

Ivermectin Toxicosis in Dogs

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P Profile

Definition

- When ivermectin, a macrocyclic lactone, is present in sufficiently high concentrations to cross the blood–brain barrier, it can cause neurologic signs in dogs.
- Toxicity may occur with products administered orally, topically, or parenterally.
 - The same dose will be absorbed faster when administered parenterally than when administered topically, but signs of toxicity can be seen in all routes with high enough doses.

Signalment

- No gender or age predisposition.
- Very young animals may have an increased risk because of their immature blood–brain barriers.
- Dogs with a mutation in the multidrug resistance gene (*ABCB1*, formerly *MDR1*) are especially sensitive to ivermectin.^{1,2}
 - Dogs with an *ABCB1* mutation are also predisposed to increased sensitivity to moxidectin, loperamide, milbemycin, and chemotherapeutic agents.
 - Common breeds with this mutation include the border collie, Australian shepherd, long-haired whippet, silken windhound, rough- and smooth-coated collies, and associated mixed breeds.
- In sensitive breeds, ivermectin toxicosis can be seen in doses as low as 100 µg/kg, although doses of 6 µg/kg have been shown to be safe in nonsensitive breeds.
- In nonsensitive breeds, a dose of >2000 µg/kg is required to produce signs of toxicosis.^{3,4}

Risk Factors

- Most cases of ivermectin toxicosis result from administration of ivermectin-containing products.
- Dogs on farms or in rural settings are at greater risk for ivermectin toxicosis because they may be exposed to products formulated for large animals.
 - Dogs can also be exposed to ivermectin through ingestion of feces from treated cows, horses, or pigs.

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Ivermectin Dose by Indication

Heartworm.....	6 µg/kg
Sarcoptic mange.....	300 µg/kg
Demodectic mange	400–600 µg/kg

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Key Point



Although ivermectin toxicosis typically does not induce pain in animals, increased vocalization caused by anxiety or altered mentation may be difficult to discern from a pain response.

Pathophysiology

- The primary mechanism of action for ivermectin is to potentiate glutamate-gated chloride receptors and γ -aminobutyric acid (GABA)-gated chloride channels.
 - At low concentrations, ivermectin potentiates the effect of glutamate.
 - At higher concentrations, glutamate-gated chloride channels are opened directly.^{5,6}
- When ivermectin binds to the receptors, the chloride channels open slowly and irreversibly, resulting in prolonged hyperpolarization or depolarization of the neuron or muscle cell, causing rapid paralysis.⁵

Signs

History

- Ataxia.
- Mydriasis.
- Altered mentation (obtundation, stupor, coma).
- Hypersalivation.
- Vomiting.
- Blindness.
- Tremors.
- Seizures.

pCO₂ = partial pressure of carbon dioxide



Patients with topical ivermectin toxicosis should be washed with mild dishwashing detergent and water before treatment is initiated.

Examination Findings

- Altered mentation—obtundation, stupor or coma.
- Ataxia.
- Bradycardia.
- Hypersalivation.
- Mydriasis.
- Absence of menace response.
- Vomiting.
- Respiratory depression.
- Tremors.
- Seizures.

Dx Diagnosis

Definitive

- History and examination findings are vital.
- Measurement of serum ivermectin concentration can confirm diagnosis, but usually results are not available immediately.
- Testing for the *ABCB1* gene mutation is available at Washington State University Veterinary Clinical Pharmacology Laboratory, Gribbles Veterinary Services in Australia, and Genetic Counseling Services in The Netherlands.

Differential

- Exposure to other toxicants (eg, ethylene glycol, methanol, heavy metals, hallucinogens, marijuana, barbiturates, opioids, benzodiazepines, mycotoxins).
- Infectious, inflammatory, traumatic, or neoplastic intracranial diseases.
- Metabolic diseases (eg, renal failure, hepatic dysfunction, diabetic ketoacidosis, electrolyte abnormalities).
- Other causes of extracranial neurologic disease.

Laboratory Findings

- CBC, serum biochemistry profile, and urinalysis are usually nonspecific but may be helpful.
- Hemoconcentration has been seen.
- Hypoglycemia may be present if tremors/seizures are prolonged.
- Prerenal azotemia may occur if patient is adipsic or vomiting.

- Nonspecific elevations in liver enzymes may be present.
- Urinalysis may help differentiate between renal and prerenal azotemia.
- Venous blood gas analysis is recommended if the patient is moderately obtunded.
- Respiratory acidosis caused by hypoventilation may be present. Partial pressure of carbon dioxide (pCO₂) >60 mm Hg is diagnostic.

