Clinicobiochemical changes in ivermectin toxicity in Doberman pinscher pups

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Abstract This study is based on naturally intoxicated Doberman pinscher pups. Six Doberman pinscher pups were overdosed 50 times of recommended ivermectin dose by the pet owner and presented to Referral Veterinary Polyclinic section of this institute in a state of coma. The pups were unable to hold their head up and had no pupillary reflex. The pups were examined clinically and samples of blood were taken for haemato-biochemical studies, before and after treatment. During intoxication there was marked haemoconcentration, increase in values of serum creatinine phosphokinase, gamma glutamyl transpeptidase but decrease in serum glucose levels. These pups were treated with isotonic dextrose normal saline, 1.0 mg/kg physostigmine and 3 mg/kg dexamethasone. Clinical improvement occurred in remaining 2 pups after 12 h of treatment. These pups were able to take a liquid diet after 3 day and became clinically normal after 2 week. The serum biochemical values gradually reached to normal in recovered pups after 2 weeks of treatment. It took a month for complete recovery from depression and blindness.

Keywords Doberman pinscher pup · Ivermectin · Overdosed · Therapeutic management

Introduction

The ivermectin is a potent and board spectrum antiparasitic drug that is extensively used in dogs in India since last 20 years (Grover et al. 2001) in spite of its only indication for heart worms in dogs (Blagburn et al. 2011). Due to ivermectin's effectiveness for endo—and ecto—parasites, some pet owners use it without the direction of registered veterinary practitioner. Such indiscriminate use of ivermectin to dogs can become life threatening in canine. Clinical and haematobiochemical changes are helpful in clinical assessment and motoring treatment. It provides the guideline for supportive therapy and other life saving measures required to be undertaken in critically ill or intoxicated patient. A little is known about the clinical and haematobiochemical picture of ivermectin intoxicated dogs. We report here the clinicobiochemical changes and the therapeutic care of ivermectin intoxicated Doberman pinscher pups.

Materials and methods

Six naturally intoxicated Doberman pinscher pups of the same litter were served as the animals for this study. These animals were admitted to the Referral Veterinary Polyclinic with a history of being dosed with 10,000 µg/kg subcutaneously of the ivermectin product used in cattle. After 4–6 h of injection, the owner observed severe depression, ataxia, recumbency, failure to rise, holding the head in improper positions, and blindness in all the medicated pups. A thorough clinical examination of all the pups was performed (Kelly 1984). Haematological examination was done following standard techniques (Jain 1986) Samples of blood were collected in sterilized tubes for serum before initiation

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of therapy for serum biochemical studies (Coles 1986). Total protein and albumin were estimated following the methods of Doumas 1975. The concentration of glucose (Teitz 1995), blood urea nitrogen (Wybenga et al. 1971), creatinine (Frankel et al. 1970), bilirubin (Zilva and Pannall 1979), and activity of creatinine phosphokinase (Moss and Henderson 1999), and gamma glutamyl transpeptidase (Tate and Meister 1985.) were estimated using commercial kit (SPAN diagnostic Ltd., Surat, India).

Statistical analysis

The data were analysed statistically using one way ANOVA and student's test was applied to determine effects of therapy (Snedecor and Cochran 1994).

Results

The detailed clinical examination revealed, severe depression, inability to rise, or hold the head up and mydriasis. Two pups were in severe depression almost to the stage of coma. Rectal temperatures ranged between 36.7 and 37.0 °C. There was absence of pupillary reflex, decreased proprioception and positioning and muscular hypotonicity. The pups revealed bilateral mydriasis with absence of pupillary reflex. The visible mucous membranes were dry and devoid of haemorrhages. There was marked haemoconcentration, increase in values of serum Creatinine phosphokinase, gamma glutamyl transpeptidase and lactic dehydrogenase levels but decrease in serum glucose levels (Table 1). There is no published report on Haemato biochemical alterations in ivermectin toxicity therefore our results could not be compared.

Based on history (i.e. overdose of ivermectin), the physical examination results and the biochemical findings the pups were treated immediately with supportive care consisting of intravenous perfusion of isotonic dextrose normal saline (0.9 % sodium chloride + 5.0 % dextrose) at 3 ml/kg body weight. The amount of fluid was calculated based on degree of dehydration and daily body requirements. Intravenous fluid therapy was continued until the pups started taking oral feed and water.

Clinical improvement was recorded on day 2 and pups were with a rectal temperature of 37.6 °C and normal skin pliability. The PCV was 34 % on day 2 and were able to sit but could not hold their heads in proper position without support. The pups were able to walk with support on day 3 of treatment, but blindness and limb weakness persisted. The treatment remained unchanged till 72 h. Thereafter dexamethasone was added at 0.20 mg/kg once daily for 3 days, followed by 0.20 mg/kg on alternate days for 4 dosing. The pups' physical condition improved gradually. It took about 2 weeks to become clinically normal and 1 month for complete recovery from depression and blindness to occur.

