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Clinical presentation and therapeutic management of ivermectin toxicity in German Spitz dog

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Abstract
Ivermectin is most common as well as widely used endecticides in dogs. Toxicity of ivermectin is observed when either given in excessive dose or accidental ingestion. A 7.5 kg year old male German Spitz dog was presented to Veterinary Clinical Complex, College of Veterinary Science and Animal Husbandry, JAU, Junagadh Gujarat. The dog was treated with ivermectin tablet by owner. Abnormal symptoms were noticed by owner after 4 hours of ingestion. Systemic clinical examination revealed lacrimation, nausea with frothy salivation, partial blindness, in-coordination with ataxia and inappetance. Therapeutic management was carried out with Inj. neostigmine @ 0.05 mg/kg BW SC, Inj. atropine sulphate @ 0.02-0.04 mg/kg BW IV and Inj. dexamethasone @ 0.25-0.5 mg/kg BW IM and Inj. Neurobion @ 0.75 ml total dose with infusion of 250 ml 5D (5%) IV. The dog recovered uneventfully after treatment.

Keywords: German Spitz dog, endecticides, ivermectin toxicity, therapeutic management

Introduction
Medicines often are causes of poisoning in both small and large animals. Generally it is expected that drug intoxications can constitute 10-30% of poisonings in animals [1,2]. Species affected are mainly dogs, cats and other companion animals, less is reported for farm animals [3]. Avermectins (ivermectin-like drugs) and milbemycins (milbemycin and moxidectin) are macrocyclic lactones share similarities, including mechanism of action. These drugs are neurotoxic to parasites by potentiating glutamate-gated chloride ion channels in parasites. Paralysis and death of the parasite are caused by increased permeability to chloride ions and hyperpolarization of nerve cells. These drugs also potentiate other chloride channels, including ones gated by gamma-aminobutyric acid (GABA). Mammals ordinarily are not affected because they lack glutamate-gated chloride channels, and there is a lower affinity for other mammalian chloride channels. Because these drugs ordinarily do not penetrate the blood–brain barrier. Ivermectin is active molecule against endo and ecto parasites *viz*. intestinal parasites, mites, bots, heartworm microfilaria, and developing larvae. Ivermectin has been demonstrated as an extremely safe drug in dogs, an increased susceptibility to the toxic effects is evident in a subpopulation of collies and collie-type dogs [4]. Clinical signs initially include salivation, vomiting, ataxia, tremors and disorientation, but these progress to weakness, recumbency, non-responsiveness, stupor and coma in some dogs. Present report deals with a case of ivermectin toxicity and its therapeutic management.

Materials and Methods
Patient data with Case History
A German Spitz dog aged of 7.5 years weighing about 9 kg was presented to college clinic with history of depression, ataxia with all four limbs, nausea with frothy salivation, in-coordination, inappetence and behavioral changes. The animal was given one ivermectin tablet of 10mg orally by owner before about 4 hours as deworming.

Clinical observation
The vital parameters were hypothermia (98.6 F) tachycardia (140 beats/min) and oligopnoea. Close physical examination reveals miasis with severe lacrimation and seizures (Fig.1).

Blood samples were collected for routine hematology and serum biochemistry. Based on anamnesis and clinical findings the case was diagnosed as ivermectin toxicity.

Fig 1: Severe lacrimation in dog affected with ivermectin toxicity

Results and Discussion

Hematology and serum biochemical (Table-1) results reveal elevated levels of Total leukocyte count and ALP. Rest of the parameters were within normal range.

Table 1: Showing Hemato-biochemical parameters of dog affected with ivermectin toxicity

Parameters	Recorded value	Reference value
Hemoglobin (g/dl)	16.20	12-18
PCV (%)	54.50	37-55
RBC ($\times 10^3/\mu L$)	7.9	5.5-8.5
MCV (fl)	68.99	60-77
MCH (pg)	2.51	19.5-24.5
MCHC (g/dl)	29.72	31-34
Platelet counts (lakhs/µL)	284	200-500
WBC ($\times 10^3/\mu L$)	17570	6-17
Neutrophil (%)	63	60-76
Lymphocyte (%)	32	12-30
Monocyte (%)	2	3-10
Eosinophil (%)	2	2-10
Basophil (%)	1	0-1
ALT (U/L)	115	10-109
AST (U/L)	11.50	13-15
Total protein (g/dl)	5.35	5.4-7.5
Albumin (g/dl)	3.20	2.3-3.1
Globulin (g/dl)	2.15	2.7-4.4
A:G	1.49	--
Total Bilirubin (mg/dl)	0.2	0-0.3
Creatinine (mg/dl)	1.35	0.5-1.7
BUN (mg/dl)	24.50	8-28

As there is no specific antidote for ivermectin toxicity, therapeutic management is comprises of symptomatic treatment, supportive therapy and managemental care. The dog was treated with Inj. neostigmine @ 0.05 mg/kg BW SC, Inj. atropine sulphate @ 0.02-0.04 mg/kg BW IV and Inj. dexamethasone @ 0.25-0.5 mg/kg BW IM and Inj. Neurobion @ 0.75 ml total dose with infusion of 250 ml 5D (5%) IV for 3 days. The dog recovered uneventfully.

The macrocyclic lactones (avermectins and milbemycins) exert their antiparasitic effects on nematodes and arthropods primarily by binding to glutamate-gated chlorine channel receptors [5]. They have an additional potentiating effect on GABA by enhancing its presynaptic release and increasing its binding to postsynaptic receptors in the peripheral nervous system [6]. Binding to glutamate gated chloride channel receptors opens the chloride channels, resulting in an influx of chloride ions and causing flaccid paralysis [7]. Ivermectin is used in a wide range of animals for internal and external parasites. Dosage regimens are vary depending on the species and parasite treated. Collie breed of dogs are more susceptible to ivermectin and tolerate only up to 0.1 mg/kg dose rate of ivermectin [4]. 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. 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 [8] or due to an autosomal recessive trait (MDR-I) gene that causes a defect in the p-glycoprotein, which is a multidrug transporter in the blood brain barrier and it helps in passage of ivermectin into the brain at low dosages and thus causes toxicity [9]. Similar clinical toxicity findings had been reported by Veena *et al.* (2016) in adult German Shepherd [10] & Sheikh *et al.* (2017) in German Shepherd cross breed dog [11]. Very low test doses are often recommended at the stars of a treatment to identify these individuals regardless of their breed. Alternatively, a blood test is now available to test for the genetic sensitivity. This genetic test (DNA test using an oral swab) for P-glycoprotein mutation will identify ivermectin sensitive dogs as also narrated by Houston *et al.* [8] and Hadrick *et al.* [12].

Conclusion

A case of successful therapeutic management of ivermectin toxicity in dog is presented. Early presentation of the animal to clinic and prompt management will result in proper recovery of animal. Much more is needed to be done to raise awareness of veterinarians, pharmacists and also pet owners to the problem of Drug's adverse reactions, off-label use and inter-species differences. These misuse and accidents could be avoided through further education of veterinarians, para-vets, pharmacists and pet owners using modern and reliable sources of information available to everyone, by appealing on the importance of proper reports on poisoning cases and adverse effects to responsible authorities and publishing such cases in expert journals.

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