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RESEARCH ARTICLE

STUDYING OF NEUROTOXIC EFFECTS OF IVERMECTIN ON DOMESTIC PIGEONS

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ABSTRACT

This study aimed to cover a part of neurotoxic effects of Ivermectin on domestic pigeons, for this purpose the up and down method were utilized to determine the intramuscular median lethal dose of Ivermectin in pigeons, functionally observed markers were used to illustrate the behavioural changes that caused by Ivermectin to each injected pigeon in addition to motor behavioural reflexes. The results of 24 hours intramuscular median lethal dose was 84.4 mg/kg, about 4-8 hours were needed to appearance of toxicosis, signs were ataxia, unilateral laying against the surface, slight to total mobility impairment, mild disturbance in muscular tone ranged from hypotonia to atonia, with passive resistance to catch, on the other hand there was absence in all examined reflexes (click, palpebral and righting). In conclusion, Ivermectin has moderate neurotoxic effect on domestic pigeons; it exhibits inhibitory central and peripheral impacts via dual Gabaergic and Glycinergic neural pathways.

INTRODUCTION

Ivermectin is a high molecular weight natural product macrocyclic lactone produced by the Actinomycete, *Streptomyces avermitilis* (Vercruysse and Rew, 2002). It is one of the most effective and widely used anti-parasitic agents ever discovered because of its' broad spectrum activity against numerous endo and ectoparasites, especially nematodes and arthropods (Geary, 2005; Omura, 2008). The antiparasitic effect of Ivermectin exerts through high affinity binding to glutamate-gated chloride ion channels in peripheral neurons leading to paralysis of motor activity and pharyngeal pumping mechanism, consequently death of parasite (Yates *et al*., 2003; Wolstenholme and Rogers, 2005). This scenario cannot happen in mammalian hosts due to absence of these channels (Raymond and Sattelle, 2002), but it still classified as a moderate neuro-etho-toxicant in mammalian (Dull and Meredith, 1998). Birds suffer from different parasitic infestations like mammals and one of recommended therapeutic agents is Ivermectin whom used via intramuscular, topical, subcutaneous and oral routes to treat some nematodes, mites, lice, and some coccidial infestations. (Ritchie *et al*., 1999). Information about Ivermectin neurobehavioral toxicity is still not enough, so that this study aimed to discover the neurotoxic effects of different doses of Ivermectin on domestic pigeon as a model for this study.

MATERIALS AND METHODS

Pigeons *Culumba livia*, were used and they purchased from local market in Baqubah City, Diyala province, Iraq, with average body weight of (200-250) gm. They were caged in (100x60x 80 cm) cages in the laboratory animal house at the College of Veterinary Medicine - University of Diyala. Birds were kept for a week for adaptation before the experiment; both of water and feed were provided *Ad* libitum. Ivermectin (2%, Doxal, Italy) was used in this study, choosing of doses was based on determining of acute (24 hrs) median lethal dose (LD_{50}) of intramuscularly injected Ivermectin according to up and down method (Dixon, 1980) this method was modified for dual purposes in determining of median lethal dose and in studying of Ivermectin neurotoxicosis (Mohammed *et al*, 2012) and (Mousa and Mohammad, 2012). Each bird was keep watched for 1hrs in order to obtain the behavioural markers and body reflexes of neurotoxicosis then for the rest of the 24hrs for lethality recording. Recorded neurotoxic markers were analysed and scored according to what mentioned in (Appendix 1) (Krejcova and Kassa, 2004) and (Durrani *et al*, 2008), while neurological reflexes were determined according to (Durrani *et al*, 2009) and (Azizpour, and Hassani, 2012).

RESULTS

The results of acute intramuscular median lethal dose of Ivermectin in pigeons was 83.4 mg\kg the utilized time for appearance of neurotoxicosis signs was 4 – 8 hours, starting dose was 100 mg/kg while the last injected dose was 80 mg/kg and the number of utilized pigeons was six individuals. The examined behavioral markers were: Bird gait which ranged from ataxia to unilateral laying against the surface, Bird mobility which ranged from slight to total mobility impairment, Bird muscular tone which ranged from hypotonia to atonia, and while there was passive difficulties in catch resistance (Table 2). The examined pigeons' body reflexes

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were the palpebral reflex which was absent in all used doses but 60 mg/kg, the same result were detected when the click reflex was examined, while there was complete absence in righting reflex with all used doses of this study (Table 3).

