Isoniazid (isonicotinic acid hydrazide) is a common, first-line antimycobacterial agent used to treat tuberculosis in humans and other animals. Although tuberculosis is rare in developed countries (only 9,421 cases of tuberculosis were reported in the United States in 2014), the use of isoniazid with its low margin of safety puts companion animals at risk of accidental ingestion. Human patients and dogs that accidentally ingest or are overdosed with isoniazid can develop acute life-threatening toxicosis.

Isoniazid isoniazid toxicosis in dogs: 137 cases (2004–2014)

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OBJECTIVE
To establish the minimum toxic dose of isoniazid in dogs, characterize the clinical signs and outcomes for dogs following isoniazid ingestion, and determine whether IV administration of pyridoxine to dogs with isoniazid toxicosis is protective against death.

DESIGN
Retrospective case series.

ANIMALS
137 dogs with isoniazid toxicosis.

PROCEDURES
The electronic database of the American Society for the Prevention of Cruelty to Animals Animal Poison Control Center was reviewed from January 2004 through December 2014 to identify dogs with isoniazid toxicosis. For each dog identified, information extracted from the medical record included signalment, estimated dose of isoniazid ingested, clinical signs, treatment, and outcome. Follow-up communication with pet owners or primary care veterinarians was performed when necessary to obtain missing information.

RESULTS
Clinical signs of isoniazid toxicosis were observed in 134 of 137 (98%) dogs and included seizures (n = 104), CNS signs without seizures (94), and gastrointestinal (41), cardiovascular (19), urogenital (4), and respiratory (1) abnormalities. Of the 87 dogs for which the outcome was available, 61 survived, 18 died, and 8 were euthanized. Probability of survival was positively associated with body weight and IV administration of pyridoxine and negatively associated with dose of isoniazid ingested and presence of seizures. Dogs that received pyridoxine IV were 29 times as likely to survive as dogs that did not receive pyridoxine IV.

CONCLUSIONS AND CLINICAL RELEVANCE
Results indicated rapid diagnosis of isoniazid toxicosis and prompt treatment of affected dogs with pyridoxine and other supportive care were imperative for achieving a successful outcome. (J Am Vet Med Assoc 2017;251:689–695)

Isoniazid is completely absorbed in the gastrointestinal tract following oral administration. It undergoes substantial first-pass metabolism, and peak plasma concentrations are achieved within 1 to 2 hours after administration. Isoniazid has poor protein binding (approx 10%) in plasma, has a small volume of distribution, and readily penetrates into the CNS and CSF. In humans, the elimination half-life of isoniazid is dependent on a patient’s ability to acetylate; the elimination half-life is 1 to 2 hours in fast acetylators and 2 to 5 hours in slow acetylators. Dogs are considered slow acetylators because of their inherent lack of NAT2. Thus, in dogs, the elimination half-life of isoniazid is 2 to 5 hours, and the lack of NAT2 increases the risk of isoniazid-induced neurologic and hepatic toxicosis. In humans patients, approximately 50% to 70% of isoniazid is excreted unchanged or as metabolites in urine within 24 hours after administration.

In both dogs and humans, clinical signs of isoniazid toxicosis are generally observed within 30 to 60 minutes after ingestion and are characterized by recurrent grand mal seizures subsequent to a decrease

ABBREVIATIONS
APCC Animal Poison Control Center
ASPCA American Society for the Prevention of Cruelty to Animals
CI Confidence interval
GABA γ-Aminobutyric acid
NAT2 N-acetyltransferase 2
P5P Pyridoxal-5-phosphate
in GABA (an inhibitory neurotransmitter) concentration and an increase in glutamic acid concentration in the CNS.\textsuperscript{6,14,15} High toxic doses of isoniazid are associated with what is known as the classic triad, which includes seizures that are refractory to conventional treatments, lactic acidosis, and coma. Patients with this classic triad of signs of isoniazid toxicosis can die without prompt diagnosis and proper treatment.\textsuperscript{8,9,14,15}

