, liver, and spleen as well as watery ingesta in the gastrointestinal tract. Cerebrospinal fluid was clear. All findings were consistent with agonal changes, and a cause for the neurologic abnormalities was not apparent. Histologic examination of specimens of spleen, kidney, lung, liver, heart, cerebrum, cerebellum, brain stem, eye, trachea, stomach, and thyroid and adrenal glands was performed. Spleen, kidney, adrenal gland, lung, and liver tissues had evidence of widespread visceral congestion that was attributed to acute cardiovascular compromise (euthanasia), but no other remarkable lesions were detected.

ABBREVIATIONS

<table>
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<td>GABA</td>
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A fluorescent antibody test of brain tissue revealed no evidence of rabies. Results of cell-culture and egg-inoculation virus isolation tests to detect West Nile virus, equine herpesvirus, and eastern, western, and Venezuelan equine encephalitis viruses were also negative. Cecal and stomach contents were devoid of toxic plants or seeds. Hay, grain, and water samples provided by the owner did not contain any toxicants, as assessed via microscopic analysis. The hay was analyzed, and although judged to be of poor quality, it did not contain any toxic plants. Brain tissue was analyzed for ivermectin content by use of liquid chromatography–mass spectrometry; 131 ppb of ivermectin was detected. Evaluation of residual paste in the plastic administration tube revealed an ivermectin content of 1.59% and no evidence of organophosphate, carbamate, organochlorine insecticide, permethrin, or petroleum products.

The second of the 3 horses treated with the ivermectin paste, a 4-year-old 419-kg (922-lb) Quarter Horse gelding (horse 2), was admitted to the teaching hospital approximately 21 hours after administration of ivermectin. The gelding had acute signs of severe ataxia in all 4 limbs and a base-wide stance. It almost fell down several times during initial evaluation. Physical examination revealed a rectal temperature within reference limits, tachycardia (60 beats/min), and tachypnea (24 breaths/min; reference range, 8 to 15 breaths/min). Oral mucous membranes were pink and moist; capillary refill time was unremarkable. The gelding had signs of severe obtundation and was hypersensitive to direct contact and loud noises. The owner described large amounts of saliva coming from the gelding’s mouth shortly before admission to the hospital. The superior and inferior larynx refill time was unremarkable. The gelding had bilateral mydriasis, decreased menace reflexes, and the tongue had appropriate movement. Muscle tremors were visible in the shoulder and gluteal regions. Bilateral mydriasis was clearly evident as well as decreased direct and indirect pupillary light reflexes and absent menace reflexes. Urination and defecation were unremarkable.

Results of a CBC, blood glucose analysis, and ammonia assay were within reference limits. Blood lactate concentration was 27.9 mg/dL (reference range, 0.36 to 18.4 mg/dL). Serum biochemical analysis revealed changes consistent with mild dehydration, including high serum concentrations of creatinine (2.1 mg/dL; reference range, 1.1 to 2 mg/dL), albumin (3.3 g/dL; reference range, 2.3 to 3.1 g/dL), globulins (4.2 g/dL; reference range, 2.2 to 3.8 g/dL), and total bilirubin (4.3 mg/dL; reference range, 0 to 4.1 mg/dL).

An IV catheter was placed in a jugular vein, and lactated Ringer’s solution was administered. An initial bolus of 20 L was followed by a continuous rate infusion at 60 mL/kg/d. Intravenous fluid administration was maintained for 72 hours until the gelding could reliably drink. Flunixin meglumine (1.1 mg/kg, IV, q 12 h) was administered for 4 days. Clinical signs progressed in severity for 36 hours after administration of ivermectin, and the degree of hypersensitivity and ataxia became more pronounced. Severe mydriasis, decreased menace reflexes, and hanging of the head. The edema was alleviated by use of cross ties to elevate the head. Approximately 15 hours after admission, the gelding appeared more stable on its feet, was increasingly aware of surroundings, and was able to prehend small amounts of hay. Bilateral mydriasis was evident for 2 days after admission, and slow menace and pupillary light reflexes remained for 3 days after admission. A CBC performed 48 hours after admission to the hospital revealed a low WBC count (2.3 X 10^3 cells/µL; reference range, 5.4 X 10^3 cells/µL to 14.3 X 10^3 cells/µL).

