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# Concurrent Ivermectin and *Solanum* spp. Toxicosis in a Herd of Horses

T.E. Norman, M.K. Chaffin, P.L. Norton, M.C. Coleman, W.B. Stoughton, and T. Mays

**Background:** Representatives from a herd of horses with acute onset of neurologic signs after administration of ivermectin presented for evaluation and treatment.

**Objectives:** Describe clinical signs of horses intoxicated by ingestion of *Solanum* sp. and administered ivermectin.

**Animals:** Six of 11 affected unrelated horses presented for evaluation and treatment. The remaining 5 affected horses were treated at the farm. Four additional horses, housed separately, were unaffected.

**Methods:** Case series is presented. Serum ivermectin concentrations were evaluated in the 6 hospitalized horses. The remnants of the tubes of ivermectin paste were analyzed for ivermectin concentration. The hay fed to the affected horses was analyzed for the presence of toxic plants.

**Results:** Serum ivermectin concentrations were higher than expected, given the dosage of ivermectin administered. The ivermectin concentration remaining in the administration tubes did not exceed specifications. The hay was heavily contaminated by 2 *Solanum* species. All horses returned to normal neurologic function with supportive care.

**Conclusions and Clinical Importance:** Horses might exhibit signs of ivermectin toxicity after appropriate dosing of the drug if they concurrently consume toxic plants of the *Solanum* family.

**Key words:** Fecal retention; Neurologic disease; Nightshade; Obtundation; P-glycoprotein.

Approximately 18 hours after administration of ivermectin paste,[a] 11 adult horses developed acute onset of neurologic signs consistent with ivermectin toxicosis.[1–7] The horses were housed together in a pen, and were fed separately from 4 unaffected horses on the farm that were also administered the ivermectin product. Because of the high margin of safety previously reported for ivermectin,[8] an investigation was undertaken to determine the cause of the neurologic signs.

## Materials and Methods

The 6 horses admitted to the Large Animal Clinic of Texas A&M University's College of Veterinary Medicine and Biomedical Science were evaluated to assess neurologic and other clinical signs of illness, as well as historical information pertinent to their present illness. Complete blood count and serum ammonia concentration determination were performed on 3 of the horses, and serum biochemical analysis was evaluated in all horses.

The ivermectin was all of 1 manufacturing lot, had been purchased at the local feed store, and was within date. The used tubes of ivermectin paste were submitted to the Texas Veterinary Medical Diagnostic Laboratory to determine ivermectin concentration in the paste using liquid chromatography, Serum samples from each horse were submitted to the California Animal Health and Food Safety Laboratory System to determine serum ivermectin concentrations using liquid chromatography-mass spectrometry. Samples of the round-baled Burmudagrass Coastal hay fed to the 11 affected horses were submitted to the Texas Veterinary Medical Diagnostic Laboratory for gross and microscopic analysis for toxic plants.

*From the Department of Large Animal Clinical Sciences, Texas A&M University College of Veterinary Medicine and Biomedical Sciences, College Station, TX (Norman, Chaffin, Norton, Coleman, Stoughton); and the Texas Veterinary Medical Diagnostic Laboratory, College Station, TX (Mays).*

*Corresponding author: Dr T.E. Norman, Mail Stop 4474 TAMU, College Station, TX 77843; e-mail: tnorman@cvm.tamu.edu*

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## Results

Horses ranged in age from 3 to 7 years old, and represented the Quarter Horse and American Paint breeds. The horses resided on a ranch in central Texas, and the intoxication occurred in early June. None of the horses were related to any other, and all were housed together in a pen with access to forage limited to a round bale of poor quality hay; no grass was in the pen because of severe drought conditions. All 6 horses were dull to obtunded and showed varying degrees of ataxia (from Grade 2/5 to Grade 4/5). The 4 most severely affected horses stood with a wide-based stance with the head in a dependent position. Facial nerve dysfunction was seen in all horses, resulting in labial flaccidity, ptosis, and weak to absent tongue tone. Mydriasis was observed in 3 horses, and delayed PLR was observed in 1. Menace was absent in 3 horses. Several of the horses would periodically become agitated, despite overall obtundation. Muscle fasciculations and head tremors were observed in 2 horses, and head pressing behavior was exhibited by 1 horse, which remained recumbent for most of the first 24 hours of hospitalization. All horses were hyperesthetic to touch, and all had normal tail and anal tone.