Discussion

Ivermectin is effective against a wide range of nematode and arthropod parasites (Booth and McDonald 1988). The drug is extensively used in dogs as an antiparasitic drug in India ignoring its recommendation of restricted use for canine heartworm diseases in developed countries (Paul and Tranquilli 1998). It is unfortunate that in India the same product is indicated for a number of species of animals (cows, buffaloes, sheep, goat and dogs) The product

Table 1 Haemato biochemical changes in ivermectin intoxicated Pups

Parameter	Days post treatment		
	0	7	14
Hb (g %)	14.00 ± 0.35	11.00 ± 0.70**	12.00 ± 0.70*
PCV (%)	48.50 ± 0.76	34.00 ± 1.41**	34.50 ± 1.06**
Total protein (g/dl)	6.10 ± 0.29	4.80 ± 0.42*	5.63 ± 0.28
Albumin (g/dl)	3.40 ± 0.30	2.85 ± 0.18*	3.15 ± 0.25
Glucose (g/dl)	64.50 ± 3.49	84.42 ± 3.53**	85.56 ± 2.47**
BUN (mg/dl)	28.54 ± 0.90	24.32 ± 2.82	28.41 ± 1.98
Creatinine (mg/dl)	1.57 ± 0.19	1.15 ± 1.41	0.88 ± 0.07**
Bilirubin (mg/dl)	1.34 ± 0.15	1.17 ± 0.21	0.93 ± 0.02**
CPK (U/L)	969.5 ± 15.69	309.5 ± 8.13**	271.5 ± 10.96**
GGT (U/L)	52.97 ± 1.47	36.88 ± 1.41*	41.53 ± 2.47*
LDH (U/L)	361 ± 13.82	239 ± 12.02**	130.52 ± 3.89**

*, ** Denotes values differ significantly at ($P \geq 0.05$) and ($P \geq 0.001$) respectively when compared with 0 day value

intended for use in cows and buffalo, the solvent glycerol formal is often used and can account for some of the manifestations of toxicity seen here. The dosage of ivermectin for dogs is 200 µg/kg body weights by subcutaneous route and for heartworm 6 mcg/kg orally. It is generally not indicated in animals below 3 months of age.

These pups were overdosed with more than 1600 times than recommended dose. Acute ivermectin toxicity has been reported at oral dose of 2500 µg/kg BW and death due to severe toxicity has reported at oral dose of 40,000 µg/kg BW. However there is a lot of variation in LD₅₀ of ivermectin and, breed and age influences greatly the safety of this drug in canine. In the present case, only 2 pups survived. The injected toxic dose, delay in presentation for treatment and young age are few prime factors for death of the 4 pups. Ivermectin toxicities have been reported in collies (Paul and Tranquilli 1998) and German shepherd breed of dogs (Upendra et al. 1995). Genetic predisposition and permeability of blood brain barrier to ivermectin in these breeds are incriminated as cause of toxic effects. Dutch national centre for information on poisoning also recorded 25 incidence of ivermectin toxicity in dogs and reported ivermectin as a dangerous drug for dogs (Wijnands-Kleukers and Fink-Gehrmann 1996). Ataxia, mydriasis and coma have been reported by earlier workers in ivermectin toxicity (Barragry 1994), but limb hypotonia and increased CPK and LDH in serum were not reported.

This treatment of ivermectin toxicity could save 50 % of the treated pups. Perhaps delay in presentation of the pups to this polyclinic could have complicated the cases which leads to death, such type of complications generally happen in poisoning case. It took nearly 2 weeks for clinical recovery in these pups and almost 1.0 month to overcome the depression and vision abnormality. Dexamethasone was administered to rectify the eye problems and was found beneficial in reducing clinical signs of mydriasis. Ivermectin produces its anti-parasitic action by potentiating release and binding of gamma amino butyric acid (GABA) at certain nerve synapses (Campbell 1985). In nematodes and arthropod GABA mediated transmission occurs in peripheral synapses while in mammals, GABA mediated transmission occurs only in central nervous system where ivermectin normally could not enter due to its macro molecular size (Campbell and Benz 1984). Increased permeability of blood brain barrier and even a specific protein receptor in brain attracts the ivermectin in certain breed of dogs. However, in ivermectin toxicity inflammation of central nervous system has been reported (Upendra et al. 1995; Campbell 1985). It could be possible that during inflammation of central nervous system the ivermectin or its metabolites entered into CNS and produced these toxic effects. Marked improvement of conditions after the use of dexamethasone also indirectly

indicates presence of inflammatory conditions of CNS in these intoxicated pups.

Supportive therapy given to these pups has managed catabolic processes in addition to restoration of fluid and electrolyte balances, nutrient support and kidney function. Use of dexamethasone in the present study was found beneficial in ivermectin toxicity.

Overdose of ivermectin can cause severe depression, coma, mydriasis and limb hypotonia in pups. Marked haemoconcentration, increase in values of serum Creatinine phosphokinase, gamma glutamyl transpeptidase and lactic dehydrogenase levels but decrease in serum glucose levels is some of the salient haemato-biochemical changes in ivermectin toxicity. Dexamethasone along with fluid therapy was useful in management of such cases. To avoid such cases ivermectin preparations for cattle should not be used in dogs.

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Compliance with ethical standards

Conflict of interest There is no conflict of interest. All the authors have gone through the content, authorship and recommended the manuscript for publication.

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