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Effects of Diphenhydramine on Lambda-Cyhalothrin-Induced Toxicity in Mice

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BACKGROUND: A first-generation antihistamine called diphenhydramine is used to treat cold and allergic rhinitis symptoms. Diphenhydramine reduces the effects of endogenous histamine on bronchial, capillary, and gastrointestinal smooth muscles by competitively inhibiting the histamine-1 (H1) receptor.

Objective: The present study was designed to evaluate the effectiveness of the antihistamine diphenhydramine in improving survival and controlling seizures in insecticide-treated mice.

Methods: Mice (males and females) were divided into (4) equal groups and treated as follows: The 1st group: was the control group (physiological saline solution + lambda-cyhalothrin at 150 mg/kg orally). 2nd group: (Diphenhydramine 10 mg/kg subcutaneously + lambda-cyhalothrin 150 mg/kg orally), 3rd group (atropine sulfate 15 mg/kg subcutaneously + lambda-cyhalothrin 150 mg/kg orally) and 4th Group (Diazepam 10 mg/kg subcutaneously + lambda-cyhalothrin 150 mg/kg orally) Diphenhydramine, atropine sulfate, and diazepam were injected 15 min before the oral administration of lambda-cyhalothrin to mice . Mice were monitored for 30 min after treatment. The onset of signs of toxicity, the time of onset of neurological seizures, and their number with the extraction of the toxicity rank value were recorded.

Results: Diphenhydramine at 10 mg/kg subcutaneously (15) minutes before oral administration of lambda-cyhalothrin at 150 mg/kg causes a slight decrease in the time of signs onset of acute toxicity compared to the control group with a slight decline in the time of the onset of nervous seizures compared to the control group, and diphenhydramine at dose of 10 mg/kg of caused a decrease in the number of seizures and onset min respectively compared to the control group, with complete prevention of death within 24 hour in all treated mice and a reduction in toxicity scores (22), compared to the control group (28).

Conclusion: Our results showed that diphenhydramine had an anticonvulsive effect on the neurological convulsions induced by lambda-cyhalothrin poisoning and the possibility of its use in controlling it and reducing the severity of signs of poisoning due to its anti-muscarinic and nicotine effects.

Keywords: Mice, Diphenhydramine, Convulsion, Lambda-cyhalothrin.

Introduction

A synthetic pyrethroid pesticide called lambda-cyhalothrin (LCT) is utilized in agricultural, residential pest management, food production protection, and zoonotic disease control [1,2]. According to studies, the toxicity of LCT in rats causes hepatotoxicity and serious kidney structural injury [3]. When LCT is used to treat

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rats, there may be an increase in the frequency of micronucleated erythrocytes and structural chromosomal abnormalities [3].

Diphenhydramine is one of the most widely used histamine (H1_) receptor antagonists in humans and veterinarians, and diphenhydramine has a central and peripheral antihistamine and anticholinergic action [4-5]. It reduces the secretions of glands associated with cholinergic nerves and thus will reduce bronchial secretions, as well as its anti-muscarinic effects at the level of the central nervous system, with an anti-nicotinic effect [6,8] .

Diphenhydramine has many clinical uses, It is one of the first-generation antihistamine that have been used in the treatment and prevention of insomnia, itching, urticaria, dizziness, and motion sickness [9]. It treats skin disorders and itching in dogs and cats, as well as its use in the treatment of eczema, laminitis, and emphysema in horses. Ketosis, acetonemia, favorable mastitis, placental retention, and emphysema [10] . Diphenhydramine has side effects, but they are not very dangerous and can disappear during the treatment period, the most prominent of which are sedation, fatigue, vertigo, tinnitus, loss of balance, blurred vision, and double vision [11,12] and nervous agitation at high doses, behavioral effects of diphenhydramine were also found in some laboratory animals and distinctive stimulatory properties in monkeys and pigeons [13] . Several studies have shown that diphenhydramine has anti-toxic effects of organophosphorous pesticides [14]. Diphenhydramine gives a high degree of protection against poisoning with physostigmine and neostigmine in rats and reduces the severity of signs of poisoning and delays their appearance, as well as reducing the incidence of signs of poisoning, its anticonvulsant effect and preventing death after methomyl poisoning in rats [6]. Diphenhydramine inhibits the effects of acetylcholine in the neuromuscular junction, as well as the activity of acetylcholinesterase enzyme in vitro and in vivo, but this action does not interfere with its effect as an antidote against poisoning caused by yeast cholinesterase inhibitors [15]. In view of the mechanism of action of diphenhydramine and its protective effect against poisoning by many insecticides, this research study shed light on the detection of the effects of diphenhydramine in the nervous seizures induced by insecticides Lambda-cyhalothrin in mice.

