Ivermectin and the Canine MDR1 Mutation: Genetic Risk Factors for Drug Toxicity

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OPEN ACCESS

Keywords

Canine, Ivermectin, MDR1 mutation

How to cite this article:

Rungsung, S., Singh, W. R., Kuotsu, K., Begam, R., Pathak, M. and Debbarma, A. 2025. Ivermectin and the Canine MDR1 Mutation: Genetic Risk Factors for Drug Toxicity. *Vigyan Varta* 6 (10): 15-19.

ABSTRACT

Ivermectin is a widely used antiparasitic drug effective against nematodes and ectoparasites in animals. While generally safe, certain dog breeds with a mutation in the MDR1 (ABCB1) gene are highly susceptible to ivermectin neurotoxicity due to impaired blood-brain barrier protection. The toxic effects regardless of administration route—include ataxia, lethargy, tremors, seizures, and coma, especially in genetically sensitive breeds such as Collies and Australian Shepherds. Toxicity arises from the action of Ivermectin on glutamate- and GABA-gated chloride channels, causing inhibition of neural and muscular activity leading to paralysis and death of the parasite. Diagnosis is based on clinical signs, exposure history, and ruling out other toxicants. There is no antidote; treatment is supportive, including decontamination, IV fluids, respiratory support, and close monitoring. With prompt care, prognosis is good, though severe cases may require extended treatment.

INTRODUCTION

Ivermectin is a semi-synthethic macrolide endectocide agent derived from the natural avermectins isolated from soil microorganism *Streptomyces avermitilis*. Avermectin is a mixture of four major components (avermectins A_{1a}, A_{2a}, B_{1a} and B_{2a}) and four minor components (A_{1b}, A_{2b}, B_{1b} and B_{2b}). The different avermectin anthelminthics such as ivermectin, abamectin, doramectin, eprinomectin and selamectin are combinations of these natural components or are their semisynthetic derivatives. Avermectins have a wide range of activity against nematodes and also ectoparasitic arthropods and hence are termed as endectocides. However, they have no activity against platyhelminths - flukes and tapeworms. Ivermectin is effective against stronglyles, ascarids, pinworms, hairworms, lungworms, bots, and intestinal threadworms in large animals. It is very effective against heartworm (*Dirofilaria immitis*) especially the immature ones in dogs but the efficacy is less on the adult heartworms. It also possesses significant ectoparasitic action against grubs, sucking lice and mites. Avermectins not only kill existing parasites but also provide short term residual protection especially after dermal application reducing re-infection rates by ectoparasites, mainly attributing to their high lipophilicity and prolonged tissue persistence.

Role of MDR1 (also known as ABCB1) in drug transport

The MDR1 gene encodes **P-glycoprotien (P-gp),** a transmembrane efflux pump expressed several barrier tissues, including the **blood-brain barrier (BBB),** intestinal epithelium, renal tubules, and hepatocytes. P-glycoprotein limits drug penetration into sensitive tissues especially the central nervous system (CNS) by transporting lipophilic xenobiotics and pharmaceuticals out of cells and into bile, urine, or the intestinal lumen. Mutation of the MDR1 (ABCB1) impairs the function of P-glycoprotein, allowing certain medications to accumulate in the central nervous system (CNS), where they may exert neurotoxic effects—even at therapeutic doses. In dogs with a defective MDR1 gene, the P-gp is either **nonfunctional or absent**, resulting in accumulation of drugs within the central nervous system, reduced hepatic and renal drug elimination, and increased systemic exposure and prolonged half-life of P-gp substrate drugs (Mealey *et al.,* 2022).

Mechanism of Ivermectin toxicity

Ivermectin toxicity has no gender or age predisposition. When ivermectin is present in sufficiently high concentration to cross the blood brain barrier, it can cause neurological signs in dogs. Toxicity may occur irrespective of the route of administration - orally, topically, or parenterally. The same dose will be absorbed faster when administered parenterally then when administered topically, but signs of toxicity can be seen in all routes with high doses. Very young animals may have increase risk of toxicity presumably due to more permeable blood-brain barrier. Some breeds of dogs are reported to be sensitive to ivermectin such as Border collie, Australian shepherd, long haired whippet, rough and smooth coated collies and associated mixed breeds. The increased sensitivity of these breeds is associated with the mutation of gene MDR1 (ABCB1) that encodes for membrane pump P-glycoprotein in the blood brain barrier.

Avermectins, including ivermectin, exert their antiparasitic effects primarily by binding to a specific class of glutamate-gated chloride channels (GluCl), which are found exclusively in invertebrates such as nematodes and arthropods. Binding of ivermectin to these channels increases chloride ion permeability,

resulting in membrane hyperpolarization, which inhibits neural and muscular activity leading to paralysis and death of the parasite. At low concentrations, ivermectin acts as a positive allosteric modulator, potentiating the effects of endogenous glutamate. At higher concentrations, it can directly activate the GluCl channels, inducing continuous chloride influx (Martin *et al.*, 2021). Ivermectin also exhibits lower-affinity binding to GABA gated chloride channels, which at high concentration cause irreversible channel activation or enhanced GABA effects further contributing to neuromuscular blockade in susceptible species. The absence of glutamate-gated chloride channels in platyhelminths such as cestodes and trematodes likely accounts for ivermectin inactivity against the platyhelminths. These channels are also absent in mammals, contributing to high safety margin of ivermectin in humans and other vertebrates (Dawson & Wafford, 2000). In mammals, the avermectins primarily target the GABA-gated and possibly the glycine gated chloride channels. Furthermore, in mammals the GABA mediated neurotransmission occurs in the CNS, where the BBB prevent uptake of the endectocides and thus provides a wide margin of safety unlike in nematodes and athropods. In mammals, the blood-brain barrier (BBB), reinforced by P-glycoprotein (P-gp) efflux transporters, effectively limits ivermectin penetration into the central nervous system, thereby preventing neurotoxicity at therapeutic doses. However, in animals with deficient P-gp function such as Collie dogs with MDR1 gene mutations ivermectin can cross the BBB more readily, leading to dose-dependent neurotoxicity, even at otherwise safe doses (Geyer *et al*., 2005).

