

Case Study

<https://doi.org/10.20546/ijcmas.2018.704.225>

Therapeutic Management of Ivermectin Toxicity in a Calf: A Case Report

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ABSTRACT

Keywords

Ivermectin toxicity,
Salivation, Ataxia,
Labored breathing

Article Info

Accepted:

16 March 2018

Available Online:

10 April 2018

A one-month-old, 30 kg calf was presented to Referral Veterinary Polyclinic ICAR-IVRI, Bareilly, with the history of anorexia, salivation, dullness, ataxia, laboured breathing and administration of bolus having a combination of fenbendazole (3000mg) and ivermectin (100mg). Clinical examination revealed pale mucous membrane, mydriasis, the absence of pupillary and menace reflex, sticky salivation, normal body temperature, tachycardia, tachypnoea, dull, depressed, sudden fall with tremors, abnormal posture and gait. Based on the history of overdosing of ivermectin drug and clinical signs presented by the animal the case was diagnosed as ivermectin toxicity. Due to the unavailability of specific antidote (picROTOXIN, physostigmine) the case was managed by administration of Activated Charcoal@ 2g/kg BW PO TID, Diazepam@ 0.5 mg/kg bid up to the disappearance of clinical signs. Aggressive fluid therapy was given to the animal for three days. Supportive treatment included inj theophylline @ 6.6mg/kg BW IM, inj Vitamin B- complex with liver extract (3ml IM), inj chlorpheniramine maleate(Avil)@ 0.5mg/kg BW IM daily for five days. The slight improvement was seen in calf after three days and complete recovery after the fifth day of the treatment.

Introduction

Ivermectin is a macrocyclic lactone comes under avermectin group is a fermentation product of Actinomycete, *Streptomyces avermitilis*, it is a mixture comprising 80% 22,23-dihydroivermectin B1a and 20% 22,23-dihydroivermectin B1b. It is very potent nematocide and endectocide but is not having activity against tapeworm and flukes (Prasad

et al., 2006). It has a wide action against flies and larvae of parasitic dipteran flies (Campbell *et al.*, 1984; McKellar *et al.*, 1996). In mammals, macrocyclic lactones bind with gamma- aminobutyric acid type A – gated chloride channels of GABA A receptors (Sieghart *et al.*, 2006). MLs binds with GABA A receptors in different sites than benzodiazepines, barbiturates, picROTOXINS in the GABA receptor (Sieghart *et al.*, 1995). In

overdoses, enough MLs permeates the blood-brain barrier that binds to GABA A receptors, as well as to glycine and voltage-gated chloride channels (Bloomquist *et al.*, 2003; Trailovic *et al.*, 2011). The preceding opening of chloride channels leads to chloride influx causes hyperpolarization and decreased firing of excitatory neurons develop clinical sign. Lower concentrations of avermectins cause excitatory signs (tremor, convulsion) due to reducing GABA effects. Gradually increase the concentration of avermectins leads to enhance GABA effect that leads to a progressive ataxia and CNS depression (Bloomquist *et al.*, 2003). So avermectins may have CNS stimulatory effect at lower concentration and inhibitory effect (ataxia, depression) at higher concentration (Merola *et al.*, 2012).

Case Report and Result

A one-month-old non-descript calf weighing 30 kg was admitted to Referral Veterinary Polyclinic of IVRI, Izatnagar with the history of anorexia, salivation, dullness and ataxia. Managemental history from owner showed administration of bolus having the combination of ivermectin (100mg/bolus) and fenbendazole (3000mg/ bolus) when the calf was showing signs of inappetence, soil licking, reduced water intake and abdominal pain. Clinical examination showed pale and cyanotic mucous membrane, mydriasis, severe weakness, dull and depressed, hypermetria and ataxia while walking and preferred recumbency with abnormal posture for a long time. Examination of the head revealed sticky salivation, slight nasal discharge, the absence of pupillary light reflex and menace reflex, normal body temperature (100.7°F), tachycardia (115/min) and tachypnoea (30/min). Distant examination of calf showed shivering, tremors and incoordination of gait while walking and abnormal posture during recumbency and a few sticky faeces with

mucus and yellowish coloured urine were observed in the calf.