Material and Methods

Drugs

1- Lambda-cyhalothrin (5%, Shanghai Molotus chemical Co LTD, China).
2- Atropine sulphate(1%, GEEVET Co LTD, India).
3- Diazepam ampule (10 mg/2 ml, Albalsam Company, Syria).
4- Diphenhydramine powder (produced by Pharmaceutical Pioneer Company Sulaymaniyah, Iraq).

Animals

All animal care and experimental procedures were performed in accordance with the Guiding Principles for the Care and Use of Laboratory Animals adopted by the College of veterinary medicine and were approved by the Ethics Committee for Animal Experimentation of the University of Mosul. Male and female mice were purchased from Laboratory animals house of the college of Veterinary medicine. (Mosul, Iraq). They were maintained in an air-conditioned room with controlled temperature (22 ± 2 °C) under a 12-h light/dark cycle [16]. They were housed in standard-size plastic cages (32 × 18 × 24 cm) with sawdust (4–6 mice per cage). The mice were allowed free access to food and water except during the experiments.

Experiment design

Effect of subcutaneous administration of diphenhydramine on lambda-cyhalothrin toxicity in mice and comparison with the main antidotes atropine sulfate and diazepam.

Twenty (20) mice (males and females) were used, with weights ranging between 23-38 grams and then divided into (4) equal groups and treated as follows: The first group: the control group (physiological saline solution + lambda-cyhlothrin at a dose of 150 mg / kg of body weight). The second group: (Diphenhydramine at a dose of 10 mg/kg body weight + lambda-cyhalothrin at a dose of 150 mg/kg of body weight), The third group (atropine sulfate at a dose of 15 mg/kg of body weight + lambda-cyhalothrin at a dose of 150 mg/kg of body weight) and the fourth group (Diazepam at a dose of 10 mg/kg body weight + lambda-cyhalothrin at a dose of 150 mg/kg of body weight) Diphenhydramine, atropine sulfate and diazepam were injected 15 minutes before the mice were oral administered with lambda-cyhalothrin, then the mice were monitored for 30 minutes after treatment. The onset of signs of

toxicity, time of onset of neurological seizures and each treatment group's level of toxicities severity received a score in accordance with previous descriptions [14]. According to the frequency of the toxicity symptoms (salivation, lacrimation, gasping, and convulsions), including the 2- and 24-hour fatalities, the following grades were assigned: Grade 1 (1-25%), Grade 2(26-50%), Grade 3(51-75%), and Grade 4(76-100%). The choice of the doses of the drug depended on a preliminary study that reported the toxicological and pharmacological effects of the drugs on mice.

Statistical analysis

We used the SPSS program to analyze the parametric data, where we used the (One-way analysis of variance ANOVA) test, and then the least significant difference LSD test was applied to it. The difference level for all tests was at a probability level of less than 0.05. The data were presented as the mean ± standard error.

Results

Effect of subcutaneous administration of diphenhydramine on lambda-cyhalothrin toxicity in mice and comparison with the main antidotes atropine sulfate and diazepam.

Oral administration of lambda-cyhalothrin at a dose of 150 mg/kg body weight (control group) led to the appearance of signs of acute toxicity within 2.6 ± 0.2 min, such as salivation, lacrimation, erection of hair and tail, shivering, difficulty breathing, lying on the cage floor, and nervous convulsions. With the prevention of death in all treated mice with poisoning score 28 (Table 1), the effect of injection of diphenhydramine at 10 mg/kg body weight subcutaneously (15) minutes before lambda-cyhalothrin in the dose 150 mg/kg body weight led to the appearance of signs of acute toxicity within 2.4 ± 0.2 min with poisoning score 22 (Table 1),while the administration of lambda-cyhalothrin at a dose of 150 mg/kg body weight with atropine sulfate 15mg/kg and diazepam 10mg/kg led to decrease the score of toxicity as 14 and 12 respectively. The injection of diphenhydramine, atropine, and diazepam 15 minutes before the oral administration of lambda-cyhalothrin led to a significant decrease in the time of onset of convulsions and a significant decrease in the number of convulsions compared to the control group (Table 2).

