

Effect of chlorpheniramine on acute dichlorvos poisoning in chicks

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Abstract

The protective and therapeutic effects of the H₁-antihistamine chlorpheniramine against an acute poisoning induced by organophosphorus insecticide dichlorvos in a 7–14 days old chicks model were evaluated and compared with that of the standard antidote atropine. Chlorpheniramine or atropine at 20 mg/kg, intramuscularly (i.m.) given immediately after oral dichlorvos dosing increased the LD₅₀ value of dichlorvos (10.85 mg/kg, orally) in the chicks by 77 and 123 %, respectively. Chlorpheniramine at 20 mg/kg, i.m. given immediately after dichlorvos (12 mg/kg, orally) significantly delayed the onset of acute signs, time of death, decreased toxicity score and increased the percentages of survivors (62.5 %) during 2 and 24 h after dichlorvos dosing. The antidotal effect of chlorpheniramine and atropine groups at a dose of 20 mg/kg, i.m. given immediately after oral dichlorvos were close to each other in delaying the onset signs of poisoning and time of death. They also significantly increased the percentages of survivors and decreased of toxicity scores. Chlorpheniramine at 20 mg/kg, i.m. significantly decreased plasma (34%) and brain (52%) cholinesterase activities in comparison with the control group. Dichlorvos dosing at 8 mg/kg, orally significantly reduced plasma (83%) and brain (93%) cholinesterase activities in comparison with the control and chlorpheniramine groups. Chlorpheniramine given after dichlorvos dosing significantly protected the plasma and brain cholinesterase from further decreased in its activities caused by dichlorvos dosing by 29 and 41%, respectively. In conclusion, the study suggests that chlorpheniramine have a protective and therapeutic effects in case of dichlorvos poisoning in chicks resembling that of atropine.

Keywords: Chlorpheniramine, Dichlorvos, Atropine; H₁-antihistamine, Cholinesterase

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تأثير الكلورفينيرامين في التسمم الحاد بالدايكلورفوس في أفراخ الدجاج

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الخلاصة

تم تقييم التأثير الوقائي والعلاجي لضاد الهستامين الكلورفينيرامين ضد التسمم الحاد بالمبيد الحشري الفسفوري العضوي الدايكلورفوس في نموذج أفراخ الدجاج بعمر 7–14 يوم وتم تقييم هذا التأثير ومقارنته بالدرياق الأساس الأتروبين. عمل الكلورفينيرامين أو الأتروبين بجرعة 20 ملغم/كغم في العضل مباشرة بعد التجريع بالدايكلورفوس على زيادة الجرعة المميتة الوسطية للدايكلورفوس (10.85 ملغم/كغم، عن طريق الفم) في الأفراخ وبنسبة وقاية 77 و 123 % على التوالي. أدى إعطاء الكلورفينيرامين بجرعة 20 ملغم/كغم في العضل مباشرة بعد التجريع بالدايكلورفوس (12 ملغم/كغم) إلى زيادة معنوية في وقت ظهور علامات التسمم الحاد وأطال معنوياً من زمن حدوث الموت كما أدى إلى التقليل من نسب حدوث علامات التسمم الحاد وقلل معنوياً من مرتبة التسمم فضلاً عن تقليله من النسبة المئوية للموت خلال 2 و 24 ساعة من التجريع بالدايكلورفوس وبشكل معنوي مقارنة بمجموعة السيطرة. كان التأثير الدرياق للكلورفينيرامين والأتروبين متقارباً فيما بينهما عند إعطائهما بجرعة 20 ملغم/كغم في العضل مباشرة بعد التجريع بالدايكلورفوس في الإطالة المعنوية من وقت حدوث علامات التسمم الحاد وزمن الموت وفي التقليل المعنوي من مرتبة