Table 1. Determination of the 24 hrs median lethal dose (LD_{50}) of Ivermectin in local pigeons by the up and down method

Variable	Results
Ivermectine	
LD_{50}	83.38 ≈ 83.4 mg\kg (i.m.)
Range of used doses	100-60 mg\kg (i.m.)
Initial dose	100 mg\kg (i.m.)
Last dose	80 mg\kg (i.m.)
Number of Pigeons used	6 (XXOXOO)
Increase or decrease among doses	20 mg\kg (20% of initial dose)
Range latency to the onset of poisoning	4 – 8 hrs. (range 6 hrs)

Table 2. Scored behavioural markers of toxicosis that caused by Ivermectin

Dose (mg\kg BW.)	Functional Observed markers				Bird Viability
	Gait	Mobility	Muscular tone	Catch difficulty	
100	4	4	-2	1	X
80	1	3	-1	1	X
60	1	2	-1	1	O
80	1	3	-1	1	X
60	1	2	-1	1	O
80	1	3	-1	1	O

O= Survive, X= Dead

Table 3. Response of pigeons' body reflexes to different Ivermectin doses

Dose (mg\Kg BW.)	Reflexes		
	Palpebral reflex	Click reflex	Righting reflex
100	-	-	-
80	-	-	-
60	+	+	-
80	-	-	-
60	+	+	-
80	-	-	-

(+) Body reflex present, (-) body reflex absent

Appendix 1. Functionally observed markers

Scores	Markers			
	Gait	Mobility	Muscular tone	Catch difficulty
-2			Atonia	
-1			Hypotonia	
0	Normal		Normal	
1	Ataxia	Normal	Hypertonia	Passive
2	Walking on tip toes	Slightly impaired	Rigidity	Normal
3	Hunched body	Moderately impaired	Fasciculation	Escape
4	Unilateral laying	Totally impaired		Flight

DISCUSSION

Ivermectin exhibits a broad-spectrum antiparisitic activity against gastrointestinal and lung nematodes as well as ectoparasites of clinical practice in domestic animals and birds (Mirhadi *et al*., 2011 and Suárez *et al*., 2013). Much of this success can be attributed to Ivermectin high therapeutic index (Dunn, 2010) which can be attributed in its turn to the high affinity of Ivermectin to bind with glutamate-gated chloride ion channels (Wolstenholme and Rogers, 2005), which found only in protostome invertebrate phyla (Wolstenholme, 2012). All what mentioned above about Ivermectin safety and selective toxicity is still not enough to exclude Ivermectin from the list of the neurotoxicant pharmaceuticals (Plumlee, 2004), where as the results that listed in (Table 1) showed moderate toxicity of Acute intramuscular median lethal dose of Ivermectin in pigeon which was 83.4 mg\kg and the onset of poisoning was happen within 4-8 Hrs. This moderate toxicity did not result from interaction between Ivermectin and glutamate-gated chloride ion channels, because simply they are not exist in pigeon already (Wolstenholme, 2012) but it resulted due to interaction between Ivermectin and GABA- gated chloride ion channels, since these channels represent the secondary target to Ivermectin (Dunn *et al*., 2011). These channels selectively conducts Chloride ion through their pores, resulting in hyperpolarization of the neuron. This causes an inhibitory effect on neurotransmission by diminishing the chance of a successful action potential occurrence. (Santhakumar *et al*., 2007) This interaction can be achieved by using high doses of Ivermectin, because these doses possibly provoke Ivermectin penetration to blood brain barrier through inhibition of p-glycoprotien, (which is highly restrict the entry of Ivermectin into the brain) leading to accumulation of Ivermectin in the brain and provoking of severe signs of neurotoxicosis and even death (Geyer, *et al*., 2009) Behavioral marks of Ivermectin toxicosis were: Ataxia, unilateral laying against the surface, slight to total mobility impairment, mild negative disturbance in muscular tone ranged from hypotonia to atonia, and passive catch difficulties (Table 2). In addition to absent of click, palpebral and righting reflexes (Table 3) All these marks give evidences to interaction between Ivermectin and GABA- gated chloride ion channels, Because these channels are abundantly distributed in pigeons' midbrain part which responsible of vision, hearing, arousal, sleep-wake, temperature regulation and motor control (Veenman *et al*., 1994) (Breedlove *et al*., 2010) also high doses of Ivermectin can irreversibly activate Glycine gated chloride ion channels in the motor neuron which located in ventral horn, consequently, interruption of all peripheral motor functions (Webb and lynch, 2007). In conclusion, Ivermectin has moderate neurotoxic effect on domestic pigeon; it exhibits inhibitory central and peripheral impacts via dual Gabaergic and Glycinergic neural pathways.

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