Other clinical signs observed in the horses included mild pyrexia (3 horses, mean = 102.0°F [101.8–102.3°F]), gastrointestinal ileus (refluent fluid was obtained from 2 horses), fecal retention requiring manual evacuation (4 horses), and urinary retention with overflow incontinence (3 horses). Four of the horses developed head and facial subcutaneous edema. Improvement in clinical signs was observed in 12–36 hours of presentation in all horses. All of the horses returned to normal neurologic

**Table 1.** Mean values and range for results of serum biochemical analysis and serum ammonia concentration results for representatives of a herd of horses showing acute onset neurologic signs after routine deworming with ivermectin.

| Analate | Reference Interval | Mean | Range | Number of Horses with Abnormal Values |
|---|---|---|---|---|
| Lactic acid[a] | 4.5–18.4 mg/dL | 28.4 | 8.3–92.9 | 3/6 |
| Glucose[a] | 58–134 mg/dL | 184 | 100–353 | 3/6 |
| Blood urea nitrogen | 7–28 mg/dL | 17.8 | 15–22 | 0/6 |
| Creatinine[a] | 1.1–2 mg/dL | 2.4 | 1.85–3.12 | 5/6 |
| Magnesium | 1.35–2.15 mg/dL | 1.5 | 1.1–1.9 | 0/6 |
| Calcium[a] | 11–13 mg/dL | 10.7 | 8.8–11.4 | 2/6 |
| Phosphorus | 1.7–3.9 mg/dL | 10.98 | 1.8–3.7 | 0/6 |
| Total protein[a] | 5.3–7.3 g/dL | 7.2 | 6.4–8 | 1/6 |
| Albumin[a] | 2.3–3.1 g/dL | 3.01 | 2.8–3.4 | 1/6 |
| Globulin[a] | 2.2–3.8 g/dL | 4.15 | 3.6–4.7 | 5/6 |
| Aspartate aminotransferase[a] | 134 – 643 U/L | 454 | 323–766 | 1/6 |
| Creatine kinase[a] | 73–450 U/L | 3319 | 173–>16000 | 3/6 |
| Alkaline phosphatase | 128–512 U/L | 189 | 145–251 | 0/6 |
| Gamma gluamyltransferase | 0–53 U/L | 20 | 15–27 | 0/6 |
| Total bilirubin[a] | 0–4.1 mg/dL | 4 | 3.2–4.9 | 2/6 |
| Sodium[a] | 132–141 mmol/L | 130 | 125–136 | 3/6 |
| Potassium[a] | 3.0–4.2 mmol/L | 3.9 | 3.0–5 | 2/6 |
| Chloride[a] | 98–105 mmol/L | 95 | 84–100 | 2/6 |
| Enzymatic carbon dioxide | 24–31 mmol/L | 28 | 25–31 | 0/6 |
| Anion gap (calculated) | 9–15 mmol/L | 11 | 9.0–14 | 0/6 |
| Ammonia | 0–50 μg/dL | 34.4 | 26.3–39 | 0/6 |

[a]Indicates analytes for which at least 1 horse was out of reference intervals.

function with supportive care within 4 days of hospitalization.

The results for serum biochemical analysis and serum ammonia concentrations are presented in Table 1. Other than mild leukocytosis in 1 horse, no abnormalities were revealed by CBC.

Evaluation of residual paste in the administration tubes from all 15 administered doses revealed an ivermectin content of 1.2%. Serum ivermectin concentrations in the 6 hospitalized horses ranged from 39 to 110 ng/mL (mean = 66 ng/mL). Gross and microscopic evaluation of the hay consumed by the 11 affected horses revealed very poor quality hay containing large amounts of both Silverleaf nightshade (*Solanum eleagnifolium*) and Western horse nettle (*S. dimidiatum*).

## Discussion

Ivermectin is a macrocyclic lactone in the avermectin family with a broad spectrum of activity against both endo- and ectoparasites. It is considered to have a wide margin of safety, with clinical signs of toxicosis in horses being elicited at no less than 10 times the recommended therapeutic dose.[8] Despite this wide margin of safety, there have been a number of reports of ivermectin toxicosis in equids,[2–7] with most reports in young horses that were inadvertently overdosed.[3–7] Reported toxic effects of ivermectin in equids include depression, reduced menace response, mydriasis, impaired vision, labial flaccidity, ataxia, and recumbency.[1–8] Ivermectin toxicity has also been reported in other species, including dogs, cats, pigs, cattle, chelonians, and frogs.[1,8]

