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Management of ivermectin toxicity in a dog using lipid emulsion: A case report

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Abstract
A six-year-old Pomeranian dog was presented with signs of ataxia, seizures, hypersalivation, and blindness presented to the outpatient department (OPD) of medicine at the Veterinary Clinical Complex (VCC), CVSc, Rajendranagar, Telangana. The dog had previously consumed a large dose of ivermectin (100 mg bolus). It had a high rectal temperature (104.3°F), normal mucus membrane, tachypnoea (70/min), tachycardia (130/min), mydriasis, no menace reflex and no pupillary light reflex, according to the clinical examination. Leucocytosis was found during the haematological examination, however the blood's biochemical profile (BUN: 16.9 mg/dl, creatinine: 1.2 mg/dl, SGPT: 57.3 U/L, SGOT: 34.6 U/L) was within the reference range. Initially, this patient had constant rate infusion therapy at 0.25 ml/kg/h, OD, and isotonic crystalloid solution (0.9% NS) at 30 ml/kg body weight for a total of 10 minutes after receiving 20% lipid emulsion (Intralipid) at 1.5 mL/kg body weight. Neostigmine 0.05 mg/kg b. wt. IV BD, dexamethasone 0.25 to 0.5 mg/kg b. wt. IM BD and ceftriaxone sodium 20 mg/kg b. wt. IV BD repeated every six hours. One oral dose of activated charcoal at 1 g/kg body weight. Five days after ingesting a high dose of ivermectin, the dog's clinical condition returned to normal state. The current case describes the effective treatment of canine ivermectin poisoning.

Keywords: Ivermectin, Intralipid-lipid emulsion, Mydriasis, hypersalivation

Introduction
Ivermectin is a widely used endectocide for dogs that can be detrimental if administered in large quantities to animals that are sensitive to the drug. The harmful effects of ivermectin on mammals are due to its similarity to vertebrate γ-aminobutyric acid ($GABA_A$) gated chloride channels, which inhibit interneurons in the central nervous system (Johnson-Arbor, 2022) [5]. Most dogs can tolerate ivermectin doses up to 2.5 mg/kg PO without exhibiting signs of clinical toxicity. Symptoms of poisoning typically include ataxia, vocalization, disorientation, hyperesthesia, blindness, weakness, mydriasis, and bradycardia. Intralipids have gained recognition as a potent antidote for treating drug toxicity over the past decade. While their effectiveness was initially demonstrated in cases of local anesthetic systemic toxicity (LAST), recent case reports suggest that they may also be effective in treating a variety of other drug toxicities (Ozcan and Weinberg, 2014) [6].

Case history and Observations
A six years old Pomeranian breed dog was presented for treatment of accidental ivermectin ingestion. On presentation it shown the Rectal Temperature (104.4 ºF), Heart Rate – 130beats/ minute, Respiration Rate-70/minute, Mucus Membrane–Pink, Pupillary Light Reflex- Absent, Menace Reflex – Absent, after consuming excess dose of Ivermectin. It also showed hypersalivation (Fig.1), ataxia and dilation of pupil (Mydriasis) (Fig.2). Blood samples were collected for haemato-biochemical examination (Table: 1, 2).

Fig 1: Dog showing Hypersalivation

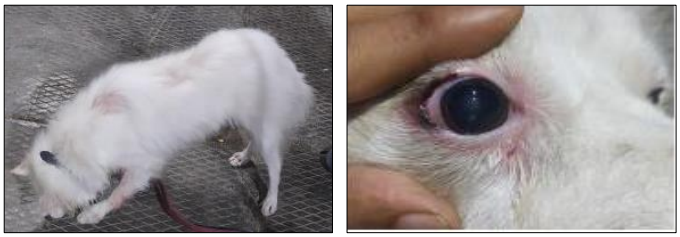

Fig 2: Ataxia and Dilatation of Pupil (Mydriasis).

