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≪Research Note≫

Acute Toxicity and Neurobehavioral Effects of Diphenhydramine in Chicks

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The present study was undertaken to examine the acute toxicity (LD50) and neurobehavioral manifestations in the open-field activity and tonic immobility tests in 7-14 day-old chicks treated with the H1-receptor antagonist diphenhydramine. Plasma and whole brain cholinesterase activities were also determined in the chicks. The LD50 of diphenhydramine in chicks was 49.3 mg/kg, intramuscularly (i.m.). The signs of diphenhydramine toxicosis in the chicks which appeared within one hour after injection included excitation, jumping, whole body tremor, ataxia, gasping, frequent defecation, paralysis and recumbency. Fifteen minutes after i.m. injection, diphenhydramine at 2.5 and 5 mg/kg decreased the general locomotor activity of the chicks in the 5-min open-field activity test, as seen by a significant increase in the latency to move from the center of the open-field arena and decreases in the numbers of lines crossed and escape jumps in comparison with control values. Diphenhydramine significantly decreased the frequencies of pecking and defecation only at 5 mg/kg when compared with respective control values. Diphenhydramine treatments at 2.5 and 5 mg/kg also significantly increased the durations of tonic immobility of the chicks and decreased their whole brain cholinesterase activity by 33 and 30%, respectively, in comparison with the control values. In conclusion, the data suggest that diphenhydramine induces central nervous system depression in chicks at doses below the LD50 value of the drug which is reported here for the first time.

Key words: Antihistamine, Behavior, Cholinesterase, Open-field, Tonic immobility

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Introduction

Diphenhydramine is an H1-receptor antagonist antihistamine widely used in veterinary and human medicines (Adams, 2001; Katzung, 2006). It possesses central and peripheral antihistaminergic and anticholinergic actions (Adams, 2001; Katzung, 2006). The reported side effects and toxic effects of diphenhydramine in man include dry mouth, blurred vision, somnolence, tachycardia, nausea or vomiting, nervousness and rarely convulsion (Jones *et al*., 1986; Simons, 1994; Radovanovic *et al*., 2000; Wahl, 2005; Skidgel and Erdos, 2006). The adverse effects of diphenhydramine in animals are hyperactivity or depression, hypersalivation, tachypnea and tachycardia (Tiwari and Sinha, 2010). Diphenhydramine overdose modulates the central nervous system (CNS) functions in a manner that may result in toxicosis (Wahl, 2005; Skidgel and Erdos, 2006; Scharman *et al*., 2006). Diphenhydramine enhances morphine-induced hyperactivity in mice (Sansone *et al*., 1987) and causes amnesia in mice (Galeotti *et al*., 2003). Mice or rats pretreated with relatively high protective doses of diphenhydramine (≥30 mg/kg, intraperitoneally or subcutaneously) prior to intoxication with anticholinesterases manifested nervousness, jumping behavior and hyperactivity (Mohammad *et al*., 1987; 1989; Faris and Mohammad, 1996a; 1997; Al-Baggou and Mohammad, 1999). Acute neurotoxic effects of diphenhydramine in mice are characterized by hyperactivity in the open-field test and increased stereotyped behavior of head bobbing, sniffing as well as biting and licking (Mohammad *et al*., 1999). The mechanism of neurotoxic effects of diphenhydramine is not clear. However, H1-antihistamines were reported to inhibit erythrocyte cholinesterase activity *in vitro* (Simon and Winter, 1970) and that of the plasma *in vitro* or *in vivo* (Fernandez *et al*., 1975; Faris and Mohammad, 1996b). Whether a similar inhibitory effect occurs on brain cholinesterase activity is not clear at present (Mohammad *et al*., 1999; 2002).