The veterinary literature contains reports of accidental\textsuperscript{6} and experimentally induced\textsuperscript{15,16} isoniazid toxicosis in dogs. In a report\textsuperscript{6} of 27 dogs with accidental isoniazid toxicosis, the amount of the drug ingested ranged from 22 to 270 mg/kg (10 to 123 mg/lb; mean ± SD, 109 ± 82 mg/kg [49.5 ± 37 mg/lb]). Clinical signs in those dogs developed within 30 minutes to 2 hours after isoniazid ingestion, with the most common sign reported being recurrent grand mal seizures followed by stupor.\textsuperscript{6} Among the dogs that developed seizures in that study,\textsuperscript{6} the lowest dose of isoniazid ingested was 37 mg/kg (17 mg/lb). In an experimental study,\textsuperscript{16} the lowest consistently lethal dose of isoniazid in dogs was 75 mg/kg (34 mg/lb), with the onset of seizures and death occurring approximately 1 to 2 hours after drug exposure. In another experimental study,\textsuperscript{15} IV administration of pyridoxine (vitamin B\textsubscript{6}) as an antidote to dogs with isoniazid toxicosis had a dose-dependent protective effect against seizures and death; dogs administered pyridoxine at a dose equivalent to the dose of isoniazid ingested (ie, 1:1 dose ratio of pyridoxine to isoniazid) survived.

Although isoniazid toxicosis has been described in dogs following accidental\textsuperscript{6} and experimental\textsuperscript{15,16} ingestion of the drug, little information is available regarding the minimum toxic dose of isoniazid in dogs, or the signalment, clinical signs, treatment, and outcome for a large number of dogs with accidental isoniazid toxicosis. The goals of the study reported here were to establish the minimum toxic dose of isoniazid in dogs, characterize the clinical signs and review outcomes for dogs following accidental ingestion of isoniazid, determine whether IV administration of pyridoxine to those dogs was protective against death, and describe various approaches used to manage dogs with isoniazid toxicosis in clinical settings.

**Materials and Methods**

**Case selection criteria**

The electronic database of the ASPCA APCC was searched to identify the records of dogs with isoniazid exposure between January 2004 and December 2014. That database contains a record of queries received by APCC personnel from both animal owners and veterinarians in the United States and Canada. Dogs were included in the study if isoniazid exposure was classified as observed or evidenced on the basis of a history of observed ingestion, missing medication, or physical evidence of tampering with medication bottles. Dogs were excluded from the study if there was evidence that other drugs in addition to isoniazid had been ingested, the medical record was incomplete, or there was a low likelihood of isoniazid exposure on the basis of information provided to and recorded by the APCC veterinary toxicologist or veterinarian.

**Medical records review**

For each dog evaluated, information extracted from the record included signalment, history, clinical signs, amount of isoniazid ingested, treatment, and outcome. The data for all dogs were recorded into a commercially available spreadsheet program.\textsuperscript{4} Clinical signs were individually analyzed and classified into the following categories: seizures, CNS signs without seizures (eg, depression, coma, ataxia, blindness, vocalization, tremors, miosis, mydriasis, and anisocoria), gastrointestinal (eg, vomiting, pylalism, and diarrhea), cardiovascular (eg, tachycardia, bradycardia, arrhythmias, and pallor), respiratory (eg, tachypnea, dyspnea, and pulmonary edema), and urogenital (eg, urinary incontinence and pigmenturia).

Investigators contacted and corresponded with pet owners and primary care veterinary staff via telephone or facsimile to obtain additional information such as more in-depth history, clarification of clinical signs, medical treatments administered, hospitalization data, and outcome. Dogs that recovered were classified as survivors, whereas those that died prior to or after hospitalization or that were euthanized while hospitalized were classified as nonsurvivors.