Clinical uses of Ivermectin

Clinically, ivermectin is a commonly used endectocide in veterinary medicine. It is useful against gastro intestinal roundworms and lungworms in horses, ruminants and pigs and heartworms (mainly prophylactic) in dogs and cats. It is also used to control lice, mange mites, horn flies, grubs, biting and sucking lice and mites It is available as chewable tablets, injectable solutions, pour-on formulations. In dogs, it is effective against otodectic, sarcoptic, and notoedric mange and control of demdectic mange. Typical dose for ivermectin in dogs are 6µg/kg for heartworm prophylaxis while 300-600µg/kg for treatment of parasitic infestations, sarcoptic mange and demodectic mange. In sensitive breeds, ivermectin toxicity can be seen in dose as low as 100-120µg/kg and doses of more than 2000 µg/kg is required to produce signs of toxicosis in non-sensitive breeds. Ivermectin has a 10-fold safety margin in other species like ruminants, equine, swine and canine except collies. Collies or Collie-mixed breeds and other susceptible dog breeds should not be treated with ivermectin or any other avermectins. Ivermectin is not recommended in puppies under 6 weeks or in pre-ruminating calves, and the injectable formulations are approved only for subcutaneous routes.

Most cases of ivermectin toxicity results from administration of ivermectin containing products. Some probable causes of ivermectin poisoning in dogs are administration error such as owner gives part of a tablet meant for larger dog to their smaller dog, doubling up of missed dose, administration to MDR1 mutation susceptible breeds and licking off topical solution by pets.

Toxic signs and diagnosis of Ivermectin toxicity

Clinical signs of ivermectin toxicity in dogs typically develop within a few hours after exposure, although onset may be delayed for up to 24 hours (Geyer *et al.,* 2005). The toxicity primarily affects the central nervous system, resulting in a range of neurological symptoms. Affected dogs often exhibit depression and lethargy, along with

disorientation characterized by ataxia and loss of coordination. Hypersalivation and excessive drooling are common, accompanied by gastrointestinal disturbances such as vomiting and diarrhea. Increased vocalization, including whining and barking, may also be observed. Pupillary dilation (mydriasis), muscle weakness, and respiratory distress may be noted. Neuromuscular signs include muscle twitching (myoclonus), tremors, and generalized seizures which in severe cases, can progress to coma. These clinical manifestations are consistent with the neurotoxic effects of ivermectin mediated through potentiation of inhibitory neurotransmission at GABA and glutamate-gated chloride channels within the central nervous system (Dawson & Wafford, 2000)

Diagnosis typically involves a thorough patient history, careful monitoring of vital signs, and a differential diagnosis to rule out exposure to other toxic substances such as ethylene glycol, methanol, heavy metals, opioids, barbiturates, benzodiazepines, and mycotoxins.

Treatment of Ivermectin toxicity

There is no specific antidote for ivermectin toxicosis. Overdosage may be treated by supportive and symptomatic therapy. If ingestion occurred less than 1-4 hrs before presentation then emesis should be induced with antiemetics such as apomorphine and xylazine in cats; activated charcoal should be administered with or without cathartic to reduce further absorption. If ingestion occurred within 24-36 hrs before presentation activated charcoal should be administered. For topical exposure, the affected area should be thoroughly cleansed with detergent and water prior to any further treatment to prevent continued absorption through the skin. Intravenous fluid therapy (e.g., Lactated Ringer's Solution) should be initiated to maintain hydration and support renal clearance. Endotracheal intubation and mechanical ventilation should be initiated for hypoventilation. Thermal support (e.g., heating blankets or warm IV fluids) should be provided in patients presenting with hypothermia, which can result from central nervous system depression.

Affected animals should be closely monitored for at least 5–7 days, as clinical signs may progress slowly, especially in breeds with MDR1 gene mutations that impair blood-brain barrier function. In severe cases, neurologic signs such as ataxia, stupor, seizures, and coma may require prolonged hospitalization and intensive care. Animals should be closely monitored for at least a week since progression of clinical signs may be slow and extensive therapy may be indicated, if required. The prognosis is generally favorable with timely and aggressive intervention. However, in severe cases, recovery may take several weeks, and treatment costs can be significant, potentially limiting therapeutic options for some owners.

CONCLUSION

Ivermectin is a highly effective antiparasitic agent, but its use requires caution in dogs with MDR1 gene mutations due to the risk of neurotoxicity. Following accurate dosing, breed-specific considerations, and early supportive treatment are essential for favorable outcomes. By raising awareness and incorporating genetic testing in the future, serious reactions to ivermectin in at-risk dogs can be prevented.

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