

Isoniazid Toxicosis in Dogs

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YOU HAVE ASKED...

How concerned should we be when dogs get into isoniazid, an antimycobacterial medication used for tuberculosis?

THE EXPERTS SAY...

Over the past 10 years, the ASPCA Animal Poison Control Center has received more than 170 reports of isoniazid poisoning, with 98% of those calls involving dogs. Of these cases, 17 (10%) resulted in death.*

Isoniazid, commonly known as INH (isonicotinylhydrazine), is a prescription human antituberculosis medication and is also used in veterinary medicine to treat infection with certain *Mycobacterium* or *Actinomyces* spp strains. Isoniazid is available in injectable,

liquid, and tablet forms; it can also be found in combination with other medications (eg, rifampicin).¹ This antimycobacterial prodrug blocks synthesis of mycolic acid, which is necessary for mycobacterial cell walls. Isoniazid depletes the CNS of pyridoxine, a precursor necessary for the activity of the enzyme glutamic acid decarboxylase.² It also decreases levels of the inhibitory neurotransmitter gamma-aminobutyric acid within the brain.²

Isoniazid plasma levels peak about 1 to 2 hours postingestion. The drug diffuses into all body fluids and cells and has low lipid solubility.¹ Isoniazid is metabolized in the liver (acetylation and dehydrazination) and excreted through the urine. The half-life is thought to be 4 hours but can be prolonged in an overdose situation.³

As little as 1 300-mg tablet of isoniazid can result in severe toxicosis in a 10-lb dog.

*Personal communication, 2015, ASPCA Animal Poison Control Center, Urbana, Illinois.

Although it is used safely in many species, isoniazid has a narrow margin of safety in dogs. The LD₅₀ of isoniazid is estimated to be as low as 50 mg/kg in dogs.^{1,4} Because dogs lack the ability to acetylate the drug, 1 tablet (300 mg) ingested accidentally by a 10-lb dog can result in severe toxicosis.^{1,4,5} In dogs, seizures can be seen at 50 mg/kg.¹

Clinical Signs and Diagnosis

Isoniazid toxicosis can result in CNS signs (eg, refractory seizures, coma), GI signs (eg, hypersalivation, vomiting, diarrhea), acid–base disturbances (eg, metabolic acidosis), hyperthermia (secondary to seizures), and organ injury (eg, myocardial injury, secondary acute kidney injury or hepatopathy) (see **Clinical Signs of Isoniazid Toxicosis**).

Severe refractory seizures are among the most common presenting complaints in isoniazid toxicosis. Because isoniazid is not a common toxicant, the veterinarian must be aware of other toxicants or differentials that can also result in seizures (see **Differential Diagnoses for Acute Seizures**).

At presentation, the patient should be triaged and assessed. Ideally, routine blood work (eg, CBC, serum chemistry panel, packed cell volume and total solids, venous blood gas) should be completed. Clinicopathologic findings may include hemoconcentration, metabolic acidosis, hypoglycemia (from protracted seizures), myoglobinuria (from grand mal seizures), elevated liver enzymes (eg, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase) and, less commonly, azotemia.^{4,6} An appropriate toxicologic history should be obtained to aid in identification of isoniazid toxicosis.

CLINICAL SIGNS OF ISONIAZID TOXICOSIS^{1,4,5}

- ▶ Ataxia
- ▶ Disorientation
- ▶ Dysphoria or euphoria
- ▶ Hypersalivation
- ▶ Vomiting
- ▶ Diarrhea
- ▶ Tachypnea
- ▶ Tachycardia or bradycardia
- ▶ Muscle weakness
- ▶ Hyperesthesia
- ▶ Seizures
- ▶ Hyperthermia
- ▶ Pigmenturia
- ▶ Coma
- ▶ Death