Tx Treatment

- There are no specific antidotes for ivermectin toxicosis.
- Oral:
 - Ivermectin is recirculated in the GI tract.
 - If ingestion occurred <1–4 hours before presentation:
 - Emesis should be induced with apomorphine (0.03 mg/kg IV or subconjunctivally once) or hydrogen peroxide (0.5 mL/kg PO up to 2 times).
 - Activated charcoal should be administered (1–2 g/kg PO once) with/without cathartic; subsequent doses without cathartic at 0.5–1 g/kg q8h.
 - Monitoring electrolyte concentrations, especially sodium, is important.
 - If oral ingestion occurred within 24–36 hours before presentation:
 - Activated charcoal should be administered once at 1–2 g/kg PO; subsequent doses at 0.5–1 g/kg q8h.
- All routes:
 - Patients with topical ivermectin toxicosis should be washed with mild dishwashing detergent and water before initiating additional treatments.
 - Crystalloid fluid therapy should be initiated for maintenance requirements and any ongoing losses (lactated Ringer's solution,

Alternative Treatments

- **Physostigmine**, an anticholinesterase agent, may be administered at 1 mg/dog IV q12h; may cause temporary improvement in neurologic status. The drug acts for a short time, but may be helpful to wake the patient for feeding.
 - Results are typically transient and inconsistent, but beneficial effects may help confirm ivermectin toxicosis.
 - Potentially toxic adverse effects include seizures, excessive salivation, tremors, urination, defecation, and lacrimation.
- **Picrotoxin**, a GABA antagonist, may cause rapid improvement in neurologic status; however, it should be used cautiously, as it may contribute to seizure activity.
- **IV lipids** have seen success in the treatment of ivermectin and other macrocyclic lactone toxicoses, but more research needs to be conducted. IV lipids have relatively few adverse effects and may be worth considering as a therapeutic option.⁷

Plasmalyte-148 [baxter.com], 0.9% saline solution).

- If hypovolemia (tachycardia, hypotension, pale mucous membranes, prolonged capillary refill time) is present, circulating fluid volume should be replaced by administering crystalloid fluid via 20 mL/kg bolus, then reassess vital signs.
 - Bolus may be repeated up to 4 times. Colloids (Hetastarch [hydroxyethyl starch; HES]) at 5 mL/kg concurrently may help correct hypovolemia.
- Endotracheal intubation and mechanical ventilation should be initiated for hypoventilation (pCO₂ >60 mm Hg).
 - Consider referral for mechanical ventilation if unavailable at primary receiving practice. Intubate patient and begin manual ventilation for transportation to specialty practice.
- Progression of clinical signs may be slow. Exposed animals should be monitored closely in the hospital or

at home for at least 1 week, as more extensive therapy may be indicated.

Supportive Treatment

- Primary treatment for ivermectin toxicosis is mainly supportive.
- External heat support if patient is unable to maintain body temperature >99°F.
 - Affected animals are usually obtunded and unable to move away from heat, so care should be taken to avoid thermal burns. Provide circulating warm water or air blankets instead of lamps or heating pads.
- Patient should be rotated q4–8h if obtunded, stuporous, or comatose.
- Consider sterile indwelling urinary catheter and closed collection system

Affected animals are usually obtunded and unable to move from heat, so care should be taken to avoid thermal burns.

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Key Point



Prognosis is usually very good if aggressive supportive care is initiated early. However, treatment can be prolonged, depending on how much was ingested.

to maintain hygiene if patient is non-ambulatory or obtunded.

- Endotracheal intubation is indicated if patient does not have a gag reflex and is unable to protect its airway.
 - Replace sterilized endotracheal tube q24h (minimum). Endotracheal tube should be suctioned and changed more frequently if excessive secretions are present.
- Seizure control can be provided with phenobarbital, pentobarbital, propofol, and etomidate. Benzodiazepines may also be considered, although they may potentiate the effects of ivermectin.
- Eyes should be lubricated q4h if blink reflex is absent or diminished because of mentation.
- Consider enteral nutrition via oral feeding, nasogastric tube, or esophagostomy tube early in treatment. If patient is high risk for aspiration, consider providing total or partial parenteral nutrition.



Follow-up

Patient Monitoring

- Respiratory rate and ventilation status should be monitored carefully.
- Venous or arterial blood gas analysis should be completed to evaluate pCO₂; mechanical ventilation is indicated if pCO₂ is >60 mm Hg.
- In intubated patients, CBC and thoracic radiographs should be obtained if aspiration pneumonia is suspected.
- Neurologic status should be assessed ≥q8h for progression or resolution of signs.

At-Home Management

- A relapse should not be expected, but owners should be instructed to continue monitoring neurologic signs for progression, especially during the first

week following exposure.

- Patients may not be fully ambulatory on discharge, so owners may need to assist the patient in walking and with hygiene.

* In General

Relative Cost

- Most dogs respond well to supportive therapy.
- Depending on the level of care required, treatment ranges from relatively inexpensive (\$\$) to very expensive (\$\$\$\$\$).

Cost Key

\$ = up to \$100
 \$\$ = \$101–\$250
 \$\$\$ = \$251–\$500
 \$\$\$\$ = \$501–\$1000
 \$\$\$\$\$ = more than \$1000

Prognosis

- Prognosis is usually very good if aggressive supportive care is initiated early.
- Depending on the dose ingested and the susceptibility of the exposed animal, treatment may be prolonged.
 - Clinical signs may take several weeks to resolve.
- Prognosis may be guarded if the dose ingested is >5 mg/kg in dogs without the *ABCB1* mutation.⁸ ■ **cb**

See Aids & Resources, back page, for references & suggested reading.

pCO₂ = partial pressure of carbon dioxide