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Ivermectin toxicity in American Pit Bull Terrier bitch and its therapeutic management

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Abstract

A two-year-old American Pit Bull Terrier cross bred bitch weighing 25 kg was admitted to clinics with history of dullness, incoordination and lateral recumbency after feeding of 80 mg tablet of Ivermectin. Clinical examination of bitch showed intermittent howling and paddling of hind legs, tachycardia, panting, hyperthermia, dry oral mucous membrane and tongue, dilated pupils and congested conjunctivae. Haemato-biochemical investigations showed severe granulocytic leukocytosis, lymphocytopenia and anemia with normal serum values of bilirubin, creatinine and urea nitrogen. Based on clinical signs and history, the case was diagnosed as ivermectin toxicity and treated with single dose of isoflupredone acetate @ 0.2 mg/kg IM with inj. DNS @ 500 ml IV, inj. RL @ 500 ml IV, inj. Neostigmine @ 0. 05 mg/kg SC, inj. Vitamin B complex @ 2 ml IV and inj. Meloxicam @ 0.25 mg/kg IV every 12 hours with monitoring of the patient. After second treatment, bitch showed good clinical improvement with disappearance of howling, regain of muscular strength and ability to stand and walk followed by food and water intake. After third treatment at 24 hours, bitch showed uneventful clinical recovery with disappearance of nervous signs and restoration of clinical parameters.

Keywords: Ivermectin Toxicity, American Pit Bull Terrier, Treatment

Managemental recklessness with respect to administration of drugs has been reported as one of the major cause of drug toxicity in animals (Bhikane *et al.,* 2017, Jadhav *et al.,* 2017 and Dey *et al.,* 2017). Antibiotics, antiparasitics and non-steroidal anti-inflammatory drugs are the drugs, which are most commonly responsible for drug toxicity in animals (Muntener *et al.,* 2010 and Xavier *et al.,* 2002). The slight overdosing of anthelmintics with narrow margin of safety or use of drugs without valid veterinarian's prescription by animal owners may lead to cases of toxicity. Being broad-spectrum endectocide, ivermectin is commonly used for treatment of ectoparasite infestations in dogs. It is an anti-parasitic drug of avermectin class synthesized from *Streptomyces avermitilis*. Ivermectin acts by binding GABA gated chloride channels and invertebrates specific glutamate gated anion channel in peripheral neuromuscular synapsis, suppressing conduction of nerve impulse (Campbell *et al.,* 1983 and Basudde, 1989). It has been widely used in veterinary medicine and is approved for use in dogs as heartworm preventive (Blagburn *et al.,* 2011). Off-label use of Ivermectin in dogs for endo as well as ectoparasite treatment is common (Plumb, 1995). Collie breeds of dogs are sensitive to ivermectin toxicity while other breeds tolerate the therapeutic dose of Ivermectin. There is breed wise variation in median lethal dose of ivermectin. The median lethal dose (LD50) of ivermectin for Beagle breed has been reported to be 80 mg/kg with no incidence of toxicity at dose rate of 2 mg/kg while Collies are more sensitive to ivermectin toxicosis (Campbell, 1989). The present case report puts one case of Ivermectin toxicity in American Pit Bull Terrier bitch due to accidental overdosing of oral ivermectin preparation.

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Case history and Observations

A two-year-old female American Pit Bull Terrier cross bred bitch weighing 25 kg and suffering from heavy tick infestation was admitted to Teaching Veterinary Clinical Complex, College of Veterinary and Animal Sciences, Udgir. History revealed first sign of dullness, incoordination while walking followed by inability to stand. Careful investigation regarding medication revealed administration of 80 mg tablet of ivermectin to bitch followed by onset of illness in 3 hours. Thorough clinical examination and haemato-biochemical investigations were carried out in the ailing bitch. Bitch was admitted to clinics in lateral recumbency and showed paddling of hind legs, intermittent howling and protrusion of tongue from mouth with dummy syndrome (Figure 1). Vital parameters revealed elevation of body temperature (103.5 ^{0}F), tachycardia (130 beats / minute), and increased respiration rate (64/min) with open mouth breathing

and panting. Pupils were dilated, conjunctival mucous membrane was congested while tongue and oral mucous membrane were completely dry.

About 2 ml of blood was collected in EDTA vial for haematology while 4 ml blood was collected in clot activator tube to harvest serum. Complete blood count analysis was done on automated veterinary specific haematology analyzer while biochemistry was done on semi-automated biochemical analyzer. Haematological analysis (Table 1) showed severe leukocytosis (35.34 x 10^9/L), granulocytosis (33.96 x 10^9/L),lymphocytopenia (0.35 x 10^9/L) and anemia (Hb- 7.1 gm/dl, PCV – 18.14%). Biochemical analysis showed normal values of bilirubin (0.62 mg/dl), creatinine (0.8 mg/dl) and blood urea nitrogen (10.8 mg/dl). Based on circumstantial evidence supported by clinical manifestations and haematological changes, the ailing dog was diagnosed for ivermectin toxicity.

The ailing dog was hospitalized and treated with single dose of Isoflupredone acetate @ 0.2 mg/kg IM. Further treatment was done with Inj. DNS @ 500 ml IV, Inj. RL @ 500 ml IV, Inj. Neostigmine @ 0.05 mg/kg SC, Inj. Vitamin B complex @ 2 ml IV and Inj. Meloxicam @ 0.25 mg/kg IV every 12 hours with monitoring of the patient for clinical response. Immediately during IV fluid therapy along with single dose of corticosteroid and neostigmine, the ailing bitch showed response to treatment. During fluid therapy oral mucous membrane and tongue regained moisture with temporary subsidence of leg paddling and howling. After completion of the first treatment, dog showed mild improvement in vital parameters with increase in alertness in the form of response to external stimuli with persistence of lateral recumbency and intermittent howling. Second treatment 12 hours later with fluids, neostigmine, vitamin B complex and meloxicam showed promising improvement. The bitch showed regain of muscular strength, ability to stand and walk some distance followed by disappearance of leg paddling and howling, normal response to external stimuli with initiation of food and water intake. A third dose of treatment 24 hours after admission showed promising clinical recovery with complete resolution of nervous signs, normal nervous demeanor and restoration of vital parameters as well as food and water intake (Figure 2).