التسمم والنسبة المئوية للموت خلال ٢ و ٢٤ ساعة من التجريع بالدايكلورفوس مقارنة بمجموعة السيطرة. عمل الكلورفينيرامين عند إعطائه في العضل بجرعة ٢٠ ملغم/كغم على التقليل المعنوي من نشاط خميرة الكولين أستراز في البلازما والدماغ بنسبة ٣٤ و ٥٢% على التوالي، في حين أدى تجريع الدايكلورفوس بجرعة ٨ ملغم/كغم إلى تثبيط معنوي عالي لنشاط هذه الخميرة في البلازما والدماغ بنسبة ٨٣ و ٩٣% على التوالي. وأدى حقن الكلورفينيرامين مباشرة بعد التجريع بالدايكلورفوس إلى الحماية المعنوية لنشاط الخميرة في البلازما والدماغ من المزيد من التثبيط المحدث بالدايكلورفوس بنسبة ٢٩ و ٤١% على التوالي. تقترح نتائج هذه الدراسة إلى أن للكلورفينيرامين تأثيرات وقائية وعلاجية في حالة التسمم بالدايكلورفوس في أفراخ الدجاج والتي تشبه إلى حد ما تأثيرات الأتروبين.

Introduction

Chlorpheniramine is an H₁-receptor antagonist (1-4). H₁-receptor blockers are previously known to inhibit erythrocyte cholinesterase in vitro and plasma cholinesterase in vitro and in vivo in experimental animals (mice and horses) (5-7). Thus H₁-antihistamines including chlorpheniramine may potentiate the toxic effect of anticholinesterase such as organophosphorus insecticide dichlorvos. However, previous studies on diphenhydramine assured that it is useful for protection and treatment against the acute poisoning of organophosphates (8-12), carbamates (13-16) and against physostigmine and neostigmine (17,18).

Chlorpheniramine is a commonly used antihistamine in human with antimuscarinic property that resemble that of the standard antidote atropine, since atropine is the drug of choice in treatment and preventing anticholinesterase poisoning (2-4).

Dichlorvos is an organophosphorus insecticide used in the fields of veterinary, public health and agriculture (19-21). It induces cholinergic nervous system hyperstimulation in mammals by inhibiting the physiological activity of acetylcholinesterase irreversibly by combining with the esteratic site of this enzyme with strong covalent bond leading to subsequent accumulation of acetylcholine at peripheral and central nervous system (19,22).

The purpose of the recent study was to evaluate and determine the effects of chlorpheniramine to protect and/or treat the chicks which acutely poisoned with dichlorvos.

Materials and methods

Animals

Broiler chicks at 7-14 days old of both sexes, weighing 40-80 g and eight chicks were used for each group. They were housed in cages (25-50 chicks/cage) in a laboratory at a temperature ranged between 32-35°C; wood shavings were provided on the floor; concentrated food and water were given ad libitum.

The insecticidal concentration solution of dichlorvos (55%, Fertil Kimy San, Turkey) used for each experiment was diluted in distilled water for oral dosing by a gavage

needle in a volume of 5 ml/kg body weight (12). Chlorpheniramine maleate (Samarra Drugs Industries, Iraq) and atropine sulphate (1%, Al-Sharq Drug Industries, Syria) were prepared in physiological saline solution to be injected intramuscularly in a volume of 2 ml/kg body weight (12).

Determination of the 24 h median lethal doses (LD₅₀) of dichlorvos alone or with chlorpheniramine or atropine

Three studies of 24 h LD₅₀ were performed in groups of broiler chicks according to up-and-down method (23). The first one for dichlorvos alone by injection of physiological saline solution immediately after oral dosing with dichlorvos while the second group with a dose of chlorpheniramine at 20 mg/kg, i.m. The dose of chlorpheniramine was chosen from previous study (18). The third group with atropine at a same dose and route of administration (20 mg/kg, i.m. immediately after oral dichlorvos dosing).

The chicks were observed separately for the appearance of signs of acute toxicity within 2 h interval and the 24 h while mortality after dichlorvos dosing were also recorded. The LD₅₀ values were determined to investigate and evaluate the protective effect of chlorpheniramine comparing the protective ratio to LD₅₀ of dichlorvos alone and with the ratio of the standard antidote atropine.

The protective ratios were calculated as follows (16):

Protective ratio = LD₅₀ of dichlorvos with chlorpheniramine or atropine / LD₅₀ of dichlorvos alone.