Diphenhydramine is continuing to attract research and clinical attentions as it is one of the leading drugs that cause poisoning in man (Scharman *et al*., 2006; Benson *et al*., 2010). Several recent studies evaluated the potential neurotoxicity and/or behavioral profiles of the drug in man or laboratory animals (Holger *et al*., 2002; Gupta *et al*., 2004; Khanwelkar *et al*., 2008; Van Ruitenbeek *et al*., 2010; Feltner and Haig, 2011). Diphenhydramine is also a potential alternative antidote against organophosphate and carba-

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mate insecticides poisoning, as it mainly reduces the muscarinic, nicotinic and CNS effects of cholinergic overstimulation (Mohammad *et al*., 1989; Faris and Mohammad, 1996a; 1997; Al-Baggou and Mohammad, 1999; Bird *et al*., 2002). The drug is clinically used in the avian species to counteract feather damaging behavioral cycle (Doneley and Doneley, 2010). H1-Antagonists can also be used in chickens intoxicated with organophosphate insecticides (Mohammad and Basher, 1995; Al-Shammary, 2008; Mousa, 2009). Hence, the safety and neurological effects of this antihistamine need to be examined furthermore and vigorously specially in laboratory animals including the chicks. In the context of the potential uses of diphenhydramine in the avian species and the interests on its neurotoxicity, the acute toxicity and neurobehavioral effects of diphenhydramine are not fully known in the chicken. The present study was undertaken to examine the acute toxicity (LD50) of diphenhydramine and its effects on neurobehavioral performances in the open-field activity and tonic immobility tests in 7−14 day-old chicks.

Materials and Methods

Day-old Cobb broiler chicks of either sex purchased from a local hatchery were used in the present study. They were maintained in batches of 30 chicks in cages with dimensions of 107×64×50 cm in a room with constant lighting at a temperature of 32−35℃. The floor litter consisted of wood shavings; water and feed were available *ad libitum*. Seven to fourteen days old chicks were used in the experiments.

Diphenhydramine HCl (obtained from the State Company for Drug and Medical Appliance-Samara, Iraq) was dissolved in physiological saline solution for intramuscular injection at a volume of 2 m*l*/kg body weight. The selections of the doses of diphenhydramine in the present study were based on our preliminary experiments in chicks and on the literature (Mohammad *et al*., 1989; Mohammad and Basher, 1995; Faris and Mohammad, 1996a, b; 1997; Mohammad *et al*. 2002). The Scientific Committee of the College of Veterinary Medicine at the University of Mosul has approved the present experiments in chicks. The experiments complied with institutional regulations addressing animal use, and proper attention and care were given to the chicks used in this study. For quality control purposes, we conducted each experiment on the diphenhydramine-treated chicks together with respective control birds manipulated in the same manner. All experiments were done between 9−12 A.M.

Determination of the Acute Median Lethal Dose (LD50) of Diphenhydramine

The acute (24 h) median lethal dose (LD50) of diphenhydramine was determined in the chicks by the up-and-down method (Dixon, 1980). Diphenhydramine was injected intramuscularly (i.m.) into the pectoris muscle at an initial dose of 60 mg/kg, with an increase or decrease in subsequent doses at 5 mg/kg. The chicks were individually observed for the appearance of signs of toxicosis for 1 h, and then the 24 h lethality was recorded. This experiment was concluded using only 6 chicks over a period of 6 days. The LD50 of diphenhydramine was determined so that the relative changes in the behavioral outcome and cholinesterase activities at the doses of diphenhydramine could be compared to a standard index of acute toxicity.

Behavioral Effects of Diphenhydramine

Twenty four chicks were randomly divided into three groups of eight birds each. The chicks were treated with either physiological saline solution at 2 m*l*/kg, i.m. (control) or with diphenhydramine at 2.5 and 5 mg/kg. These doses of diphenhydramine did not produce overt signs of toxicosis as found in a preliminary experiment. The open-field activity of each chick was monitored 15 min after the diphenhydramine administration (Mohammad and Faris, 2006; Al-Badrany and Mohammad, 2007). Each chick was placed alone on the center of the arena of an open field box (60×60×23 cm); the arena was divided into 16 equal squares and 50 g of wheat grains were scattered on the surface. In the open-field test the following behavioral responses were measured by two experimenters within 5 minutes as described earlier (Al-Baggou *et al*., 1999; Mohammad and Faris, 2006; Al-Badrany and Mohammad, 2007):