Haematological examination

Haematology revealed leukocytosis ($28 \times 10^3/\text{cmm}$), accompanied by slight neutrophilia and monocytosis, normal erythrogram (TEC- $9 \times 10^6/\text{cmm}$, Hb – 13 gm/dl) and normal thrombocyte ($420 \times 10^6/\text{cmm}$) count. On the basis of history and clinical signs, the case was diagnosed as Ivermectin toxicity because the margin of safety is much higher for fenbendazole than ivermectin for the calf. The calf was treated with Activated charcoal @ 2g/kg BW PO TID for one day, Diazepam @ 0.5 mg/kg twice in a day, IV up to the disappearance of signs. Aggressive fluid therapy Rintose @ 50ml/kg BW IV OD was given to the animal for three days. Supportive treatment included liver extract with vitamin B complex (B1+B2+B6+B12) @ 3ml IM, chlorpheniramine maleate @ 0.5 mg/kg BW IM and Theophylline @ 6.6 mg/kg BW IM BID for five days. Recovery from all clinical parameters was started after three days of treatment. Calf started taking milk from the third day of treatment with normal defecation and urination. Pupillary light reflex and menace reflex, mydriasis, salivation and nasal discharge were slightly cured after the 3rd day of successive treatment but slight ataxia was shown by the calf. Complete recovery was seen after the fifth day of treatment.

Discussion

Ivermectin is a GABA agonist which causes paralysis in susceptible arthropods and nematodes. It has been used for psoroptic mange, lice and Hypoderma larvae infestation in cattle. The activity of GABA finds only in the CNS and it does not readily cross the blood-brain barrier (Merck manual 11th edition). Avermectin induces paralysis via

glutamate-gated Cl⁻ channels which are only present in invertebrates (Arena *et al.*, 1995; Cully *et al.*, 1996). Avermectins have the affinity with GABA receptors in invertebrate receptors is about one hundredfold higher than the mammalian brain (Schaeffer and Haines, 1989). Ivermectin probably binds to glutamate-activated Cl⁻ channels found in nematode nerve or muscle cells, which causes hyperpolarization by increasing permeability of chloride ions through the cell membrane; this results in paralysis of the parasite (Ikeda, 2003). The multidrug resistance gene (MDR 1) encoded to the P-glycoprotein pump which is present in intact Blood-Brain Barrier and protects from the neurotoxic effects of ivermectin (Wolstenholm *et al.*, 2005; Schinkel *et al.*, 1996). Ivermectin has minimum 10 fold Margin of safety than normal dose 0.2 mg/kg (Oral/SC) in adult cattle. Acute toxic signs are CNS depression, listlessness, ataxia, recumbency followed by death (Prasad *et al.*, 2006). Calves can show toxic symptoms in only three times of the

therapeutic doses of ivermectin, Toxic signs are ataxia, hypermetria and tremor and Colics. Generally, young animals are more sensitive to overdosing, react strongly and the prognosis is poorer than for adult animals (WHO Acute Hazard classification). Overdose of both fenbendazole and ivermectin amalgamation was reported in the calf but the margin of safety is higher for fenbendazole than ivermectin. The oral administrative dose of fenbendazole to cattle @ 7.5gm/ kg body weight was not causing any adverse effect (Prasad *et al.*, 2006). Avermectins may have stimulatory CNS effects (tremors) at lower concentrations but inhibitory effects (ataxia, depression) at higher concentrations (Merola *et al.*, 2012). Ivermectin toxicity produces signs in animals are mydriasis and depression followed by ataxia, recumbency and death (Canga *et al.*, 2007; Prasad *et al.*, 2006). Ivermectin toxicity is pursued GABA mediated cholinergic effects leading to symptoms like salivation, dyspnoea, diarrhoea and ataxia in calves (Basudde, 1989).