Effect of different doses of chlorpheniramine on the acute dichlorvos toxicity

Chicks were divided randomly into four groups of chicks (8 per group) and injected intramuscularly with different doses of chlorpheniramine at 0 (physiological saline solution) (control group), 10, 20, 40 mg/kg, body weight immediately after oral dosing with dichlorvos at 12 mg/kg, body weight. The LD₅₀ of dichlorvos (10.85 mg/kg, orally) was not used in other experiments because of such a dose would produce death in about 50% of the chicks, instead of that, the dose of dichlorvos (12 mg/kg, orally) (represents approximately 111 % of the oral LD₅₀ value of dichlorvos) was predetermined to cause appearance of

acute signs of poisoning and to assured death in all the experimental chicks.

Thereafter, the chicks were individually observed for occurrence of acute signs of poisoning characteristic of cholinergic toxicity (8–10). The signs of poisoning that recorded were salivation, lacrimation, gasping, tremor, frequent defecation, recumbency and convulsions. The time of dichlorvos administration, the onset of acute signs of poisoning and time of death during the 2 h and 24 h after oral dichlorvos dosing also have been recorded.

The toxicity score was determined which indicates the severity of toxicosis for each group and have been calculated by summing the grades of the percentage of occurrence of acute signs of poisoning (which were salivation, lacrimation, gasping, tremor, frequent defecation, recumbency and convulsions) as follows (16):

- 1= 1 – 25%
- 2= 26 – 50%
- 3= 51 – 75%
- 4= 76 – 100%

So that, the higher grades of occurrence percentages of acute signs of poisoning for each group of the experiments will be reach 28 of the toxicity score.

Comparative antidotal effects of chlorpheniramine and atropine on dichlorvos-induced toxicosis

Twenty four chicks were divided randomly into three groups (8 chicks for each group) which were control that given physiological saline solution immediately by intramuscular injection route after oral dichlorvos dosing. The two remaining groups of chicks were treated immediately after dichlorvos dosing (12 mg/kg, orally) with a same single protective dose 20 mg/kg, i.m. for each of chlorpheniramine or atropine.

The time of administration and the signs of acute cholinergic manifestations were recorded. The onset of acute signs of poisoning and time of death during the 2 h were also recorded. The death time were observed at 2 and 24 h after oral dichlorvos dosing. The toxicity score was scored to each groups as mentioned above.

Measurement of plasma and whole brain cholinesterase activity

This experiment consisted of thirty-two chicks were randomly divided into four groups of eight chicks for each as following:

1. Group-1 (control group): that injected intramuscularly with physiological saline solution (2ml/kg) immediately after oral dosing with distilled water (5ml/kg).
2. Group-2 (chlorpheniramine group): consisted of intramuscular injection by chlorpheniramine at a single dose 20 mg/kg immediately after oral dosing with distilled water.

3. Group-3 (dichlorvos group): included injection by physiological saline solution immediately after oral dosing with dichlorvos at a dose 8 mg/kg.

4. Group-4 (dichlorvos + chlorpheniramine group): this interaction group were given chlorpheniramine (20 mg/kg, i.m.) at time 0 min after oral dosing with dichlorvos (8 mg/kg).

Fifteen minutes after oral dichlorvos or distilled water dosing, each chick were sacrificed to have been collected the blood and whole brain. The blood samples were collected from the jugular vein and putted in tubes contain heparin (1 : 10) as anticoagulant substance (24) and submitted for centrifugation at 3000 rpm for 15 min to obtain the plasma. Thereafter, the plasma cholinesterase activity were measured at the same time. The whole brain samples were kept by freezing at -20°C until determination of cholinesterase activity within 3 days. The whole brain are homogenized on an ice container with a glass homogenizer (Karl Kolb, Germany) in a pH 8.1 of barbital-phosphate buffer solution at 3 ml/100 mg of brain.