**Statistical analysis**

Descriptive statistics were generated for all demographic variables, clinical signs, isoniazid dose ingested, and outcome. Age was evaluated as both a continuous and categorical (young \([\leq 1\text{ year old}]\) or adult \([>1\text{ year old}])\) variable. Dogs that died or were euthanized were combined and analyzed together in the nonsurvivor category. The isoniazid dose ingested (reported in mg/kg) was estimated on the basis of the dog’s body weight, the number of isoniazid tablets ingested, and the concentration of isoniazid in those tablets. Treatment with pyridoxine was classified as yes or no regardless of the route (IV, PO, or rectal) of administration. The distribution of data for continuous variables such as age, weight, and isoniazid dose ingested was assessed for normality by use of the Shapiro-Wilk test, and all those variables were found to have nonparametric distributions. The Wilcoxon test was used to assess the respective relationships between each continuous variable and the presence of seizures (yes or no), whether the dog was treated with pyridoxine (yes or no), and outcome (survivor or nonsurvivor). The Bonferroni correction was used when multiple pairwise comparisons were indicated. The respective associations between each categorical variable and the presence of seizures and outcome were assessed by use of a Fisher exact (when the count within \(\geq 1\text{ cell was} < 5\)) or \(\chi^2\) test. Individual variables that were associated \((P < 0.25)\) with out-
come were individually entered into logistic regression models for presence of seizures or outcome. Logistic fit and inverse prediction were used to estimate the probability of seizures following ingestion of various isoniazid doses.

**Results**

**Dogs**

During the evaluation period, the APCC received queries regarding isoniazid ingestion for 172 dogs, of which 35 were excluded from the study because exposure to isoniazid was considered unlikely to cause the clinical signs reported, multiple drugs or compounds in addition to isoniazid were ingested, or the medical record was incomplete. Thus, 137 dogs were evaluated in the study.

The 137 dogs evaluated included 69 (50.4%) males and 60 (43.8%) females; the sex was not recorded in the record for 8 (5.8%) dogs. Age was recorded for 133 dogs, and the median age for those dogs was 1 year (range, 0.13 to 13 years). Body weight was recorded for 135 dogs, and the median body weight for those dogs was 11 kg (24.2 lb; range, 1.22 to 45 kg [2.7 to 99 lb]). Forty-four breeds were represented in the study population, with the most common being Labrador Retriever (n = 19 [13.9%]), Chihuahua (10 [7.3%]), German Shepherd Dog (7 [5.1%]), Beagle (6 [4.4%]), Boxer (6 [4.4%]), Maltese (6 [4.4%]), Miniature Dachshund (6 [4.4%]), Border Collie (5 [3.6%]), Golden Retriever (5 [3.7%]), and mixed breed (5 [3.6%]); all other breeds were represented by ≤ 4 dogs.

**Isoniazid dose ingested**

The amount of isoniazid ingested was recorded for 130 of the 137 dogs. The median amount of isoniazid ingested was 300 mg (range, 50 to 8,400 mg). The most frequently reported source of isoniazid ingested was 300-mg tablets, with dogs ingesting a mean of one 300-mg tablet (range, 0.5 to 30 tablets). The estimated median isoniazid dose ingested on the basis of body weight was 59.5 mg/kg (27.0 mg/lb; range, 2.0 to 1,061.9 mg/kg [0.91 to 482.7 mg/lb]). Of the 137 dogs, ingestion of isoniazid was observed in 28 (20.4%) and strongly suspected but not actually observed in the remaining 109 (79.6%).