Nine days after the ivermectin was administered, the gelding was discharged from the hospital. At that time, all clinical signs resolved with the exception of mild proprioceptive deficits in both hind limbs. When a follow-up telephone interview was conducted 6 months later, the owner reported that the gelding was clinically normal.

The third of the 3 horses, a 13-year-old 491-kg (1,080-lb) Quarter Horse gelding (horse 3), was admitted to the teaching hospital at the same time as horse 2. Physical examination findings were similar to those of horse 2 with the exception of respiratory rate, which was unremarkable. The gelding was responsive to surrounding activity, but was quiet and had signs of depression. Bilateral mydriasis, decreased menace reflexes, and decreased direct and indirect pupillary light reflexes were detected. Occasional twitching of the shoulder muscles and upward jerking of the head were observed, as was hypersensitivity to direct touch. The inferior lip was flaccid, and there were mild signs of ataxia in all 4 limbs. Proprioceptive deficits and limb weakness were apparent in forelimbs and hind limbs. Results of a CBC, serum biochemical analysis, blood lactate assay, and urinalysis were within reference limits. Results of a CBC performed 48 hours after admission were also unremarkable. The gelding was treated similarly as horse 2. The mild clinical signs persisted for 24 hours and then steadily improved. Within 48 hours after admission to the hospital, ocular reflexes were unremarkable and the mydriasis had resolved. The gelding appeared clinically normal 72 hours after admission to the hospital and 93 hours after receiving the ivermectin paste. When the owner was contacted 6 months later, the gelding was reportedly clinically normal.

**Discussion**

Ivermectin is a semisynthetic lactone in the avermectin family that has broad antiparasitic activity. Since the introduction of ivermectin to the United States in 1983, it has become a commonly used product for the treatment of nematode and arthropod parasites. Toxic concentrations of ivermectin have been reported for several animal species, including dogs, cats, pigs, cattle, horses, cheloniids, and frogs. Ivermectin toxicity is an uncommonly reported condition in equids, and to date, all reports have involved young equids that received an overdose of the drug. To the authors’ knowledge, this is the first detailed report of ivermectin toxicity in adult horses after administration of the recommended dosage of anthelmintic.

Ivermectin is well absorbed after oral, parenteral, or topical administration because of its high solubility in lipids. The drug was initially sold for IM admin-
istration in horses; however, injection-site reactions and associated clostridial infections were undesirable sequelae.2,6 Mydriasis (at 3.0 and 6.0 mg/kg [1.4 and 2.7 mg/lb]) and a toxic shock syndrome (at 12.0 mg/kg [5.5 mg/lb]) in which horses became depressed, ataxic, and recumbent are other reported adverse effects of IM administration of ivermectin in horses.8,9

The commercially available 1.87% ivermectin paste is generally considered safe and is administered orally at a dose of 0.2 mg/kg. It is common practice for owners to administer a complete tube of ivermectin paste to an adult full-sized horse. In the 3 horses of the present report, the actual dosage of ivermectin received was 0.27 mg/kg (0.12 mg/lb), 0.29 mg/kg (0.13 mg/lb), and 0.24 mg/kg (0.11 mg/lb), respectively. Evaluation of the actual paste used in these 3 horses revealed a concentration of 1.59% ivermectin, which was slightly less than the 1.87% claimed by the manufacturer. Studies10,11 in horses that received oral ivermectin paste at 2.0 mg/kg (0.9 mg/lb) for 2 consecutive days resulted in 5 of 11 horses developing impaired vision, ataxia, and depression. In another report,8 9 times the recommended dose was administered orally to 12 horses every 3 weeks, and 1 horse developed mild signs of depression, decreased menace reflexes, and slow pupillary light reflexes.