The barbital-phosphate buffer solution were composed from 3.507 g sodium chloride, 0.1237 g sodium barbital, and 0.063 g potassium di-hydrogen phosphate. The pH of the buffer would be corrected after that to 8.1 by adding hydrochloric acid or sodium hydroxide (1 Normality for each), then distilled water would be added up to 100 ml of solution volume (25–27).

Plasma and whole brain cholinesterase activities were determined by an electrometric method that described by the previous studies (25–27).

The enzyme activity expressed as $\Delta\text{pH}/30$ min and was calculated as follows (26,27):

$$\text{Cholinesterase activity } (\Delta\text{pH}/30 \text{ min}) = (\text{pH}_1 - \text{pH}_2) - \Delta\text{pH of blank}$$

The percentage of cholinesterase inhibition in plasma and tissue homogenate was calculated using the following equation (27):

$$\text{ChE inhibition } (\%) = \frac{\text{ChE activity (in control)} - \text{ChE activity (with inhibitor)}}{\text{ChE activity (in control)}} \times 100$$

Statistics

Parametric data that included multiple means (times of onset, death and $\Delta\text{pH}/30$ min) were analyzed statistically by the one way analysis of variance and submitted then to the least significant difference test (28,29). Non-parametric data (survival percentages and percentages of occurrence of acute signs of toxicity) were statistically analyzed by Fisher's exact probability test. The non-parametric grades of toxicity scores were analyzed statistically by Kruskal-Wallis and then to Mann-Whitney *U*-test (29,30). The level of statistical significance for all the experiments was at $P < 0.05$.

Results

Effect of chlorpheniramine and atropine on the LD₅₀ value of dichlorvos

The acute 24 h LD₅₀ value of dichlorvos alone in chicks was 10.85 mg/kg, orally (Table 1). The chicks intoxicated by dichlorvos showed signs of acute poisoning by cholinergic overstimulation ranged between 2 – 8 min. The signs in chicks were include salivation, lacrimation, gasping, tremor, frequent defecation, recumbency and convulsions before death during 7 – 15 min.

Intramuscular injection of chlorpheniramine at a dose of 20 mg/kg immediately after oral dosing with dichlorvos

increased the oral 24 h LD₅₀ value of dichlorvos to become 19.16 mg/kg with an increased in a protection ratio to reach 1.77 (77 %) (Table 1). Whereas, atropine when given by intramuscular route at a dose of 20 mg/kg immediately after oral dosing with dichlorvos increased the 24 h LD₅₀ value of dichlorvos to be 24.22 mg/kg, orally and a protection ratio also increased to became 2.23 (123 %) (Table 1).

Chlorpheniramine and atropine injection at the same single dose (20 mg/kg, i.m.) and time of administration decreased the occurrence of signs of acute dichlorvos toxicity.

Table 1: Determination of the 24 h LD₅₀ of dichlorvos alone and with chlorpheniramine or atropine by the up-and-down method.

LD ₅₀	Variables	Results
Dichlorvos + Saline	24 h LD ₅₀	10.85 mg/kg, orally
	Range of the doses	5–15 mg/kg, orally
	Initial dose	15 mg/kg, orally
	Last dose	10 mg/kg, orally
	Number of chicks	6 (XXOOXO) *
	Increase or decrease in dose	5 mg/kg, orally
	Range of onset time of poisoning	2–8 min
	24 h LD ₅₀	19.16 mg/kg, orally
	Range of the doses	15–25 mg/kg, orally
	Initial dose	15 mg/kg, orally
Dichlorvos + Chlorpheniramine	Last dose	20 mg/kg, orally
	Number of chicks	6 (OXXOX) *
	Increase or decrease in dose of dichlorvos	5 mg/kg, orally
	Range of onset time of poisoning	13–31 min
	Protective ratio**	1.77 = 77 %
	24 h LD ₅₀	24.22 mg/kg, orally
	Range of the doses	15–25 mg/kg, orally
	Initial dose	15 mg/kg, orally
	Last dose	25 mg/kg, orally
	Number of chicks	5 (OXOOO) *
Dichlorvos + Atropine	Increase or decrease in dose of dichlorvos	5 mg/kg, orally
	Range of onset time of poisoning	4–25 min
	Protective ratio**	2.23 = 123 %

Chlorpheniramine and atropine (20 mg/kg, i.m.) were injected immediately after oral dichlorvos dosing.