**Clinical signs**

One hundred thirty-four of 137 (97.8%) dogs developed clinical signs of isoniazid toxicity. Clinical signs were not observed but were inferred or evidenced in the remaining 3 (2.2%) dogs; the estimated doses of isoniazid ingested by those 3 dogs were 2, 6.3, and 8.8 mg/kg (0.9, 2.9, and 4 mg/lb). The most commonly reported clinical sign was seizures. Of the 132 dogs for which the seizure status was known, 104 (78.8%) had seizures. The lowest estimated dose of isoniazid ingested by a dog that subsequently developed seizures was 19.8 mg/kg (9.0 mg/lb). Dogs that developed seizures had a lower median body weight (P = 0.021) and ingested a higher dose of isoniazid (P < 0.001) on a milligram-per-kilogram basis than dogs that did not develop seizures. Thirty-seven of the 104 (36%) dogs that developed seizures subsequent to isoniazid ingestion died or were euthanized (ie, were classified as nonsurvivors), whereas all 28 dogs that did not develop seizures were classified as survivors. Results of the logistic fit and inverse prediction model indicated that an isoniazid dose of 22.2 mg/kg (10.1 mg/lb; 95% CI, 1.6 to 32.3 mg/kg [0.73 to 14.7 mg/lb]) had a 50% probability of causing seizures and a dose of 48.6 mg/kg (22.1 mg/lb; 95% CI, 38.5 to 70.2 mg/kg [17.5 to 31.9 mg/lb]) had an 80% probability of causing seizures (Figure 1).

A total of 288 clinical signs were reported for the 134 dogs that developed clinical signs following isoniazid ingestion. The most common clinical sign category recorded was seizures (n = 104 [36%]) followed by CNS signs without seizures (94 [33%]), which included ataxia (33), altered mentation (17), tremors (12), blindness (8), vocalization (8), agitation (5), coma (4), aggression (3), anisocoria (3), and mydriasis (1). The next most commonly reported clinical sign category was gastrointestinal abnormalities (n = 41 [14%]), which included vomiting (24), ptyalism (15), and diarrhea (2). Other clinical signs recorded included hyperthermia (n = 33 [11%]), cardiovascular abnormalities (19 [7%]), urogenital abnormalities (4 [1%]), and aspiration pneumonia (1 [0.3%]). All dogs (n = 6) that developed blindness and survived regained their vision.

**Pyridoxine treatment and outcome**

Information regarding both pyridoxine treatment and outcome was available for 66 dogs, of which pyri-
Isoniazid was administered to 35. Pyridoxine was administered IV to 28 dogs, orally to 6 dogs, and rectally to 2 dogs (1 dog was administered pyridoxine by both the IV and rectal route). All dogs that were treated with pyridoxine had seizures, and pyridoxine administration was significantly ($P < 0.001$) associated with dogs being classified as survivors. The majority (33/35 [94%]) of dogs that developed seizures and received pyridoxine were classified as survivors. The 2 dogs with seizures that were treated with pyridoxine and classified as nonsurvivors were euthanized. One dog was euthanized after 4 days of pyridoxine treatment because it remained in a comatose state, and the other was euthanized for unknown reasons. Of the 31 dogs that did not receive pyridoxine, 26 (84%) had seizures and 5 (16%) did not. Of the 26 dogs that had seizures and were not treated with pyridoxine, 11 (42%) were classified as survivors and 15 (58%) were classified as nonsurvivors. All 5 dogs that did not have seizures and were not treated with pyridoxine were classified as survivors. Dogs that received pyridoxine IV were approximately 29 times (OR, 28.7; 95% CI, 6.5 to 207.8; $P < 0.001$) as likely to survive as dogs that were not treated with pyridoxine by the IV route.

