Ivermectin

Ivermectin is a macrocyclic lactone (ML) used to treat parasitic infections in dogs and cats.[1]

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Overview

⚠ The lipophilic properties of MLs enable different routes of administration (ie, oral, cutaneous, injectable).[2,3]
- As GABA agonists, MLs stimulate presynaptic release of GABA and increase its binding to postsynaptic receptors.
- It is thought that MLs bind to glutamate-gated chloride channels in the central nervous system (CNS), resulting in hyperpolarization of the neurons.[4]

⚠ Nematodes utilize GABA as their primary neurotransmitter, and prolonged stimulation of GABA release can lead to neuromuscular blockade, paralysis, and death.[3]

⚠ In mammals, MLs have low neurotoxic properties, as they do not readily cross into the brain of mammals (except under certain circumstances—see **Toxicity**).
- Ivermectin is largely excreted in feces as an unmetabolized parent compound.

Toxicity

⚠ Clinical signs of toxicity include ataxia, mydriasis, altered mentation, hypersalivation, vomiting, blindness, retinopathy, tremors, seizures, bradycardia, and/or respiratory depression.
- With acute intoxication, signs may occur within a few hours.
- In animals being treated daily (eg, for demodicosis), clinical signs may occur after several days of ivermectin treatment.[1]

⚠ Ivermectin is especially toxic when administered to dogs with a homozygous mutation in the multidrug resistance gene (*ABCB1-1Δ*, formerly MDR1) at a dose higher than 0.1 mg/kg.[5,6]
- The absent P-glycoprotein allows the influx of ivermectin into the CNS.[7]
- Collies are overrepresented, but Australian shepherd dogs, Shetland sheepdogs, and other herding breeds may harbor the mutation, making them susceptible to ivermectin and other drugs.[8]

⚠ Dogs without the P-glycoprotein abnormality can tolerate ivermectin at doses as high as 2.5 mg/kg before clinical signs of toxicity are seen.[9,10]

⚠ Young animals may be susceptible to ivermectin toxicosis because of an immature blood–brain barrier.

⚠ Cats are thought to tolerate doses of 0.2-1.3 mg/kg, although toxicity has been reported in kittens at lower doses.[1,11]

⚠ Toxicity can occur when ivermectin is administered topically, orally, or parentally (ie, IM, IV, SC) or ingested through feces of treated horses, cows, or pigs.

Diagnosis

⚠ History of administration or inadvertent ingestion of ivermectin is important in diagnosing toxicity.

⚠ Ivermectin concentrations in the brain are the most important determinant of toxicity.[1]
- Can also be detected in blood, liver, or adipose tissue, but there is little correlation between concentration in the

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blood and development of clinical signs

⚠ Testing can be conducted for the *ABCB1-1Δ* gene mutation in animals that develop clinical signs after ivermectin administration.

⚠ CBC, serum chemistry profile, and urinalysis results typically note nonspecific changes (eg, hemoconcentration, prerenal azotemia, hypoglycemia, elevations in liver enzymes) but may be helpful.[12,13]
- Respiratory acidosis may be present secondary to hypoventilation.

Treatment & Prognosis

⚠ There are no specific antidotes for ivermectin toxicosis.
- Animals with oral exposure should be properly decontaminated when possible.
  - —If oral ingestion occurred within 1 to 4 hours of presentation, vomiting should be induced with apomorphine (0.03 mg/kg IV or subconjunctivally) or hydrogen peroxide (dogs only; 0.5 mL/kg PO).
- Ivermectin undergoes enterohepatic recirculation in the GI tract, so multiple doses of activated charcoal (1-2 g/kg PO once with or without cathartic; subsequent doses without cathartic at 0.5-1 g/kg 3 times a day) may be beneficial.
- Electrolyte concentrations, especially sodium, should be monitored when activated charcoal is administered.[14]
- Animals with topical exposure should be washed with mild dishwashing detergent before additional treatment is initiated.

⚠ Crystalloid fluid therapy should be provided for maintenance and any ongoing losses.

⚠ In animals with hypoventilation (pCO_2 >60 mm Hg), endotracheal intubation and mechanical ventilation should be initiated.
- Referral to a 24-hour facility may be required for ongoing support of a patient that requires mechanical ventilation.

⚠ Physostigmine, an anticholinesterase agent, may be administered at 1 mg/dog IV twice a day but generally causes only temporary improvement in neurologic status.[15]
- Picrotoxin, a GABA antagonist, may improve neurologic status but also may contribute to seizure activity and should be used cautiously.[12]

⚠ Recently, use of IV lipid emulsion has been described for treatment of animals with ML toxicity, including ivermectin.[16-20]
- IV lipid emulsion is effective in humans with lipid-soluble drug toxicoses and appears to be beneficial in animals with ivermectin toxicosis.[16-20]
- The recommended dose of a 20% solution is a 1.5-mL/kg bolus administered over 15 minutes, then 15 mL/kg administered over 60 minutes.[21]
  - —The dose can be repeated if clinical signs of toxicosis recur.
  - —IV lipid emulsion has reportedly reversed blindness and accelerated recovery in affected dogs.[16]

CBC = complete blood count, CNS = central nervous system, GABA = gamma-aminobutyric acid, GI = gastrointestinal, ML = macrocyclic lactone, pCO_2 = partial pressure of carbon dioxide

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WORDS OF CAUTION
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⚠ Mildly to moderately affected animals have a fair-to-good prognosis for recovery with aggressive supportive care.

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