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Toxicity (Ivermectin) Occurring in German Shephered (Puppy) Male Dog: A Case Study

[1]Prerit K. Singh and [2]R.P. Diwakar

[1]Pratap Clinic of Veterinary and Veterinary Medicine Manipuri (Uttar Pradesh), India
[2]Department of Veterinary Microbiology Collage of Veterinary Science and Animal Husbandry Acharya Narendra Deva University of Agriculture and Technology, Kumarganj Ayodhya (UP) - 224229, India

Abstract: A 3 month old german shepered male puppy weight 10 kg was coming to pratap clinic of veterinary and veterinary medicine Manipuri Uttar Pradesh, for treatment. Earlier puppy was treated for tick infestation as per the owner told by given about 100 mg of ivermectin tablet orally. Owner observed some clinical sign after 8 to 10 medication. Clinical examination revealed hypothermia (101.2°F), tremors, ataxia, partial blindness, dilated pupil, weakness, incardination, no responsiveness, unable in defecation and behavioural changes. Therapeutic management was done by the administration of avil 1ml, neurokind 1.5 ml, RL 100 ml, NS 150ml, manitol 1-2ml/kg BW IV stat, vetacept 1ml/day, lasix 1.5ml repeated 10 hourly and dexamethasone @ 0.25-0.5mg/kg BW IM BID, rectal enema for passing feaces to withdrawal ivermectin on first day and with infusion of 150ml dextrose (5%) IV. The dog recovered uneventfully after treatment.

Key words: Ivermectin · Toxicity · Ataxia · Treatment

INTRODUCTION

Ivermectin is a macrocyclic lactones produced from a fungus first isolated from a soil sample in Japan, *Streptomyces avermitilis*. The ivermectins are a class of chemicals that have a novel mode of action against nematode and arthropod parasites [1]. Ivermectin is an antiparasitic drug belonging to the avermectin family of compounds. Ivermectin is a mixture of 80% or more of an analog of avermectin B1a and 20% or less of an analog of avermectin B1b. These compounds are 2 of 4 ivermectins produced by the actinomycete *Streptomyces avermitilis.* Although similar in structure to the macrocyclic lactones, ivermectins have no antibacterial or antifungal activity. They do have a broad spectrum of activity against nematode and arthropod parasites of both plants and animals [2]. All major gastrointestinal and lung nematodes and certain ectoparasites of cattle, sheep, horses and swine, intestinal nematodes, ear mites and sarcoptic mange of dogs, infective-stage heartworm and microfilariae of dogs and certain intestinal nematodes of chickens are effectively eliminated by ivermectin [3]. Ivermectin is an agonist for the neurotransmitter gamma-amino butyric acid (GABA). GABA is a major inhibitory neurotransmitter. In mammals, GABA-containing neurons and receptors are found in the central nervous system (CNS), while in arthropods and nematodes GABA is found in the peripheral nervous system (neuromuscular junction). This difference in location of GABA receptors may be the reason for the large margin of safety of Ivermectin-containing products in mammals [1]. The binding of Ivermectin to neuronal membranes increases the release of GABA, which binds to the GABA-receptor chloride-channel complex of postsynaptic neuronal membranes causing an influx of chloride ions. The chloride ions hyperpolarize the neuronal membranes making less excitatory and decreasing nerve transmission. The hyperpolarization of neuronal membranes (at the neuromuscular junction) mediates a flaccid paralysis in arthropods and nematodes. Ivermectin is only slightly metabolized by the liver. The majority of Ivermectin is excreted in feces [1]. Clinical signs of Ivermectin toxicosis in vertebrates should then relate to diffuse cerebral and cerebellar dysfunction. Whereas negligible penetration of Ivermectin through the blood brain barrier has been reported in most species [4].

Corresponding Author: R.P. Diwakar, Department of Veterinary Microbiology, C.V.Sc & A.H and UAT, Kumarganj Ayodhya (U.P), India.