Outcome was available for 87 of the 137 (63.5%) dogs. The majority (61/87 [70%]) of dogs were classified as survivors, and of the 26 (30%) dogs that were classified as nonsurvivors, 18 (69%) died and 8 (31%) were euthanized. The median body weight of dogs that were classified as survivors (14.6 kg [32.1 lb]; range, 1.8 to 37.6 kg [4.0 to 82.7 lb]) was significantly ($P = 0.006$) greater than that of dogs that were classified as nonsurvivors (4.5 kg [9.9 lb]; range, 1.2 to 45 kg [2.6 to 99 lb]). Survival was also significantly associated with the dose of isoniazid ingested ($P = 0.036$) and treatment with pyridoxine ($P < 0.001$). The median dose of isoniazid ingested by dogs that were classified as survivors (50.4 mg/kg [22.9 mg/lb]; range, 2.0 to 666.6 mg/kg [0.91 to 303.0 mg/lb]) was significantly less than that ingested by dogs classified as nonsurvivors (132.7 mg/kg [60.3 mg/lb]; range, 29.4 to 1,061.9 mg/kg [13.4 to 482.7 mg/lb]). The lowest dose of isoniazid ingested by a dog that subsequently died was 29.4 mg/kg. Among the dogs that were not treated with pyridoxine, the median dose of isoniazid ingested by dogs that were classified as survivors (19.8 mg/kg) was significantly ($P = 0.002$) less than that ingested by dogs that were classified as nonsurvivors (132.7 mg/kg). Additionally, among the dogs classified as survivors, the median dose of isoniazid ingested by dogs that were treated with pyridoxine (66.4 mg/kg [35.2 mg/lb]) was significantly ($P = 0.002$) greater than that of dogs that were not treated with pyridoxine. Age ($P = 0.55$) and sex ($P = 0.32$) were not significantly associated with outcome.

Discussion

The use of isoniazid for the treatment of human patients poses a risk for inadvertent exposure of dogs to the drug. For dogs that weigh < 10 kg (22 lb), ingestion of one 300-mg tablet of isoniazid will cause severe clinical signs and potentially death. Most dogs that were inadvertently exposed to isoniazid in the present study had clinical signs attributable to CNS hyperexcitability similar to those previously described for dogs and human patients with acute isoniazid toxicosis. Although body weight and the amount of isoniazid ingested were significantly associated with survival in the present study, those criteria should not be used as the sole predictors of outcome. In the present study, the development of seizures was a significant predictor of outcome; 36 of 104 (35%) dogs that developed seizures died or were euthanized, whereas all 28 dogs that did not develop seizures survived. Moreover, dogs that developed seizures and were treated with pyridoxine IV were 29 times as likely to survive as dogs that developed seizures and were not treated with pyridoxine. That finding supported the results of other studies in which IV administration of pyridoxine was an effective antidote for isoniazid toxicosis in clinically affected dogs and rats.

Isoniazid ingestion results in CNS hyperexcitability owing to a decrease in GABA concentrations subsequent to pyridoxine inhibition and enhanced elimination. Isoniazid affects pyridoxine metabolism. It binds with P5P, the active form of pyridoxine, to form isonicotinylhydrazide, which is readily excreted in the urine and leads to pyridoxine depletion. Isoniazid derivatives also inhibit pyridoxal phosphokinase, which is an important enzyme in the metabolism of pyridoxine to P5P. Pyridoxal-5-phosphate is an important cofactor of glutamic acid decarboxylase, which is responsible for the synthesis of GABA from glutamic acid.

Therefore, depletion of P5P, whether because of enhanced excretion or inhibited production, decreases GABA synthesis. Overall, the toxic mechanisms of isoniazid and its derivatives cause a decrease in GABA concentration and uninhibited CNS excitation, which can culminate in life-threatening seizures. In addition to causing CNS signs, isoniazid and its major metabolites also have a role in other clinical syndromes in both dogs and humans such as a decrease in lactate metabolism, mild self-limited hepatoxicosis, and rhabdomyolysis. Metabolic acidosis and hyperlactatemia are common sequelae of isoniazid toxicosis and are thought to be caused by both seizure activity and indirect inhibition of the conversion of lactate to pyruvate by the liver.