1. Latency to move from the center of the arena.
2. Number of lines crossed by both feet (ambulation).
3. Number of escape jumps.
4. Frequency of defecations.
5. Scoring of distress calls (vocalization):
   0: no calls
   1: 1−2 calls
   2: 3−4 calls
   3: 5 calls or ＞
6. Scoring of pecking behavior
   0: no pecking
   1: 1−2 times
   2: 3−4 times
   3: ≥5 times

After the open-field activity test, each chick was subjected to tonic immobility test (Hennig *et al*., 1984; Mohammad and Faris, 2006) by holding the chick in both hands and placing it on a wooden table for 15 seconds, the hands were then withdrawn and the chick was timed to upright itself and standing unaided.

In vivo Effect of Diphenhydramine on Plasma and Whole Brain Cholinesterase Activities

Thirty minutes after the diphenhydramine treatments mentioned above, the chicks were euthanized to obtain the plasma and whole brain for determining the cholinesterase activity by an electrometric method (Mohammad, 2007; Al-Badrany and Mohammad, 2007; Mohammad *et al*., 2008). The whole brain was homogenized on an ice bath by a glass homogenizer in a pH 8.1 barbital-phosphate buffer solution (1.237 g sodium barbital, 0.163 g potassium dihydrogen phosphate and 35.07 g sodium chloride/L of distilled water) at 3 m*l*//100 mg wet weight (Al-Badrany and Mohammad, 2007; Mohammad, 2007). To measure cholinesterase activity, the reaction mixture contained 3 ml distilled water, 0.2 m*l* plasma or whole brain homogenate and 3 m*l* of pH 8.1 buffer described above. Initial pH of the mixture (pH1) was meas-

ured with a glass electrode using a pH meter (Hanna, Romania), and then 0.10 m*l* of the substrate 7.5% acetylthiocholine iodide was added to the mixture which was incubated at 37℃ for 30 min. At the end of the incubation period, the pH of the reaction mixture (pH2) was measured. The enzyme activity in units of ΔpH/30 min was calculated as follows:

Cholinesterase activity (ΔpH/30 min)＝(pH1－pH2)－ΔpH of blank

The blank was without the plasma or brain homogenate sample. The % of cholinesterase inhibition was calculated as follows:

% Cholinesterase inhibition＝[Cholinesterase activity (without diphenhydramine)－Cholinesterase activity (with diphenhydramine)/Cholinesterase activity (without diphenhydramine]×100

Statistics

The parametric data as multiple means were statistically analyzed by the one way analysis of variance followed by the least significant difference test (Petrie and Watson, 1999). Non-parametric data were subjected to the Mann-Whitney-U-test (Petrie and Watson, 1999). The accepted level of statistical significance was at $p<0.05$.

Table 1. **Determination of 24-h median lethal dose (LD50) of diphenhydramine administered intramuscularly (i.m.) in chicks by the up-and-down method**

Variable	Result
LD50	49.3 mg/kg, i.m.
Range of the doses used	60−45＝15 mg/kg, i.m.
Initial dose	60 mg/kg, i.m.
Last dose	45 mg/kg, i.m.
Number of chicks used	6
Number of chicks died	4
Increase or decrease in dose	5 mg/kg, i.m.
Range of latency to onset of poisoning	1−2＝1 min

Results

The acute (24 h) LD50 of diphenhydramine in chicks was 49.3 mg/kg, i.m. (Table 1). The signs of diphenhydramine toxicosis in the chicks which appeared within one hour after injection included excitation, jumping, whole body tremor, ataxia, gasping, frequent defecation, paralysis and recumbency.