Haematological examination

Haematological parameter	0 day	Reference range (Merck veterinary manual 11 th edition)
Hb (g/dl)	13	8.0-15.0
PCV (%)	30	24-46
TEC (X10 ⁶ /cmm)	9	5.0-10.0
TLC (10 ³ /cmm)	28	4.0-12.0
Neutrophils %	48	15-45
Lymphocytes %	43	48-75
Monocytes%	9	2-7
Eosinophils%	0	2-15
Basophil%	0	0-2
Platlet count (million/cmm)	420	100-800

Fig: On the day of clinical examination



Fig.1 Recumbency

Fig.2 Mydriasis

Fig.3 Ataxia

The severity of toxicity depends on the route of administration and pharmacokinetic properties. Ivermectin is highly fat soluble, have a large volume of distribution, and gathering in fat tissue resulting in a long elimination half-life (Vercruyssen *et al.*, 2002; Chittrakarn *et al.*, 2009). Subcutaneous administration of ivermectin delay's absorption than the oral route, but leads to an overall higher availability in plasma, a longer duration of action, and better efficacy (Molento *et al.*, 2004). The ivermectin area under the plasma concentration-time curve (AUC) obtained after oral administration of the ivermectin at 0.2 mg/kg/Body Weight ($2476 \text{ ng d ml}^{-1}$) was higher than subcutaneous administration (459 ng d ml^{-1}) (Lanusse *et al.*, 1997). In cattle, plasma concentrations of 0.5–1 ng/mL are required for optimal anthelmintic activity against most gastrointestinal and lung nematodes (Lifschitz *et al.*, 1999b); plasma concentrations of 0.5 ng/mL also control *Hypoderma spp.* flies (Alvinerie *et al.*, 1994). Also, intra-ruminal administration of ivermectin in cattle exposed that the bioavailability was 26% of that following subcutaneous administration (Chiu *et al.*, 1990). Current studies show that ivermectin is not metabolised in the rumen (Andrews *et al.*, 1996). In intestinal epithelium presence of P-glycoprotein responsible for comparatively less bioavailability by oral route administration (McKellar *et al.*, 1996; Molento *et al.*,

2004). CYP3A4 finds in liver and intestine is the main isoform of the P450 enzyme responsible for ivermectin metabolism (Zeng *et al.*, 1998). In liver and in the intestine CYP3A4 enzyme is responsible for the metabolism of many drugs (Lown *et al.*, 1993; Thummel *et al.*, 1996). A large fraction of administered ivermectin is excreted in the faeces and the concentration of ivermectin in dung over time is dependent on its route of administration (Herd, 1995). In cattle, 80 percent of the dose administered by subcutaneous injection is excreted in the dung during the first 35 days post-treatment (Sommer *et al.*, 1992). Before administering new formulations of endectocide compounds results in special importance to the evaluation of pharmacokinetic behaviour and faecal excretion profiles of that drug. The investigation into the environmental impact, concerning pasture-land ecology is extremely important because the impact of faecal excreted ivermectin lead to potential effects on insect populations and dung degradation (Lumaret *et al.*, 1993). In livestock administered ivermectin is partially excreted through the faeces and caused bad impact and hampers to development and fertility of coprophagous invertebrates (fly larvae, dung beetles, etc.) populations, which feed or breed on the dung of livestock. However, it prevents normal dung decomposition and recycling, has not been demonstrated (WHO Acute Hazard classification).

Ivermectin toxicity is result of faulty managemental practices by dairy farmer. Due to lack of specific antidote such toxicities could be managed by supportive therapy and monitoring of patient till complete clinical recovery. Indiscriminate use of ivermectin leads to harmful effect on environmental health and life cycle of many useful organisms so judiciously use of the drug because it affects not only livestock health but also all living systems.

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How to cite this article:

Pankaj Kumar Patel, Sawita Kumari Patel, Sonam Bhatt, Desh Deepak, Arun Prabhakar, Brijesh Patel, Chandrama Rabha and Dixit, S.K. 2018. Therapeutic Management of Ivermectin Toxicity in a Calf: A Case Report. *Int.J.Curr.Microbiol.App.Sci.* 7(04): 1964-1969.
doi: <https://doi.org/10.20546/ijcmas.2018.704.225>