In the present study, seizures and death were reported in dogs that ingested isoniazid at estimated doses as low as 19.8 and 29.4 mg/kg, respectively. Given the severity of clinical signs, high likelihood of seizures, and poor prognosis associated with seizure-like signs, dogs with known or suspected isoniazid ingestion at doses ≥ 20 mg/kg (9.1 mg/lb) or that have substantial clinical signs of toxicosis should be immediately treated with pyridoxine, the antidote. Pyridoxine can be acquired from human hospitals or pharmacies. For dogs with isoniazid toxicosis, pyridoxine should be diluted to a 5% to 10% solution and administered IV over 30 to 60 minutes at a dose equal to the amount of isoniazid ingested on a gram-per-gram basis or, if the amount of isoniazid ingested is unknown, beginning at a dose of 70 mg/kg (32 mg/lb). In the present study, clinicians frequently reported that seizures in dogs with isoniazid toxicosis ceased immediately after initiation of

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IV administration of pyridoxine. Numerous human patients with isoniazid toxicosis have remained in a prolonged comatose state following pyridoxine administration, which was reversed by the administration of an additional 3 to 5 g of pyridoxine. Because the injectable formulation of pyridoxine may not be readily available to veterinarians, rectal administration of crushed pyridoxine tablets has been anecdotally reported to be of some benefit for the treatment of dogs with isoniazid toxicosis. However, pyridoxine is slowly absorbed by the rectal mucosa, and rectal administration should not be substituted for IV administration unless the IV formula cannot be obtained.

Pyridoxine has a wide margin of safety, but rare adverse effects, such as peripheral neuropathy, associated with excessive pyridoxine administration have been reported in humans, rats, and dogs. In dogs, oral administration of pyridoxine at a dose of 200 mg/kg/d (91 mg/lb/d) for 40 days has been associated with ataxia and muscle weakness. However, dogs with acute isoniazid toxicosis do not require long-term treatment with pyridoxine, and the risks of pyridoxine-induced adverse effects in such dogs are generally considered minimal.

In addition to pyridoxine, dogs with acute isoniazid toxicosis should undergo appropriate decontamination, supportive care, and monitoring. Decontamination via emesis should only be performed within 1 hour after isoniazid ingestion or for patients in which isoniazid ingestion is known or strongly suspected but that have not yet developed clinical signs of toxicosis. Emesis should not be performed in patients with clinical signs because of the risk for aspiration of gastric contents and possible induction of seizure activity. Gastric lavage with the patient anesthetized and its airway protected is another option for decontamination. Oral administration of activated charcoal with a cathartic reduces absorption of isoniazid in humans, rats, and rabbits if given within 1 hour after ingestion of the drug and might have a similar effect in dogs. Decontamination or oral administration of activated charcoal was performed for very few dogs evaluated in the present study because most of the dogs had impaired neurologic function and the risks associated with such treatment were considered too great. Supportive care may include fluid therapy, antiemetics (to prevent secondary aspiration pneumonia), thermoregulatory measures, and nursing care. Intravenous fluid therapy is imperative for dogs with clinical signs of isoniazid toxicosis because they are often hyperthermic, have CNS dysfunction which precludes oral fluid intake, and are hemodynamically unstable at the time of diagnosis and commonly develop metabolic acidosis and hyperlactatemia. The purpose of IV fluid therapy is to prevent dehydration, treat hypotension, enhance perfusion, and potentially facilitate urinary elimination of isoniazid. Fluid therapy should be tailored to each patient on the basis of hemodynamic variables such as blood pressure, lactate concentration, pulse quality, capillary refill time, and heart rate. Monitoring of critically ill patients with isoniazid toxicosis should include frequent assessment of blood pressure, ECG, and other cardiac, neurologic, and respiratory variables. Blood gas analysis should be performed as necessary to assess the patient’s acid-base status, oxygenation, and ventilatory function.