Fifteen minutes after treatment, the pattern of 5-min open-field activity of chicks injected with a single dose of diphenhydramine at 2.5 and 5 mg/kg, i.m. is shown in Table 2. Generally, diphenhydramine did not produce overt signs of toxicosis. However, both doses of diphenhydramine decreased the general locomotor activity of the chicks as seen by a significant increase in the latency to move from the center of the open-field arena and decreases in the numbers of lines crossed and escape jumps in comparison with the control values (Table 2). Diphenhydramine significantly decreased the frequencies of pecking and defecation only at 5 mg/kg when compared with respective control values (Table 2). Diphenhydramine treatments also significantly increased the durations of tonic immobility of the chicks in comparison with the control values (Table 2).

Diphenhydramine at 2.5 and 5 mg/kg, i.m. decreased plasma cholinesterase activity by 29 and 15%, respectively, in comparison with the control values (Table 3). But the reduction in plasma cholinesterase activity did not attain statistical significance. However, diphenhydramine treatments significantly decreased whole brain cholinesterase activity by 33 and 30%, respectively, in comparison with the control values (Table 3).

Discussion

The LD50 value of diphenhydramine (49.3 mg/kg, i.m.) is the first report of acute toxicity of this antihistamine in chicks. The toxic signs are characterized by excitatory and stimulatory effects before paralysis. We have used doses of diphenhydramine up to 20 mg/kg, i. m. in chicks without showing clinically overt adverse effects; and these doses were found to antagonize organophosphate poisoning in

Table 2. **Effects of diphenhydramine on 5-minute open-field activity and tonic immobility test in chicks**

Variable	Diphenhydramine (mg/kg, intramuscularly)		
	0 (saline-control)	2.5	5.0
Latency to move (seconds)	5.1±0.8	54.3±15.3*	59.5±9.2*
Lines crossed	32.3±4.0	8.9±2.2*	4.9±0.5*
Escape jumps	1.4±0.3	0.1±0.1*	0.0±0.0*
Distress calls (scores)	3.0±0.0	3.0±0.0	2.9±0.1
Pecking (scores)	2.0±0.3	1.0±0.4	0.1±0.1*
Defecations	1.3±0.3	0.8±0.3	0.4±0.2*
Duration of tonic immobility (seconds)	2.5±0.4	43.3±9.6*	51.0±4.4*

Values are mean±SE of 8 chicks/group. Each chick was subjected to open field activity test 15 min after the diphenhydramine injection, followed by the tonic immobility test.
* Significantly different from the respective control value, $p<0.05$.

Table 3. **Inhibition of plasma and whole brain cholinesterase activities in chicks treated intramuscularly with diphenhydramine**

Diphenhydramine (mg/kg)	Plasma		Whole brain	
	ΔpH/30 min	% inhibition	ΔpH/30 min	% inhibition
0 (saline-control)	0.48±0.07		0.33±0.02	
2.5	0.34±0.04	29	0.22±0.04*	33
5.0	0.41±0.03	15	0.23±0.03*	30

Cholinesterase activity values are mean±SE, $n=8$ chicks/group. Cholinesterase activity was determined 30 min after the diphenhydramine injection.
* Significantly different from the respective control value, $p<0.05$.

chicks (unpublished observations). Similarly, mice or rats can tolerate diphenhydramine up to 30 mg/kg, given intraperitoneally or subcutaneously (Mohammad *et al*., 1987; 1989; Faris and Mohammad, 1996a; 1997; Al-Baggou and Mohammad, 1998; 1999). However, the reported LD0 values of diphenhydramine (mg/kg) in rats are 500, orally and 475, subcutaneously, whereas in mice it is 164, orally and 127, subcutaneously (Barnes and Eltherington, 1973). This discrepancy in the LD50 values of diphenhydramine between rodents and chicks could be attributed to species variation and the routes of administration.