Discussion

Ivermectin is an endectocide drug of avermectin class, which is indicated as heartworm preventive (Booth and McDonald, 1988). Being broad spectrum, it has been widely employed in the management of both endoparasites as well as ectoparasite infestations in pet as well as farm animals. Ivermectin is having high therapeutic index being effective at 6 µg/kg as heartworm preventive while safe at even 300 µg/kg daily off label use in canine demodicosis (Mulller, 2004). Ivermectin is safe drug with high affinity to glutamate gated chloride channels in parasites (Wolstenholme and Rogers, 2005) which are absent in mammalian hosts (Raymond and Sattelle, 2002). GABA gated chloride channels are located in central nervous system in mammals and ivermectin does not cross blood brain barrier except Collie dog breed (Campbell *et al.*, 1983). The incidence of ivermectin toxicity was reported due to administration of higher dose rates exceeding the safety of margin leading to occurrence of poisoning syndrome consistent with GABA receptor modulation (Lovell, 1990).

The prominent clinical signs observed in ailing bitch were lateral recumbency, paddling of hind legs, protrusion of tongue, intermittent howling, and dilated pupils with elevated body temperature, respiration and heart rate. Sheikh *et al.* (2017) reported hypothermia, ataxia, partial blindness, dilated pupil, negative pupillary light reflex, incoordination and behavioral changes in German shepherd cross bred dog suffering from ivermectin toxicity. Dey *et al.* (2017) reported severe depression, ataxia, recumbency, failure to rise, holding the head in improper positions and blindness in Doberman pinscher pups administered with excess of ivermectin. Singh *et al.* (2018) reported tremors, ataxia, partial blindness, dilated pupils, weakness, incoordination and behavioral changes in Pomeranian pup suffering from ivermectin toxicity. The clinical findings of dilated non-responsive pupils, localized muscle group fasciculation around the face and hind limbs and no response to external stimuli are in agreement with those reported by Hopkins *et al.* (1990) in a 5-year-old male Doberman pinscher dog suffering from ivermectin toxicity.

Oral ivermectin is absorbed rapidly compared to subcutaneous route even though having same bioavailability for both routes (Plumb, 1995). Hopper *et al.* (2002) reported more rapid onset and severe toxicity in Collie dogs given oral dose of ivermectin compared to slow onset in dogs treated by subcutaneous route. The rapid and severe ivermectin toxicosis in bitch after oral administration of ivermectin in high dose in the present study is in agreement with the findings of Plumb

Table 1: Haematological parameters in American Pit Bull Terrier Bitch with Ivermectin Toxicity

Sr. No.	Parameter	Before treatment (0 day)	After recovery (10^{th} day)	Normal values
1.	TEC (X 10^6/µl)	2.49	3.54	5.5-8.5
2.	Hb (gm %)	7.1	9.6	12-18
3.	PCV (%)	18.14	25.87	37-55
4.	MCV (fl)	73	73	60-77
5.	MCH (pg)	28.4	27	19.5-24.5
6.	MCHC(g/dl)	39.8	37	31-34
7.	TLC (X 10^3/µl)	35.34	21.76	6-17
8.	Neutrophils (%)	96.1	86.7	62-87
9.	Monocytes (%)	2.9	4.9	2-4
10.	Lymphocytes (%)	1.0	8.4	12-30
11.	Thrombocytes (X 10^3/µl)	245	459	200-500

Fig. 1: Lateral recumbency with dummy syndrome in bitch due to ivermectin toxicity

Fig. 2: Completely recovered, healthy and active bitch after treatment

(1995) and Hopper *et al.* (2002). In the present case of ivermectin toxicity in American Pit Bull Terrier bitch, severe granulocytic leukocytosis was observed. Bhikane *et al.* (2017) also reported granulocytic leukocytosis in Deoni calf suffering from ivermectin toxicity. The anemia in present case might be attributed to blood sucking activity of bigger engorged ticks with high density on the body of bitch.

Numerous authors treated ivermectin toxicosis ailing dogs with mixed results regarding therapeutic success. Dey *et al.* (2017) treated Doberman pinscher pups with normal saline, physostigmine and dexamethasone and got mixed success. Sheikh *et al.* (2017) treated German shepherd cross breed dog with atropine sulphate, neostigmine, nervine tonic, dexamethasone and dextrose 5%. Neostigmine is an anticholinesterase drug, which competitively inhibits acetylcholine (ACh) from attaching to acetylcholinesterase (AChE) binding sites leading to persistence of ACh thereby enhancing impulse transmission across neuromuscular junction leading to transient increase in mental alertness (Muhammad *et al.*, 2004). In the present case treatment with neostigmine and single dose of corticosteroid along with fluids and B complex showed promising clinical recovery within 24 hours. As such, there is no specific antidote to ivermectin toxicity, symptomatic treatment with neostigmine as physiological antagonist of ivermectin in brain proved helpful in successful clinical recovery of dog presented in early stages of toxicosis.

Conflict of Interest

Authors declare that there is no conflict of interest. Both authors have gone through the content of manuscript, authorship and recommended the manuscript for the publication.

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