In dogs, a hallmark of isoniazid toxicosis is seizures that are refractory to traditional anticonvulsants. Isoniazid-induced seizures are difficult to control because most veterinary hospitals do not keep pyridoxine on hand, and affected patients may need to be administered a constant rate infusion of propofol or otherwise anesthetized to control seizures until pyridoxine can be obtained. Traditional anticonvulsants such as diazepam, midazolam, levetiracetam, and phenobarbital should be used in conjunction with pyridoxine because they synergistically improve GABA function in the CNS. Although those convulsants are readily available to veterinarians, they must be administered in conjunction with pyridoxine because they will not prevent or ameliorate isoniazid-induced seizures when administered alone. Pyridoxine is the antidote for isoniazid toxicosis and is necessary for the successful management and treatment of severely affected patients. Results of 1 study indicate IV administration of diazepam (1 mg/kg [0.45 mg/lb]) in combination with pyridoxine at an amount equal to that of isoniazid ingested provides synergistic protection against seizures and death, whereas administration of pyridoxine alone prevents death but does not eliminate seizures. In that study, IV administration of diazepam alone failed to prevent or stop isoniazid-induced seizures at all doses evaluated but did provide some protection against death at a dose of 6 mg/kg (2.7 mg/lb); however, that dose was associated with severe CNS depression (eg, respiratory depression and coma). Many dogs evaluated in the present study were administered a benzodiazepine followed by a barbiturate (typically phenobarbital) to control seizures with little success. When pyridoxine was not readily available, the use of propofol or isoflurane to induce and maintain anesthesia was anecdotally successful in reducing or resolving isoniazid-induced seizures in some dogs.

The ASPCA APC records indicated that many dogs with isoniazid toxicosis evaluated in the present study had abnormally high alanine aminotransferase and alkaline phosphatase activities indicative of hepatopathy, findings that were similar to those of other studies involving dogs and human patients with isoniazid toxicosis. It is believed that isoniazid induces oxidative stress, mitochondria dysfunction, and apoptosis, which result in hepatopathy. The hepatotoxicity of isoniazid for any species or individual is dependent on the activity of NAT2 and cytochrome P450 2EI, the 2 primary enzymes responsible for metabolizing the drug. Dogs inherently lack NAT2, which is responsible for the metabolism of isoniazid to acetyl isoniazid and the acetylation of toxic acetyl hydrazine to nontoxic diacetyl hydrazine. Glutathione depletion is believed to be involved in the development of oxidative stress, and administration of glutathione precursors such as N-acetylcysteine and other hepatoprotectants, such as...
S-adenosylmethionine, may be indicated for patients with severe hepatopathy. For most patients, isoniazid-induced hepatopathy is mild and self-limiting and typically resolves within 6 to 7 days after ingestion of the drug.39 Regardless, liver enzyme activities should be serially monitored in all patients with isoniazid toxicosis until they are within reference limits. For the dogs with abnormally increased activities of hepatic enzymes evaluated in the present study, no clinically relevant sequelae were reported, and some received supportive treatment with S-adenosylmethionine, the clinical benefit of which was unknown.

Some patients with isoniazid toxicosis may benefit from hemodialysis. Although hemodialysis has been used to successfully treat isoniazid toxicosis in human patients,30,31 to our knowledge, the use of hemodialysis for the treatment of isoniazid toxicosis in veterinary patients has not been described. However, routine use of hemodialysis for the treatment of patients with isoniazid toxicosis may not be necessary owing to the short half-life of the drug and the availability of an effective antidote (pyridoxine).

Patients with isoniazid toxicosis should also be monitored for rhabdomyolysis, a condition that, albeit infrequent, has been reported in both humans and dogs following isoniazid ingestion.17,19 A 6-month-old Rottweiler developed acute kidney injury subsequent to rhabdomyolysis after a prolonged period of isoniazid-induced seizures.17 The authors of that report17 postulated that the release of myoglobin subsequent to prolonged seizure activity resulted in acute renal tubular necrosis and injury. Seizure-induced rhabdomyolysis, although rare, can cause acute kidney injury and should be on the rule-out list for any patient that has a substantial increase in creatinine kinase activity and myoglobinuria following prolonged seizure activity.