Administering ivermectin orally results in a high maximum plasma concentration faster than with parenteral formulations, and plasma concentrations of ivermectin are detectable for 20 days.8 Ivermectin is only slightly metabolized by the liver; most is excreted in the bile and eliminated from the body in feces.8,12,13 Studies12,13 have revealed that 90% of the drug is excreted in feces 4 days after treatment but is detectable in fecal material for 40 days. The closely related drug moxidectin, also commonly used in equine parasite control products, is metabolized similarly but is excreted slower than ivermectin and persists in plasma longer.12,14 These properties may have important implications because toxicity associated with moxidectin could result in a longer recovery than ivermectin.

The mechanism of action of ivermectin involves potentiating the release of the inhibitory neurotransmitter GABA, causing an influx of chloride ions and hyperpolarization of neuronal membranes.2,3 This sequence of events inhibits neuromuscular transmission and leads to flaccid paralysis of invertebrates, in which GABA receptors are located in the peripheral nervous system.2 In mammals, GABA receptors are located only in the CNS and an intact blood-brain barrier protects from the neurologic effects of ivermectin.1,3

Clinical signs following an ivermectin overdose are variable within and among species of animals and may include mydriasis, ataxia, stupor, tremors, depression, coma, drooling, emesis, labored breathing, vision impairment, lethargy, and recumbency.2,3 In a previous study,11 horses received an overdose of ivermectin to establish safe doses of the drug, and signs of toxicosis included inferior lip droop, depression, ataxia, mydriasis, depressed respiration, and recumbency. In another study,8 a mule foal with bilateral blindness and absent menace and pupillary light reflexes had an unremarkable electroretinogram, indicating the blindness was the result of cortical depression.

Several reports15–18 exist of ivermectin toxicosis in dogs, some of which include dogs that recovered with supportive treatment. Although some of the affected dogs received an overdose of ivermectin, there is also a breed sensitivity to the drug.1,16,19 For example, Collies have a multidrug-resistance gene (mdr1) that encodes for P-glycoprotein, which is an integral part of the blood-brain barrier that functions to keep ivermectin from entering the CNS.1 Dogs possessing a deletion mutation of the mdr1 gene are unable to synthesize P-glycoprotein appropriately and have a high sensitivity to ivermectin.7 Case reports20,21 also exist of dogs treated for moxidectin toxicosis. Two case reports22,23 of ivermectin toxicosis involved 3 kittens and an adult cat, in which all of the kittens died despite treatment. There are also 2 studies24,25 of avermectin toxicosis in cattle in which clinical signs of incoordination, muscle fasciculations, drooling, apparent blindness, ataxia, and loss of menace reflexes were detected 20 to 48 hours after administration.

In equids, there is 1 report3 of a neonatal foal to which 2.1 mg/kg (1.0 mg/lb) of ivermectin paste was administered orally and which, within a few hours, became ataxic and began head pressing and walking into objects. Supportive care was implemented, and approximately 75 hours after administration, the foal had signs of neurologic improvement and appeared clinically normal after 5 days.7 Another horse had neurologic signs for 3 days after IV administration of parenteral ivermectin.3 Ivermectin toxicosis in a zebra foal and miniature mule foal has been reported, both of which developed ataxia and blindness after receiving oral paste.4,5 Foals that accidentally received overdoses (5 to 10 times the recommended dose) of orally administered moxidectin paste developed clinical signs similar to those associated with ivermectin toxicosis.26,27 The American Society for the Prevention of Cruelty to Animals Animal Poison Control Center identified 9 horses with a moxidectin overdose in 2 years, with only 5 horses having clinical signs 6 to 18 hours after drug administration.28 In affected horses, signs lasted for 36 to 168 hours. One was an adult horse, and the rest were foals < 4 months of age.