DIFFERENTIAL DIAGNOSES FOR ACUTE SEIZURES

- ▶ Toxicoses
 - Bromethalin
 - Metaldehyde
 - Methylxanthine
 - Lead
 - Amphetamines
 - Organophosphates or carbamates
 - Selective serotonin reuptake inhibitors
 - Xylitol (secondary hypoglycemia)
 - Ethylene glycol
 - Strychnine
 - 5-Fluorouracil (5-FU)
 - Ivermectin
 - Fluoroquinolone antibiotics
 - Lamotrigine
 - Ibuprofen
 - Metronidazole
 - Phenylbutazone
- Vilazodone
- Diphenhydramine
- Phenylpropanolamine
- 5-Hydroxytryptophan (5-HTP)
- *Brunfelsia pauciflora* (yesterday-today-and-tomorrow plant)
- *Cycad* spp (Sago palm)
- Zinc phosphide
- ▶ Other conditions
 - Idiopathic epilepsy
 - Inflammatory conditions (eg, granulomatous meningoencephalitis)
 - Infectious diseases (eg, distemper, rabies)
 - Anatomic abnormalities (eg, hydrocephalus)
 - Neoplasia
 - Hypoglycemia
 - Hypernatremia

TABLE

MEDICATIONS USED TO TREAT ISONIAZID TOXICOSIS IN DOGS AND CATS^{1,4,5}

Drug	Use	Dose
Pyridoxine hydrochloride 100 mg/mL**	Antidote	71 mg/kg diluted in IV fluids to 5%–10%; administer via slow IV over 30–60 min
Activated charcoal	Minimizes absorption from the GI tract	1–5 g/kg PO once
Diazepam	Anticonvulsant	0.25–0.5 mg/kg IV as needed***
Dolasetron	Antiemetic	0.6–1 mg/kg IV or SC twice a day
Levetiracetam	Anticonvulsant	20–60 mg/kg IV 3 times a day or as needed***
Maropitant	Antiemetic	1 mg/kg SC once a day
Midazolam	Anticonvulsant	0.25–0.5 mg/kg IV as needed***
Ondansetron	Antiemetic	0.6–1 mg/kg IV or SC twice a day
Phenobarbital	Anticonvulsant	4–20 mg/kg IV as needed***

**Available at human hospitals and some veterinary distributors; B complex has only 2 mg/mL of pyridoxine.

***As needed = each time a patient seizes, or until the loading dose is complete

Treatment and Prognosis

Decontamination is rarely possible in these cases because of the rapid onset of signs (30 minutes to 2 hours*). If the animal is clinically normal, emesis can be attempted in the practice. Emesis should not be induced in patients with clinical abnormalities because of risk for aspiration pneumonia. If an animal is clinically affected and has ingested a large number of pills, gastric lavage may be necessary under anesthesia (with a protected airway).

With isoniazid toxicosis, pyridoxine (vitamin B₆) should be administered promptly. Pyridoxine is considered the antidote for this toxicosis because it is a direct antagonist of isoniazid and will quickly reverse the clinical signs. Dosing should be based on the equivalent amount (mg

for mg) of isoniazid that was ingested. If the amount of isoniazid ingested is unknown, the suggested dose is 71 mg/kg (*Table*).

Other treatments include anticonvulsant therapy, fluid therapy, and supportive care. Immediate IV access should be established. If the patient presents with grand mal seizures, anticonvulsants should be implemented until pyridoxine can be given; however, anticonvulsant therapy is often ineffective until pyridoxine is administered. A balanced maintenance crystalloid should be administered to enhance urinary excretion of isoniazid, to help perfuse the patient, and to minimize acute kidney injury secondary to myoglobinuria. Other treatments include thermoregulation, blood glucose and serum

chemistry profile monitoring, and supportive care. Liver enzymes should be rechecked 3 to 5 days after discharge.

Overall, the prognosis for isoniazid toxicosis is fair if pyridoxine can be administered quickly. Although this human medication may not be a common toxicant ingested by dogs, it can be life-threatening. In dogs that fail to respond to therapy or have significant CNS signs, the prognosis is guarded to grave.

Conclusion

Veterinarians should be aware of isoniazid toxicosis. When in doubt, an animal poison control center should be consulted. Owners should be cautioned about the dangers of human prescription medications. The aggressive use of decontamination, use of the antidote pyridoxine, and supportive care are necessary to ensure good outcome. ■

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