TABLE 1. The effect of diphenhydramine, atropine sulfate, and diazepam on the toxicity of lambda-cyhalothrin.

Groups	Onset of sings of toxicity (minute)	Salivation	Hair erection	Difficulty breathing	Flicker	Tail erection	Lying on the cage floor	Toxicity rank
Normal saline + lambda-cyhalothrin 150 mg/kg	2.6±0.2	80	80	100	100	100	100	28
Diphenhydramine 10mg/kg + lambda-cyhalothrin 150 mg/kg	2.4±0.2	60	40	60	60	60	100	22
Atropine sulphate 15mg/kg + lambda-cyhalothrin 150 mg/kg	1.8±0.4	20	20	100	40	40	40	14
Diazepam10mg/kg + lambda-cyhalothrin 150 mg/kg	1.6±0.4	0	0	100	40	20	40	12

n = 5, the observations are mean ± SEM to the onset of toxicity

TABLE 2. Anticonvulsant effects of diphenhydramine, atropine sulfate and diazepam on lambda-cyhalothrin-induced seizure.

Groups	Onset of convulsion (minute)	Number of convulsions
Normal saline + lambda-cyhalothrin 150 mg/kg	5.8 ±0.6	8.0±6.31
Diphenhydramine 10mg/kg + lambda-cyhalothrin 150 mg/kg	4.4±0.5	6.3±0.32*
Atropine sulfate 15mg/kg + lambda-cyhalothrin 150 mg/kg	0.0±0.0 *a	0.0±0.0 *a
Diazepam10mg/kg + lambda-cyhalothrin 150 mg/kg	0.0±0.0 *a	0.0±0.0 *a

n = 5, the observations are mean ± SEM
*P<0.05, as compared to 1st group
a P<0.05, as compared to 2nd group

Discussion

Diphenhydramine is an antihistamine (H1) and it is one of the first generations that competes with histamine at the H1 receptor that is found in many parts of the body [17]. Anticholinergic by inhibiting the response to acetylcholine by muscarinic receptors, which is similar to the action of atropine [18-19] .

Other studies have shown that diphenhydramine may be a stimulant or depressant of the central nervous system, and patients may suffer from discomfort, nervousness and inability to sleep when treated with it [20].

This study came to demonstrate the effect of diphenhydramine as an anticonvulsant, and its use similar to antidote, atropine sulfate and diazepam in cases of acute poisoning with different insecticides in mice due to its anti-muscarinic and nicotinic receptor properties that distinguish it from atropine sulfate [7, 21, 22] .

The insecticide lambda-cyhalothrin showed signs of acute poisoning represented by muscarinic and nicotinic signs, and stimulation of the central nervous system. This stimulation leads to signs of acute poisonings, such as muscarinic salivation, lacrimation, hair and tail erection, and frequent defecation. The nicotinic signs are shivering on the floor of the crouch. In addition to signs of toxicity at the level of the central nervous system, represented by difficulty breathing, irritability or lethargy, paralysis, nervous convulsions, and then death due to suffocation due to inhibition of the respiratory center in the brain (medullary medulla) [23,24]. Insecticides also acted with diphenhydramine at dose (10) mg/kg body weight subcutaneously (15) minutes before lambda-cyhalothrin dose (150) mg/kg of body weight orally on delaying the time of the onset of nervous seizures with a significant reduction in the number of times the occurrence of nervous seizures and causing A protective effect represented by reducing the percentages of signs of acute poisoning and reducing the rank of poisoning [22]. Diphenhydramine had an important role in the significant prolongation of the time and last appearance of signs of acute poisoning, as well as reducing the number of nervous seizures and delaying their appearance. The injection of atropine sulfate and diazepam in reducing the severity of the signs of acute poisoning also worked to reduce and prevent the occurrence of the number of seizures, as in carbaryl and lambda-cyhalothrin [25]. Our study and its results showed that the antihistamine (H1-) diphenhydramine had an anti-convulsive effect on the neurological convulsions induced by toxic dose of lambda-cyhalothrin and the possibility of its use in controlling it and reducing the severity of signs of toxicity as a result of its anti-muscarinic and nicotine effect.