* X mean death and O refer to the survival

** Protective ratio = LD₅₀ of dichlorvos with chlorpheniramine or atropine / LD₅₀ of dichlorvos alone.

Effect of different doses of chlorpheniramine on the acute dichlorvos toxicity

Administration of dichlorvos–saline at 12 mg/kg, orally (control group) produced acute signs of poisoning characteristics of parasympathetic overstimulation during 3 min of dosing which were salivation, lacrimation, gasping, tremor, frequent defecation, recumbency, convulsions and

the time of death occur during the first 7 min in 100 % of the chicks from dichlorvos dosing (Table 2). Chlorpheniramine at doses 10, 20 and 40 mg/kg, i.m. injected immediately after oral dosing with dichlorvos delayed the onset of acute signs of poisoning, time of death and decreased the percentages of occurrence of acute signs (Table 2) leading to decrease of toxicity scores (Figure 1).

Table 2: Effect of different doses of chlorpheniramine on the acute dichlorvos toxicity.

Chlorpheniramine (mg/kg)	Mean time of onset (min ± S.E.)	Mean time of death (min ± S.E.)	% survival (2 h)	% survival (24 h)	The percentages of occurrence of acute signs of toxicity								
					Salivation	Lacrimation	Gasping	Tremor	Frequent defecation	Recumbency	Convulsion	Toxicity score	
0 (control)	3.00± 0.27	7.00± 0.85	0	0	100	87.5	100	100	100	100	100	100	28
10	6.00± 0.46 *	6.50 ±0.65	50 *	37.5	100	62.5	100	62.5	87.5	100	75	25	
20	8.13± 0.71 *,†	14.00± 2.08 *,†	62.5 *	62.5 *	75	50	62.5	37.5 *	62.5	75	50 *	18 *	
40	4.38± 0.38 †,‡	11.63± 1.82 *,†	0	0	87.5	75	87.5	62.5	87.5	100	75	25	

Chlorpheniramine was injected intramuscularly immediately after dichlorvos (12 mg/kg, orally), *N* = 8 chicks/group.

* Significantly different from the respective control group, *P*<0.05.

† Significantly different from the respective chlorpheniramine (10 mg/kg, i.m.) group, *P*<0.05.

‡ Significantly different from the respective chlorpheniramine (20 mg/kg, i.m.) group, *P*<0.05.

The best recorded dose of chlorpheniramine in this experiment was at 20 mg/kg, i.m. because it significantly (*P*<0.05) delayed the onset of acute signs and time of death (Table 2), significantly decreased toxicity score (Figure 1) and increase the percentages of survivors to 62.5 % during 2 and 24 h corresponding to control group (Figure 2).

No significant differences found at doses of chlorpheniramine 10 and 40 mg/kg, i.m. in increasing the survivors during the 24 h interval and in decreasing the toxicity scores (Table 2) (Figure 1 and 2).

Comparative antidotal effects of chlorpheniramine and atropine on the toxicity caused by dichlorvos

Chicks of the control group showed signs of acute poisoning induced by dichlorvos (12 mg/kg, orally) during 3 min which were salivation, lacrimation, gasping, tremor, frequent defecation, recumbency, convulsions and death during 4 min and the percentage of survivors are 0 % (Table 3).

Chlorpheniramine group at 20 mg/kg, i.m. given immediately at time 0 min after dichlorvos dosing significantly (*P*<0.05) delayed the onset of acute signs of

poisoning (11 min), increased the time of death (18 min) after dichlorvos and decreased the percentages of occurrence of acute signs (Table 3).