Diagnosis of ivermectin toxicosis in most animal species is made on the basis of history of exposure, clinical signs, and response to treatment.17 In the 3 horses of the present report, the diagnosis was presumptively made on the basis of an ivermectin concentration of 131 ppb in the brain tissue of horse 1, which was similar to brain concentrations in dogs with fatal ivermectin toxicosis.7,29 Serum or plasma concentrations of ivermectin are not diagnostically helpful because they only confirm that the affected animals were treated with ivermectin.18 Ivermectin concentration in brain tissue is more informative than plasma concentration, and the brain tissue concentration should be negligible in mammals with an intact blood-brain barrier. In a herd of Murray Gray cattle, cattle with ivermectin toxicosis had an avermectin concentration of 36 µg/kg (25.3 µg/lb) in their brain tissue, compared with 4 µg/kg (1.8 µg/lb) in unaffected cattle.23,24 In dogs, reported ivermectin brain concentrations were 52 and 134 ppb in 2 Collies that died of toxicosis.29 Physohystamine is an anticholin-
estrate agent that can cause a transient improvement of clinical signs in dogs with ivermectin toxicsis, and response to the drug in a comatose dog can be used to support a diagnosis of ivermectin toxicosis.17

A specific antidote for ivermectin toxicosis is unavailable, and treatment is usually supportive with nursing care, anti-inflammatory medications, and IV administration of fluids. Corticosteroids are commonly used in the treatment of small animal intoxications; however, in 2 of the horses in the present report (horses 2 and 3), we did not administer corticosteroids because we believed the clinical signs were receptor mediated and not associated with inflammation.15,16,22 Intravenous administration of fluids may be of limited benefit because ivermectin is primarily eliminated in feces, not urine, and diuresis does not increase the excretion of the drug or its metabolites.17 Animals that are unable to eat or drink because of cortical depression or dysphagia may require maintenance IV fluid administration as part of supportive treatment.

Picrotoxin is recommended as a reversal agent for ivermectin toxicosis in dogs, and it functions as a GABA-receptor antagonist by blocking the chloride ion channels.17,18 Neuronal excitability caused by picrotoxin administration may lead to seizures; therefore, the agent has a narrow margin of safety.3 The effects of picrotoxin were evaluated in a group of calves with experimentally induced ivermectin toxicosis, and no discernible beneficial effects were detected.24 Treatment with physostigmine may hasten the recovery period in comatose dogs, but there are important concerns about adverse effects and potential toxicity of the drug.10 In a case report,23 neostigmine was used to treat 3 cats with ivermectin toxicosis, 1 of which survived. There is also a report2 of a foal with moxidectin toxicosis that was treated with sarmazenil to act as a competitive GABA-receptor antagonist, but it is unknown whether the drug played a role in the successful recovery.

In the 3 horses of the present report, the manner by which the ivermectin was able to reach the CNS is unknown, but it is suspected that ivermectin crossed an impaired blood-brain barrier, resulting in a variable magnitude of clinical signs. Etiologies for ivermectin toxicosis in other species include genetic mutations leading to a higher unbound plasma ivermectin concentration and ivermectin-specific transport mechanisms,17,23 overdosage,4,13 and disruption of the blood-brain barrier attributable to interaction with other drugs, systemic disease, or consumption of toxic plants.10 An immature blood-brain barrier such as that in neonates and foals may be more permeable to ivermectin than a mature blood-brain barrier.23,26 It is also possible that the blood-brain barrier is unable to deny entry to extremely high doses of ivermectin in any species at any age.5,16