The commercially available 1.87% ivermectin paste is administered PO at a dose of 0.2 mg/kg. Enteral administration of ivermectin to equids results in bioavailabilty of 36.5% of the administered dosage of ivermectin.[9] Regardless of the route of administration, ivermectin is eliminated mostly in the feces, with less than 2% of ivermectin eliminated in the urine.[9] Elimination of circulating drug is achieved through excretion in the bile, which is facilitated by P-glycoprotein in the biliary canaliculi. Excretion of ivermectin is prolonged with anorexia or reduced feed intake, presumably because of slowed gastrointestinal transit and reduced flow of bile.[9,10]

Plants of the *Solanum* (nightshade) species are found throughout North America, and their toxicity varies by species, climate, soil type, and season.[10] All species readily grow in pastures, and may become hay adulterants. *Solanum eleagnifolium* (Silverleaf nightshade) and *S. dimidiatum* (Western horse nettle) are among those more readily consumed by horses in hay and at pasture. The nightshade toxins include a mixture of alkaloids, steroidal glycoalkaloids, and cholinesterase inhibitors. Solanine is a glycoalkaloid common to all *Solanum* spp. that is poorly absorbed by the gastrointestinal tract, and acts as a local irritant to in-contact mucosal surfaces, causing abdominal pain, anorexia, and salivation.[10–12] Necropsy findings of affected animals are consistent with gastrointestinal irritation and hemorrhage.[11] The steroid alkamine is more readily absorbed than the intact glycoalkaloids, and causes central nervous system signs, including apathy, drowsiness, salivation, dyspnea, trembling, weakness, prostration, coma, and mydriasis.[11,12]

*Solanum eleagnifolium* is an herbaceous perennial with white-haired leaves and short, stiff spines on the leaves and stems. It has blue to violet flowers, and produces yellow berries. It grows prolifically throughout the southwestern United States, including Texas.[8] Clinical signs in horses after ingestion include abdominal discomfort, diarrhea, trembling, progressive muscular weakness, dyspnea, ataxia, obtunded mentation, and coma.[13] Hamsters gavaged with a preparation of *S. eleagnifolium* suffered a 75% death rate and had histologic evidence of gastric and small intestinal mucosal necrosis.[14]

*Solanum dimidiatum* is an herbaceous perennial with small prickles along the stems and midribs of the leaves. Flowers are purple and produce pale yellow berries that ripen in early autumn.[15] It thrives in disturbed ground and overgrazed pasture, and is found in the southern Midwest, including Texas.[14] Its toxic effects have best been described in cattle, in which it has been reported to cause diarrhea, abdominal pain, weight loss, and dehydration acutely, and cerebellar dysfunction with chronic ingestion.[14,15]

The horses in this report were administered a commercially available ivermectin product at appropriate dosages less than 24 hours before developing neurological signs consistent with those described in previous accounts of equid ivermectin toxicosis.[2–7] The horses were also kept confined overnight in a pen where access to forage was limited to poor quality hay containing both silver leaf nightshade and western horse nettle. Some of the clinical and clinicopathologic findings in the horses, including muscular weakness, muscle tremors, tachycardia, central nervous system depression, gastrointestinal dysfunction, increased muscle enzymes, and decreased serum calcium are consistent with the toxic effects of the glycosidic steroidal alkaloids found in *Solanum* spp.[10–16] Fever and electrolyte abnormalities in several horses might have been a reflection of gastrointestinal irritation, which is a well described effect of solanine.[12–14,16] The urinary and fecal retention observed in several of the horses has not been described in previous reports of either ivermectin or *Solanum* spp. toxicosis, and the mechanism of these clinical abnormalities remains unknown.

The paste that remained in the tubes after administration to the affected horses contained 1.2% ivermectin, which was less than the label claim of 1.87%. Only a very small volume of paste remained in the tubes, so the actual concentrations may have been slightly higher or lower than what was reported. Despite the fact that the horses did not receive an excessive dosage of ivermectin, their serum concentrations of ivermectin were higher than anticipated, given published pharmacokinetic curves of PO-administered ivermectin.[9,17] Given the time that had elapsed from the administration of ivermectin to the time of blood collection, the expected serum concentration of ivermectin given a standard dose (0.2 mg/kg PO) would be in the 18–30 ng/mL[17] range. In the 6 horses described in this report, concentrations ranged from 39 to 110 ng/mL, which are higher than the expected serum concentrations.