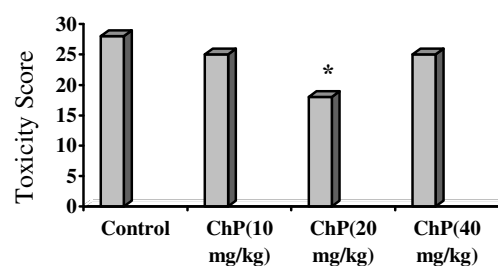


Figure 1. Effect of different doses of chlorpheniramine on the toxicity score of acute dichlorvos poisoning Chlorpheniramine (ChP) was injected intramuscularly immediately after dichlorvos (12 mg/kg, orally), *N* = 8 chicks/group.

* Significantly different from the respective control group, *P*<0.05.

Chlorpheniramine significantly decreased the toxicity score (Table 3 and Figure 3) and increased the percentages of survivors during 2 h (75 %) and 24 h (62.5 %) comparing to that of control group values (Table 3 and Figure 4).

Atropine at the same dose (20 mg/kg, i.m.) injected immediately after oral dichlorvos dosing significantly increased the onset of acute signs, time of death (Table 3), decreased the toxicity score (Figure 3) and decreased the percentages of death in chicks corresponding to control group (Figure 4).

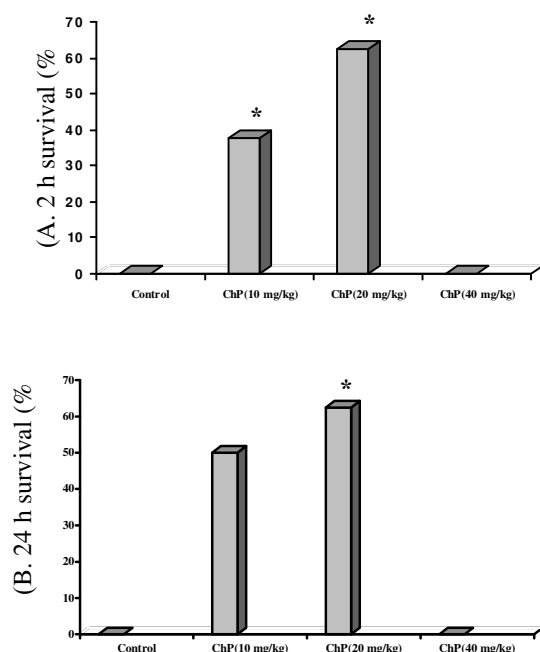


Figure 2. Effect of different doses of chlorpheniramine on the percentages of survival of chicks from acute dichlorvos poisoning.

Chlorpheniramine (ChP) was injected intramuscularly immediately after dichlorvos (12 mg/kg, orally), $N = 8$ chicks/group.

* Significantly different from the respective control group, $P < 0.05$.

The antidotal efficacy of chlorpheniramine in the treatment of dichlorvos poisoning was close to that of atropine with exception that chlorpheniramine significantly increased the onset of acute signs and time of death, furthermore, this dose decreased the gasping, tremor and recumbency more than that of atropine (Table 3).

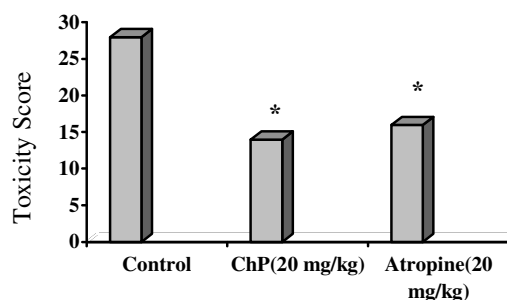


Figure 3. Comparative antidotal effects between chlorpheniramine (ChP) and atropine sulphate on the toxicity caused by dichlorvos.

Chlorpheniramine and atropine were injected intramuscularly immediately after dichlorvos (12 mg/kg, orally), $N = 8$ chicks/group.

* Significantly different from the respective control group, $P < 0.05$.