The horses in the present report were not closely related, did not receive an overdose of ivermectin, and were not previously ill or receiving any additional medications. The same brand and box of ivermectin paste had previously been administered to the same 3 horses without resulting in clinical abnormalities. The exact cause of ivermectin toxicosis in the 3 horses is unknown. One possible cause is ingestion of a toxic plant that resulted in impairment of the blood-brain barrier. There are anecdotal reports of other adult horses that developed clinical signs of ivermectin toxicosis when treated with the appropriate dosage of ivermectin. In February 2006, 4 horses died of an unknown cause after deworming with a paste formulation of ivermectin and subsequent development of neurologic signs.31 In 1989, 8 of 14 horses dewormed with ivermectin developed clinical signs similar to the 3 horses in the present report.30 In that situation, the only difference in management between the 8 affected horses and the 6 unaffected horses was diet; the affected animals consumed hay containing silverleaf nightshade (Solium elegans).30 Two of the 8 horses died, and brain tissue concentrations of ivermectin in those horses were 115 and 672 ppb. The investigators of that study30 concluded that ingestion of silverleaf nightshade may disrupt the blood-brain barrier or promote absorption of ivermectin into the brain.

Silverleaf nightshade is an upright, prickly perennial that grows in large aggregates throughout the southwestern United States and Mexico. It is occasionally found in the Midwest and Pacific Northwest regions of the United States. The plant contains a toxic agent (glycoalkaloid solanine) that can yield gastrointestinal and CNS abnormalities when ingested.30 The ripe berries are more toxic than the leaves of the plant, and typically, animals will not consume the plant unless alternatives are unavailable. Although not confirmed in the 3 horses of the present report, it is possible that the horses may have ingested silverleaf nightshade, contributing to their illness. The hay these horses consumed was evaluated, and although it was of poor quality, no evidence of silverleaf nightshade was detected. The strict stall confinement of the horses prevented them from access to silverleaf nightshade in a pasture, leaving the only possible route of exposure as a hay source. The amount of consumed silverleaf nightshade needed to interact with ivermectin is unknown, as is the duration of exposure to the plant. Additional studies are needed to evaluate whether ingested toxic plants and ivermectin interact in horses, leading to neurologic signs and possible death.

References

In anesthetized red-tailed hawks, positioning in sternal recumbency resulted in the greatest lung and air-sac volumes and lowest lung density, compared with right lateral and dorsal recumbency. Additional studies are necessary to determine the physiologic effects of body position on the avian respiratory system. (Am J Vet Res 2009;70:1155–1160)

### Objective
To determine the effects of body position on lung and air-sac volumes in anesthetized and spontaneously breathing red-tailed hawks (*Buteo Jamaicensis*) as measured via computed tomography.

### Animals
6 adult red-tailed hawks (sex unknown).

### Procedures
A crossover study design was used for quantitative estimation of lung and air-sac volumes in anesthetized hawks in 3 body positions: dorsal, right lateral, and sternal recumbency. Lung volume, lung density, and air-sac volume were calculated from helical computed tomographic (CT) images by use of software designed for volumetric analysis of CT data. Effects of body position were compared by use of repeated-measures ANOVA and a paired Student t-test.

### Results
Results for all pairs of body positions were significantly different from each other. Mean ± SD lung density was lowest when hawks were in sternal recumbency (−677 ± 23 CT units), followed by right lateral (−647 ± 23 CT units) and dorsal (−630 ± 19 CT units) recumbency. Mean lung volume was largest in sternal recumbency (28.6 ± 1.5 mL) followed by right lateral (27.6 ± 1.7 mL) and dorsal (27.0 ± 1.5 mL) recumbency. Mean partial air-sac volume was largest in sternal recumbency (27.0 ± 19.3 mL) followed by right lateral (21.9 ± 16.1 mL) and dorsal (19.3 ± 16.5 mL) recumbency.

### Conclusions and Clinical Relevance
In anesthetized red-tailed hawks, positioning in sternal recumbency resulted in the greatest lung and air-sac volumes and lowest lung density, compared with positioning in right lateral and dorsal recumbency. Additional studies are necessary to determine the physiologic effects of body position on the avian respiratory system.