Table 1: Haematological alteration before and after treatment

	Parameter unit	Unit	Before treatment	After treatment	Reference value
Haematological changes	Haemoglobin	gm%	11.4	10.8	11.9-18.9
	PCV	%	34.3	32.7	35-57
	Total erythrocyte count	$\times 10^6/\mu l$	4.80	4.42	4.95-7.87
	Total leucocyte count	$\times 10^3/\mu l$	50.1	10.46	5.0-14
	Neutrophiles	%	86	65	58-85
	Lymphocyte	%	12	28	8-21
	Monocyte	%	2	5	2-10
	Eosinophils	%	0	2	0-9
	Basophiles	%	0	0	0-1
	Platelet	$\times 10^3/\mu l$	506	447	117-460

Table 2: Biochemical alteration before and after treatment

	Parameter unit	Unit	Before treatment	After treatment	Reference value
Biochemical changes	SGPT	IU/L	57.3	64.8	10-109
	SGOT	IU/L	34.6	32.7	13-60
	Total protein	mg/dl	6.32	5.87	5.45-7.5
	Albumin	mg/dl	2.91	3.14	2.3-3.1
	Globulin	mg/dl	3.41	2.73	2.7-4.5
	Blood urea nitrogen	mg/dl	16.9	18.5	8-28
	Creatinine	mg/dl	1.2	0.97	0.5-1.7

Treatment

1. 20% lipid emulsion (Intralipid) @ 1.5 mL/kg body weight, IV over 10 minutes followed by constant rate infusion @ 0.25ml/kg/h, OD for 4 days (Clarke *et al.*, 2011) [2].
2. Isotonic crystalloid solution (0.9% NS) @ 30ml/kg body weight IV BD for 4 days
3. Neostigmine @ 0.05 mg/kg body weight SC repeated 6 hourly,
4. Dexamethasone @ 0.25-0.5 mg/kg body weight IM BD, for 3 days
5. Ceftriaxone sodium @ 20 mg/kg body weight IV BD for 4 days.
6. Activated charcoal @1 g/kg body weight given once orally.
7. There are no specific antidotes for this type of toxicosis. Hence, intravenous administration of lipids is a relatively new approach in managing toxicity from lipophilic compounds. This method has been utilized in human medicine for treating toxicity from lipophilic local anesthetics and cardiotoxic drugs, often resulting in a significant improvement in the patient's clinical status (Bates *et al.*, 2013) [1].

Discussion

Ivermectin is a macrocyclic lactone widely used in both small and large animal practices. It is part of the avermectin family of compounds and is derived from the bacterium *Streptomyces avermitilis*. The drug's high efficacy in preventing and treating internal and external parasites at low doses accounts for its broad safety margin (Canga *et al*, 2009) [3]. Ivermectin works by enhancing the activity of glutamate-gated chloride channels and g-aminobutyric acid-gated chloride channels in the nervous system, leading to functional abnormalities (Wolstenholme and Rogers, 2005) [7].

Intra Lipid Emulsion (ILE) (Fig.4) is increasingly being used in both human and veterinary toxicology as a treatment for intoxication with lipid-soluble drugs. There are two main theories regarding the possible mechanisms of action of Intra lipid emulsion. The first theory suggests that the lipid, in the form of ILE, serves as an energy substrate for the heart. In instances of cardiovascular collapse due to substances like local anesthetic agents, the enhanced supply of myocardial

energy substrate can improve cardiac performance. The second, and more widely accepted theory, is known as the "lipid sink" theory. According to this theory, when supraphysiologic doses of ILE are administered, the drug is partitioned into a lipid compartment in the bloodstream based on its lipid solubility (Fernandez *et al.*, 2011) [4]. After 5 days of cautious therapy with ILE and other supportive drugs the dog's condition improved significantly with good recovery and was back to normal (Fig.5).

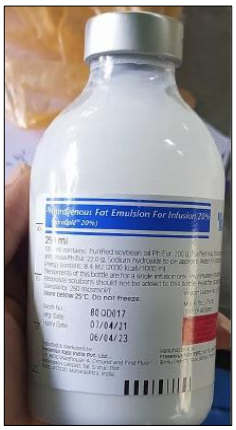

Fig 4: Intralipid Emulsion

Fig 5: Recovered dog after 5 days of treatment with ILE.

Conclusion

Intravenous Lipid Emulsion (ILE) is generally considered a safe treatment method that could be taken into account for various toxicities causing neurological or cardiovascular instability in the field of veterinary medicine. This therapy could be a potential game-changer in handling such critical situations.

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