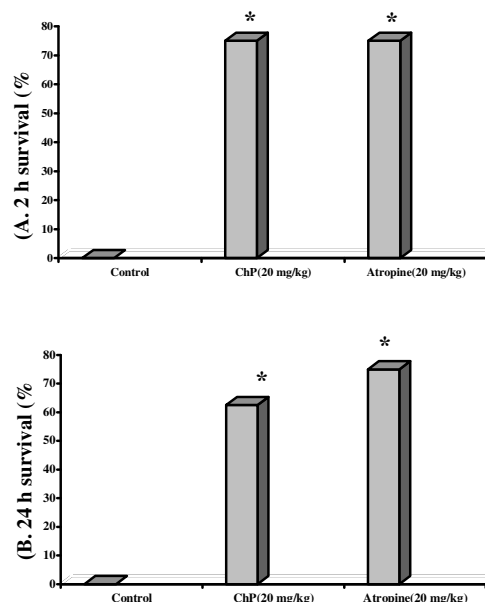


Figure 4. Comparative antidotal effects between chlorpheniramine (ChP) and atropine on the percentages of survival of chicks from acute dichlorvos poisoning.

Chlorpheniramine and atropine were injected intramuscularly immediately after dichlorvos (12 mg/kg, orally), $N = 8$ chicks/group.

* Significantly different from the respective control group, $P < 0.05$.

Effect of dichlorvos and chlorpheniramine on the plasma and whole brain cholinesterase activity

Chlorpheniramine at 20 mg/kg, i.m. significantly ($P<0.05$) decreased plasma and brain cholinesterase activities by 34 and 52% respectively in comparison with the control group value (Table 4). Dichlorvos dosing at 8 mg/kg, orally significantly ($P<0.05$) reduced plasma by

83% and brain by 93% of cholinesterase activities in comparison with the control and chlorpheniramine groups values (Table 4). Chlorpheniramine given at 20 mg/kg, i.m. after oral dichlorvos dosing (8 mg/kg) protect the plasma and brain cholinesterase from further decreased in its activities that induced by oral dichlorvos dosing by 29 and 41%, respectively (Table 4).

Table 3: Comparative antidotal effects between chlorpheniramine and atropine on the toxicity caused by dichlorvos.

Groups	Mean time of onset (min ± S.E.)	Mean time of death (min ± S.E.)	% survival (2 h)	% survival (24 h)	The percentages of occurrence of acute signs of toxicity							Toxicity score
					Salivation	Lacrimation	Gasping	Tremor	Frequent defecation	Recumbency	Convulsion	
Dichlorvos-saline (control)	2.5± 0.19	3.88± 0.58	0	0	100	87.5	100	100	100	100	100	28
Dichlorvos + Chlorpheniramine	10.83± 2.04 *	17.5± 0.5 *	75 *	62.5 *	50*	37.5	37.5*	50*	50*	62.5	25*	14*
Dichlorvos + Atropine	7.25± 0.88*,†	11.5± 2.5*,†	75 *	75 *	50*	25*	50*	87.5	50*	100	25*	16*

Chlorpheniramine and atropine (20 mg/kg, i.m.) were injected immediately after dichlorvos (12 mg/kg, orally), $N = 8$ chicks/group.

* Significantly different from the respective control group, $P<0.05$.

† Significantly different from the chlorpheniramine group value, $P<0.05$.

Table 4: Effect of dichlorvos and chlorpheniramine on the plasma and whole brain cholinesterase activity.

Groups	Plasma		Whole brain	
	Δ pH/30 min (mean ± S.E.)	% inhibition	Δ pH/30 min (mean ± S.E.)	% inhibition
Control	0.35 ± 0.013	-----	0.29 ± 0.018	-----
Chlorpheniramine	0.23 ± 0.007 *	34	0.14 ± 0.005 *	52
Dichlorvos	0.06 ± 0.008 *,†	83	0.02 ± 0.007 *,†	93
Dichlorvos + Chlorpheniramine	0.16 ± 0.005 *,†,‡	54	0.14 ± 0.012 *,‡	52

Chlorpheniramine (20 mg/kg, i.m.) was injected immediately after dichlorvos (8 mg/kg, orally). Cholinesterase activity was determined 15 min after oral dichlorvos dosing. $N = 8$ chicks/group.

* Significantly different from the respective control group, $P < 0.05$.

† Significantly different from the respective chlorpheniramine group, $P < 0.05$.