Diphenhydramine treatments at doses of 2.5 and 5 mg/kg, i. m. decreased general locomotor activity. These doses represent about 1/20 and 1/10 of the LD50 value of diphenhydramine in chicks, respectively. The decreases in open-field activity (delayed movement and decreased ambulation and escape jumps) and increased duration of tonic immobility induced by diphenhydramine in chicks suggest the CNS depressant action of the drug. Limited information is available on the pharmacological profile of diphenhydramine in birds. The present findings suggest that the lower doses of diphenhydramine (2.5 and 5 vs. the LD50 of 49.3 mg/kg, i.m.) could be depressant or sedative in chicks. Sedative agents such as metoclopramide (Al-Zubaidy and Mohammad, 2005) and ketamine (Mohammad *et al*., 2005) produced similar effects on open field and tonic immobility behavioral responses in chicks. Depressants of the CNS are known to decrease ambulation and related activities in chicks and rodents in the open-field tests, whereas stimulants increase them (Cory-Slechta, 1989; Mohammad and Yakoub, 1997; Frankel *et al*., 2007; Tsueyoshi *et al*., 2007). Diphenhydramine was found to disrupt psychomotor performance and produce sedative effects in healthy human volunteers (Gupta *et al*., 2004). It is possible that further studies in chicks would reveal the suitability of our current behavioral tests in monitoring the behavioral effects of newer generation of H1-antihistamines in this animal model. The behavioral paradigms of open-field activity and tonic immobility tests present novel tasks and challenging environment for the test animal to deal with according to the activity status of the CNS (Hennig *et al*., 1984; Corey Slechta, 1989; Al-Baggou *et al*., 1999; Tsueyoshi *et al*., 2007).

In contrast to the present findings, doses of diphenhydramine as much as 50 and 100 mg/kg, subcutaneously produced stimulatory action in the open field activity tests as well as stereotyped behavior in mice (Mohammad *et al*., 1999). These doses are much higher than the doses of the drug used in the chicks of the present study. Similarly, doses of diphenhydramine >30 mg/kg were reported to produce stimulatory effects in mice or rats (Mohammad *et al*., 1987; 1989; Faris and Mohammad, 1996a; 1997; Al-Baggou and Mohammad, 1998). In the present study, the signs of diphenhydramine toxicosis also included excitatory responses. It appears therefore that lower doses of diphenhydramine could exert a depressant action whereas the higher ones could be stimulatory in chicks. This effect of diphenhydramine is also seen in animals (Tiwari and Sinha, 2010) and man (Radovanovic *et al*., 2000; Wahl, 2005). However, it is not known whether the behavioral effects of diphenhydramine are attributed to the antihistaminic (H1-antagonism), antimuscarinic or to both actions of the drug.

The decreases in plasma (pseudo) and brain (true) cholinesterase activities of the chicks are in support of previous findings that H1-receptor antagonists inhibit erythrocyte (true) or plasma cholinesterase activities (Simon and Winter, 1970; Fernandez *et al*., 1975; Faris and Mohammad, 1996b). It has been also suggested that such an inhibition by diphenhydramine could be weak, as it is reversible (Fernandez *et al*., 1975), but effective in preventing further toxic inhibition of cholinesterase activity by anticholinesterase insecticides (Al-Baggou' and Mohammad, 1999). In accordance with our results, cholinesterase inhibitors were also reported to decrease open-field activity in young rats (Moser, 2000) and chicks (Al-Badrany and Mohammad, 2007). Motor behavioral changes in rats occurred concomitantly with depression of brain cholinesterase (Moser *et al*., 1998). Therefore, the behavioral changes were attributed to depressed brain cholinesterase rather than the peripheral anticholinesterase action (McDaniel and Moser, 2004). In this context, it is also possible to attribute, at least partly, the behavioral changes induced by diphenhydramine in the chicks of the present study to the central cholinesterase inhibitory action of the drug.

In conclusion, the data suggest that diphenhydramine induces CNS depression in chicks at doses well below the LD50 value of the drug which is reported here for the first time.

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