We had only limited access to the medical records for most dogs evaluated in the present study. Therefore, it was not possible to determine why some dogs that ingested high doses of isoniazid survived without being treated with pyridoxine, whereas dogs that ingested lower doses of isoniazid did not survive regardless of whether they received pyridoxine. It is possible that the time between isoniazid ingestion and examination by a veterinarian or contact with the APCC differed among dogs. The duration from isoniazid ingestion to veterinary examination was not routinely recorded for most dogs and was not evaluated in the present study. Isoniazid ingestion was not observed for 109 of the 137 (79.6%) dogs evaluated in the present study, and it is likely that the onset of clinical signs of toxicosis was also unobserved in those dogs. The owners of many dogs evaluated in this study found their pet seizing; therefore, the duration of that seizure activity was unknown, and many dogs died before they could receive medical treatment. It seems safe to assume that the longer patients have clinical signs of isoniazid toxicosis, especially seizures, before treatment, the more likely they are to die regardless of the dose of the drug ingested or treatment administered.

Limitations of the present study included its retrospective nature, a small sample size, and the lack of complete medical records for all cases. Because of the retrospective nature of the study, information regarding diagnostic test results, treatments administered, and hospitalization data (eg, physiologic variables) was not uniformly available for all cases. The retrospective nature of the study also precluded implementation of a standardized treatment protocol for each case. Despite those limitations, results indicated that survival of patients with isoniazid toxicosis was positively associated with body weight and treatment with pyridoxine and negatively associated with the dose of isoniazid ingested and the presence of seizures. The findings of this study also supported the current recommendation to treat dogs with isoniazid toxicosis with a 5% to 10% solution of pyridoxine at a dose equivalent to the amount of isoniazid ingested on a gram-per-kilogram basis, IV, over 30 to 60 minutes.

Isoniazid is an antimycobacterial agent commonly used to treat tuberculosis in human patients and can cause acute toxicosis in dogs following inadvertent ingestion. Many veterinarians are unfamiliar with isoniazid; therefore, rapid diagnosis of toxicosis, consultation with the ASPCA APCC, and prompt treatment of affected dogs with pyridoxine and other necessary supportive care are imperative for achieving a successful outcome.

Acknowledgments

The authors declare that there were no conflicts of interest.

Footnotes

a. Microsoft Excel, Microsoft Corp, Redmond, Wash.

References

A technique of needle redirection at a single craniolateral site for injection of three compartments of the equine stifle joint

Meredith R. A. Herdrich et al

OBJECTIVE
To determine accuracy for a technique of needle redirection at a single craniolateral site for injection of 3 compartments of the equine stifle joint, describe the external needle position, and identify the location of the needle tip within each joint compartment.

SAMPLE
24 equine cadaver stifle joints.

PROCEDURES
Stifle joints were placed in a customized stand. After the needle was placed, external needle position was measured and recorded. Each joint compartment (medial and lateral compartments of the femorotibial joint and the femoropatellar joint) was injected with a solution containing iodinated contrast medium, water, and dye. Radiography, assessment of intra-articular location of the needle tip, and gross dissection were performed to determine success of entering each joint compartment. Student t tests and an ANOVA were used to compare mean values.

RESULTS
Overall accuracy was 19 of 24 (79.1%), and accuracy for individual joint compartments was at least 21 of 24 (87.5%). Mean depth of needle insertion to access each compartment of the stifle joint was 5.71 cm. Mean angle of insertion (relative to the long axis of the tibia) was 82.1°, 80.3°, and 18.5° for the medial compartment of the femorotibial joint, lateral compartment of the femorotibial joint, and femoropatellar joint, respectively. Student t tests and an ANOVA were used to compare mean values.

CONCLUSIONS AND CLINICAL RELEVANCE
Results supported that this was an accurate technique for successful injection of the 3 equine stifle joint compartments. (Am J Vet Res 2017;78:1077–1084)