Consent for publication

Not applicable.

Conflict of interest

The authors have no competing interests to declare.

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Authors' contributions
Contributed to the conceptualization and experimental design of this study, conducted experiments and performed data analysis furthermore wrote the manuscript.

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تأثير الدايفنهيدرامين على السمية المحدثة باللامدا سيهالوثرين في الفئران

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الخلفية العلمية: يستخدم الجيل الأول من مضادات الهيستامين المسمى ديفينهيدرامين لعلاج أعراض البرد والتهاب الأنف التحسسي. يقلل ديفينهيدرامين من تأثيرات الهيستامين الداخلي على العضلات الملساء في الشعب الهوائية والشعيرية والجهاز الهضمي عن طريق تثبيط تنافسي لمستقبلات الهيستامين -١.

الهدف: صممت الدراسة الحالية لتقييم فعالية ضادات الهيستامين دايفينهايدرامين في تحسين البقاء على قيد الحياة والسيطرة على النوبات في الفئران المعالجة باللمبدا سيهالوثرين.

الطرائق: تم تقسيم الفئران (ذكور وإناث) إلى (٤) مجموعات متساوية وعولجت على النحو التالي: المجموعة الأولى: كانت مجموعة السيطرة (محلول ملحي فسيولوجي + لامدا-سيهالوثرين ١٥٠ ملغم/كغم من وزن الجسم عن طريق الفم). المجموعة الثانية: (دايفينهايدرامين ١٠ ملغم/كغم تحت الجلد + لامدا سيهالوثرين ١٥٠ ملغم/كغم عن طريق الفم) المجموعة الثالثة (أتروبين ١٥ ملغم/كغم تحت الجلد + لامدا سيهالوثرين ١٥٠ ملغم/كغم عن طريق الفم) والمجموعة الرابعة (ديازيبام ١٠ ملغم/كغم تحت الجلد + لامدا-سيهالوثرين عند ١٥٠ ملغم/كغم من وزن الجسم عن طريق الفم) تم حقن دايفينهايدرامين و أتروبين و ديازيبام قبل ١٥ دقيقة من تجريع الفئران بـ لامدا-سيهالوثرين. تمت مراقبة الفئران لمدة ٣٠ دقيقة بعد العلاج و تم تسجيل ظهور علامات التسمم ووقت ظهور النوبات العصبية وعددها مع استخراج قيمة مراتب التسمم.

النتائج: ادى حقن دايفينهايدرامين ١٠ ملغم/كغم من وزن الجسم تحت الجلد (١٥) دقيقة قبل التجريع الفموي لامدا-سيهالوثرين بجرعة ١٥٠ ملغم/كغم من وزن الجسم الى زيادة طفيفة في وقت ظهور علامات التسمم الحاد مقارنة بمجموعة السيطرة مع انخفاض طفيف في وقت ظهور النوبات العصبية مقارنة بالمجموعة الضابطة ، وأدى حقن ديفينهيدرامين بجرعة ١٠ ملغم/كغم من وزن الجسم إلى انخفاض عدد النوبات التي مقارنة بمجموعة السيطرة ، مع الوقاية الكاملة من الموت خلال ٢٤ ساعة في جميع الفئران المعالجة وانخفاض درجات السمية (٢٢) ، مقارنة بمجموعة التحكم (٢٨).

الخلاصة: أظهرت نتائجنا أن الديفينهيدرامين له تأثير مضاد للاختلاج على التشنجات العصبية الناجمة عن التسمم بلامبدا سيهالوثرين وإمكانية استخدامه في السيطرة عليه وتقليل شدة علامات التسمم بسبب تأثيره المضاد للعلامات المسكرينية و النيكوتينية.

الكلمات المفتاحية: الفئران ، ديفينهيدرامين ، اختلاج ، لامدا سيهالوثرين.