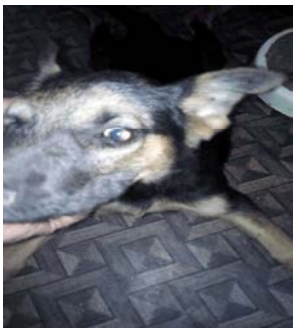

Fig. 1a: Dilated pupil before treatment

Fig. 1b: Normal pupil after treatment

History and Clinical Observations: A 3 month old german shephered male puppy weight 10 kg was coming to pratap clinic of veterinary and veterinary medicine Manipuri Uttar Pradesh, for treatment with complaint of depression, ataxia, partial blindness, dilated pupil (Figure 1a), negative pupillary light reflex, weakness, in coordination and behavioral changes. The dog was treated for tick infestation by owner for tick infestation. About 100 mg tablet of ivermectin was given orally. Abnormal clinical signs were observed by owner 8 to 10 hours after medication. Clinical examination revealed hypothermia (101.2°F), mydriasis, Superficial blood vessels appear on eye ball, tachycardia, dysponea with respiration rate of, in-coordination, seizures and unable to stand properly.

RESULTS AND DISCUSSION

Important way to reduce the ivermectin toxicity is only by therapeutic managemental care, supportive therapy and symptomatic treatment as there is no specific antidote against ivermectin toxicity. The puppy was treated with the administration of avil 0.5-1ml, neurokind 1-2ml, Ringer lactose 100ml, Normal saline 150ml, Manitol 1-2ml/kg BW IV stat, vetacept 1ml/day, lasix 1.5ml repeated 10 hourly and dexamethasone @ 0.25-0.5mg/kg BW IM BID, rectal enema for passing feaces to withdrawal ivermectin on first day and with infusion of 20 ml dextrose (5%) IV. The puppy recovered uneventfully after treatment.

Collie breed of dogs are more susceptible for ivermectin and can tolerate up to 0.1 mg/kg dose rate of ivermectin [5]. The margin of safety for ivermectin in most breeds of dog is well over 100 times the recommended dose but in Collies it is about 16 times the usual dose. Hadrick *et al.* [6] reported that in two Australian shepherds receiving ivermectin at oral dosage of 0.17 mg/kg and 0.34 mg/kg respectively. Occurrence of toxicity in selective breeds, may be due to the reason that these breeds have comparatively more permeable blood brain barrier to the drug [7] or due to an autosomal recessive trait (MDR-1) gene that causes a defect in the p-glycoprotein, which is a multidrug transporter in the blood brain barrier and this leads to passage of ivermectin in to the brain at low dosages thus causing toxicity [8].

In dogs, an oral preparation of ivermectin in sesame oil induced mydriasis at a dosage of 2.5 mg/kg, tremor at a dosage of 5 mg/kg, severe tremor and ataxia at a dosage of 10 mg/kg and death at a dosage of 40 mg/kg [2]. Depression, ataxia, coma and death have followed treatment of dogs with products intended for use in horses or cattle, at a dosage of 0.2 mg/kg [9, 10].

The published maximum tolerated dose of ivermectin in cattle is 5 times the usual therapeutic dose of 0.2 mg/kg body weight. Doses in cattle greater than 1 mg/kg body weight may cause depression, ataxia and sometimes death [2]. Ivermecrtin toxicosis was observed in dogs in many studies. Hopkins *et al*. [4] showed tremors, dilated pupils and blindness in male Dober pinscher dog administered invermectin orally in a dose of 115 mg. In clinical trials, Beagles and other research dogs had advice effects (mydriasis, tremor and ataxia) at single oral doses ranging from 2.5 mg/kg to 10 mg/kg, with deaths occurring at doses in excess of 9.4 mg/kg [11].

In this case report, the puppy was so young that the blood brain barrier might not have been fully developed / well developed to lead the toxicity. Side effects of urgent concern are dilated pupils and drunken gait which can progress to respiratory paralysis and death if medication is not withdrawn and supportive care is not initiated. Unfortunately, ivermectin toxicity cannot be reversed and therefore, it is best to treat the animal as per symptoms to the best our potential and ability.

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