‡ Significantly different from the respective dichlorvos group, $P < 0.05$.

Discussion

As expected, the signs of dichlorvos poisoning that have been seen in the chicks were characteristic of cholinergic overstimulation (7-10,12). Dichlorvos induced toxicity occur due to irreversibly inhibiting of the enzyme acetyl cholinesterase activity which lead to higher level of accumulation of the neurotransmitter acetylcholine at the nerve endings causing subsequent parasympathetic hyperstimulation of the muscarinic and nicotinic receptors in autonomic and central nervous system (19,21,22). Chlorpheniramine was found to increase the LD₅₀ value of dichlorvos in chicks nearly like the standard antidote atropine, this finding is in accordance with the previous study on the protective effect of chlorpheniramine against physostigmine and neostigmine (18). This result was in accordance with previous studies on other antihistamines like diphenhydramine when it used against organophosphate insecticides poisoning (7-12), against carbaryl and methomyl (13,14,16,18) and against physostigmine and neostigmine toxicity (15,17,18) that result suggested the protective effect of antihistamine chlorpheniramine against dichlorvos induced toxicity by a mechanism assumed to its effect on muscarinic receptors like the drug of choice atropine in the protection and treatment of insecticidal poisoning (1-4).

The best dose of chlorpheniramine in chicks, as found in experiments, is at 20 mg/kg, i.m. given immediately after oral dichlorvos dosing that are increased the LD₅₀ value of dichlorvos, increased the time of onset and death, decreased the toxicity score and increased the numbers of survivors significantly. The higher dose of chlorpheniramine (40 mg/kg, i.m.) was found to potentiate the toxic effect of dichlorvos while the small dose (10 mg/kg, i.m.) produced little effect on intoxicated chicks, this will suggest the protective ability of the drug chlorpheniramine in a dose dependant way and also suggest that the dose (40 mg/kg, i.m.) is nearly to the toxic dose of chlorpheniramine in chicks that potentiate toxicity. So that, the optimal method in the treatment of poisoning was to use such dose as antidote.

Chlorpheniramine was compared with the standard antidote atropine by using the same route, time of administration and dose (20 mg/kg, i.m.) from both. They are close to each other in their protective and therapeutic effects against dichlorvos induced toxicity in the chicks, these results are in accordance to previous studies on diphenhydramine against dichlorvos induced toxicity (9,18).

The inhibition of cholinesterase activity in the plasma and whole brain by dichlorvos are expected due to mechanism of its toxic action of dichlorvos, such findings are found in the previous studies (7,18,19,21,22) due to combination of this insecticide with the enzyme acetyl

cholinesterase by a covalent bond so, the activity is reduced. Chlorpheniramine like diphenhydramine was found to decreased the cholinesterase activity in the samples of plasma and brain of the chicks, this finding is in agreement with study of effects of antihistamine on erythrocyte cholinesterase in vitro and plasma cholinesterase both in vitro and in vivo (5-7,12). On other hand, chlorpheniramine was found to decreased the cholinesterase inhibition induced by anticholinesterase effect of dichlorvos in the plasma and brain in chicks and it may be assumed to the interaction of chlorpheniramine and dichlorvos on the level of cholinesterase by a mechanism that involves protection of acetyl cholinesterase from further inhibition by the anticholinesterase inhibitors (5-7). Furthermore, chlorpheniramine did not potentiate the inhibitory action of the organophosphate insecticide dichlorvos on the true and pseudocholinesterase like that found in the previous study that the antihistamines increased the anticholinesterase effect on plasma cholinesterase in horse (6). However, reduced the enzyme activity of the true cholinesterase is the most important factor in poisoning induced by the anticholinesterase inhibitors (19,21,22).

In conclusion, the study suggests that chlorpheniramine have a protective and may be of therapeutic value in case of dichlorvos poisoning in chicks resembling that of atropine, and it may be useful in the protection and treatment of organophosphorus insecticides in chicks. Furthermore, intensive studies would be needed to evaluate and applied these effects of chlorpheniramine with other organophosphate and carbamate insecticides poisoning in the different models of animals.

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