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SOME ADVERSE EFFECTS OF LAMBDA- CYHALOTHRIN (ICON 1 E)® THE MOST RECENT SYNTHETIC PYRETHROIDAL INSECTICIDE

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ABSTRACT

Lambda-cyhalothrin which is a recent pyrethroid insecticidal agent, elicited a concentration - dependent negative inotropic and chronotropic effects on isolated perfused rabbit heart with an increase in coronary outflow which might be of cholinergic nature. A relaxant effect was achieved on the rat thoracic aortic strip preparations which was abolished in presence of atropine indicating the acetyl choline like effect of the compound . Lambda- cyhalothrin produced stimulatory effect followed by relaxation on rat phrenic nerve diaphragm preparation indicating the depolarizing neuromuscular blocking activity of the drug. A transient hypotensive effect was traced, the effect revealed the peripheral cholinergic effects of the compound. Moreover, spraying healthy rabbits with lambda- cyhalothrin for 5 successive days in an effective concentration (1mg/40 ml) did not produce any changes on the blood picture , liver and kidney functions . Meanwhile the compound sprayed in double effective concentration (2mg/40ml) induced a significant decrease in erythrocytes , leucocyte counts , Hb% and P. C. V. % with a significant prolonged prothrombin time after 14 , 21 and 28 days of last spray . It also elicited a significant elevation of sAST, sALT, alkaline phosphatase , serum bilirubin, blood urea nitrogen, creatinine and uric acid

INTRODUCTION

Insect manifestation is a common problem in Veterinary practice affecting animals as well as birds reducing the gain in body weight, growth rate, milk , egg, fur production and leather industry, producing the great loss in economic status .

Lambda-cyhalothrin is the most recent synthetic pyrethroidal insecticide with a broad spectrum activity against house fly and mosquitos[1] . Due to the very low rates of application , formulated products of lambda - cyhalothrin are unlikely to present any acute hazards in normal use. The low dosages required to bring about rapid control of house flies and mosquitos make this new pyrethroid insecticide particularly cost -effective. Coupled with its good residual activity , lambda - cyhalothrin can be adopted as a powerful tool in integrated pest management program for the control of medically important pests and vectors[1].

Certainly, lambda - cyhalothrin is a very effective insecticide against malaria vector *Anopheles albimanus*[2] and malaria vector *Anopheles gambiae*[3] .

It has been reported that lambda -cyhalothrin showed a considerable promise against organophosphorus - resistant adults culex tarsalis mosquitos[4].

A preliminary evaluation was undertaken on the safety aspects in mosquitos net impregnation with lambda- cyhalothrin, on the operators and users of the treated nets . The detection by HPLC of one of the principal metabolites of lambda -cyhalothrin, 3-phenoxy benzoic acid (3-PBA) in blood samples in very small quantities showed that absorption of the insecticide was minimum[5].

Literature on the pharmacodynamics and adverse effects of lambda-cyhalothrin are relatively very few . Hence, the present study was carried out to investigate the effects of that agent on cardiovascular, neuromuscular junction, blood picture, liver and kidney functions of laboratory animals that eventually could explain and control the adverse effects , if any that could be issued.

MATERIALS AND METHODS

Drug :

Lambda-cyhalothrin [acyano-3-phenoxy benzyl -3-(2-chloro3,3-trifluro-prop-1-enyl)- 2 ,2 dimethyl -cyclopropane carboxylate] insecticidal agent obtained as a solution from Zeneca ltd. manufactured by Zeneca Public Health, England, which contain 8-9 gm of the synthetic pyrethroid lambda-cyhalothrin per liter of water as an emulsifiable concentrate.

Methods:

The method described by Furchgott[6] was used for studying the effect of lambda-cyhalothrin on the isolated rat thoracic aortic strip. A spiral strip of about 3 cm length of aorta was mounted in 50 ml organ bath in kreb's solution at 37°C aerated with carbogen gas .

The method described by Langendroff [7] was used for studying the effect of lambda-cyhalothrin on the isolated perfused rabbit heart using Gun's apparatus . The rate of coronary outflow was estimated by counting the number of perfused fluid drops voided per minute before and after drug administration using a graduate cylinder and stop watch.

The method described by Bulbring [8] was used for studying the effect of the drug on the neuromuscular junction , rat's phrenic nerve diaphragm preparation . The preparation was mounted in 50ml capacity organ bath containing kreb's solution at 37°C and aerated with carbogen gas . The preparation was stimulated indirectly by square pulse wave (25mv) with 40 HZ frequency and duration of 0.5 m/sec.

For investigating the effect of lambda-cyhalothrin on the blood pressure, the method described by Jackson [9] was adopted using mongrel dogs anaesthetized with pentobarbital sodium (30 mg/kg b.wt.) . The femoral artery and vein were cannulated. Heparin (500 units / kg b.wt.) was injected intravenously as anticoagulant. The blood pressure was recorded using strain gauge blood pressure transducer PT 400, connected to MD4 oscillograph.

The effects of different concentrations of lambda-cyhalothrin and their mechanifm of action were investigated on isolated organs and intact animals.