In the majority of reports of equid ivermectin toxicosis, the animals were given an inappropriately high dose of the drug, resulting in high serum levels that presumably overwhelmed the blood-brain barrier, resulting in high central nervous system concentrations.[3,4,6,7] In the 6 horses described here, the dose of ivermectin was not excessive, yet the serum levels were increased above the expected concentrations. This finding suggests that there was either increased absorption, decreased excretion, or both of ivermectin from the gastrointestinal tracts of these horses. *Solanum* toxins are known gastrointestinal irritants[10–12,16] and might have caused irritation of the intestinal mucosa, resulting in enhanced absorption of ivermectin.

The horses were dysphagic and anorectic, resulting in reduced feed intake, and 5 had evidence of abnormal gastrointestinal motility (2 with nasogastric reflux, 4 with fecal retention; 1 with both). It is therefore possible that ivermectin elimination was reduced, which would further increase serum concentrations of ivermectin. It might have been useful to quantitate this elimination through fecal ivermectin analysis, but this line of investigation was not pursued. Given that the normal oral bioavailability of ivermectin paste is 36.5%,[9] however, increasing the bioavailability of the product to 100% would achieve levels only approximately 3 times the normal dose, which would be insufficient to cause neurological signs.[9] Therefore, it is likely that *Solanum* toxins also resulted in dysfunction of the blood-brain barrier, allowing high concentrations of ivermectin to enter and accumulate in the central nervous system, resulting in the severe clinical signs reported above. One potential way we might have documented ivermectin in the central nervous system was testing ivermectin levels of the cerebrospinal fluid. This was discussed, but as cerebrospinal levels of ivermectin are unknown for horses, the interpretation of this information would have been difficult.

There have been previous reports of adult horses developing neurologic signs consistent with ivermectin toxicosis after receiving an appropriate dose of the drug.[2,13] Because some of the horses reported had known concomitant exposure to *Solanum* spp., it was postulated that there might be an interaction between the substances that increased the horses' sensitivity to the neurologic effects of ivermectin.[13] Two studies have been performed in rabbits that demonstrated the ability to induce neurologic signs consistent with ivermectin toxicosis with a standard clinical dose of the drug by pretreating the animals with dried *S. eleagnifolium*.[13] In one of the studies, increased brain concentrations of ivermectin were also demonstrated,[13] suggesting disruption of the blood-brain barrier. Serum concentrations of ivermectin were not obtained in the rabbits, so it is unknown if absorption, elimination, or both of the drug were altered.

These experiments demonstrate that the consumption of *Solanum* spp. increases mammalian sensitivity

to the neurologic effects of ivermectin.[13] The authors speculated that the toxins from *S. eleagnifolium* might have interfered with the function of P-glycoprotein, allowing accumulation of ivermectin in the brain, similar to the reported genetic defect in the protein in herding dogs.[13] Interference with or competition for P-glycoprotein has also been postulated to be a mechanism of drug interaction promoting ivermectin toxicity in people.[18] Moreover, there is evidence that coadministration of ivermectin with the P-glycoprotein substrate loperimide both increased the elimination half-life of ivermectin, and decreased resistance of *Haemonchus contortus* to the administered ivermectin.[19] Nematode resistance to ivermectin has been associated with alterations in P-glycoprotein gene expression (the so-called multidrug resistance, or MDR gene), and ivermectin and moxidectin induce overexpression of P-glycoprotein in nematodes.[19] In vivo and in vitro studies have demonstrated that interference with P-glycoprotein in resistant nematodes increases their susceptibility to ivermectin.[19] Recently, it was shown that solamargine, a steroidal glycoalkaoid found in the Chinese herb *Solanum incanum*, downregulates the expression of P-glycoprotein in multidrug resistant cancer cells.[20] This supports the theory that other steroidal glycoalkaoids derived from plants of the *Solanum* spp. may also alter P-glycoprotein expression and function.

It yet remains unknown what, if any, effects the toxins of *S. eleagnifolium* and *S. dimidiatum* have on the P-glycoprotein transporter, but evidence with other compounds and in other species suggests that this would be a potential mechanism by which exposure to *Solanum* spp. could increase susceptibility to ivermectin neurotoxicity in horses. More work is needed to elucidate the interactions between *Solanum* spp. and ivermectin absorption, elimination, and disposition in the horse, and to determine the role of these plants in the toxicity of ivermectin in horses.

## Footnote

[a] Zimecterin, Merial Limited, Duluth, GA

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