Effects of lambda-cyhalothrin spray were studied on the blood , liver and kidney functions of healthy rabbits . Thirty healthy rabbits of both sexes (1.5-2 kg b.wt.) were accomodated in metabolic cages, well confined and supplied with clean food and water ad. libitum. Animals were physically examined and were presumed healthy during the experiments. Lambda-cyhalothrin (ICON 1E) suspended in distilled water is ready to be sprayed . Rabbits were divided into three groups (ten rabbits each) .

The first group was used as control. Meanwhile , the second and third groups were sprayed with lambda-cyhalothrin for 5 successixe days in concentrations, 1 mg/40 ml (single effective concentration) and 2mg/40 ml (double effective concentrations) , respectively.

Two blood samples were collected from ear vein prior to spray and at 7, 14, 21 and 28 days post spray for haematological, liver and kidney function tests . First part of the blood sample was used for haematological studies [10-12] and second sample of blood was used for liver [13- 15] and kidney [16, 17] function tests.

Statistical analysis :

The significance of the data was calculated using Student's t- test[18] .

RESULTS AND DISCUSSION

Lambda-cyhalothrin produced a concentration dependent relaxant effect on the rat thoracic aorta . Lower oncentrations of the drug (0.1 , 0.5 mg / 40 ml water) induced a slight inhibition of rat thoracic aorta, whereas, higher concentrations (1,2,4, mg / 40ml water) , elicited a marked relaxant effect (Fig. 1).

Several attempts were made to determine the site of action of the drug . Noradrenaline (10μg/ml) produced its stimulatory effect in the presence of the drug (1mg/40ml) indicating the absence of an alpha - adrenergi blocking activity of the drug . The probability of histamine like activity of the drug was excluded since the drug (1 mg/ 40 ml) produced an inhibitory effect in presence of mepyramine maleate (100 μg/ml) (Fig. 2 A, B).

The probability of beta - adrenoceptor effect of the drug was also excluded since the drug (1mg/40 ml) produced its inhibitory effect in presence of propranolol (3 mg/ml) (Fig. 2 C). Lambda - cyhalothrin has been found to possess an acetyl choline - like activity as the drug (1 mg / 40 ml) failed to produce its effect in the presence of atropine sulphate (10μg/ml) (Fig. 2 D).

Lambda-cyhalothrin produced a concentration - dependent inhibitory effect on the isolated perfused rabbit's heart. Lower concentrations (0.1, 0.5 mg/40ml) induced slight inhibition , while higher concentrations (1,2,4 mg/40ml) elicited a marked inhibition of myocardial contraction (Fig. 3).

An attempt was made also to locate the site of action of the drug on the isolated rabbit heart. The possibility of beta - adrenoceptor - blocking effect of the drug was tested by adding isoprenaline (20 μg/ml) in the presence of lambda-cyhalothrin (1mg/40ml). Isoprenaline produced its stimulatory effect indicating the absence of beta - adrenoceptor blocking effect of the drug (Fig. 4A).

The probability of an acetyl choline - like effect of the drug was tested by blocking the muscarinic receptors with atropine sulphate (10μg/ml) . Complete blockage was tested by acetyl choline (10μg/ml). The addition of lambda-cyhalothrin (1mg/40ml) failed to

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produce its inhibitory effect indicating the acetyl choline like effect of the drug on the isolated perfused rabbit's heart (Fig. 4B) . Moreover, on interaction of lambda-cyhalothrin with the central nicotinic receptors could be ruled out by the fact that drugs interacting with nicotinic receptors as ganglionic blockers could possibly stimulate the isolated heart preparation [19].

Lambda-cyhalothrin (1mg/40ml) caused about 10% increase in coronary outflow after one minute from addition of the drug . The increase reached 40%, 75% and 90% after 5, 10 and 15 minutes, respectively, and achieved its maximum of 100% after 20 minutes.

The flow dropped to 60% , 20% and to initial level after 25, 30 and 60 minutes , respectively (Fig. 5). The increase in coronary outflow supported our findings of vascular smooth muscles relaxation.

On the rat phrenic nerve diaphragmatic muscle indirectly stimulated, the drug produced a stimulatery effect followed by inhibition of the muscle activity in a concentration-dependent manner. Lower concentrations (0.5, 1 mg / 40ml) produced a slight stimulation followed by a slight inhibition. Meanwhile , the higher concentrations (1,2mg/40ml) produced a marked stimulation followed by a marked inhibition of the skeletal muscle preparation (Fig. 6).

The addition of neostigmine (10μg/ml) was found to be ineffective in the presence of lambda-cyhalothrin (1mg/40ml) (Fig. 7) , suggesting that lambda- cyhalothrin induced a skeletal muscle relaxation by a depolarizing neuromuscular blocking activity as neostigmine did not produce any effect in its presence .

Different concentrations of lambda -cyhalothrin were injected intravenously in the femoral vein. It was observed that lambda-cyhalothrin in concentrations of 0.5, 1, 2, 4 mg/40ml induced a concentration-dependent hypotensive effect (20,30,35,40 mm. Hg , respectively (Fig. 8). An attempt was made to investigate the hypotensive effect of the drug . The possibility of cholinergic activity of the drug was tested by blocking the peripheral cholinergic receptors with atropine sulphate (10μg/kg.b.wt.). Lambda- cyhalothrin (1mg/40ml) failed to induce its hypotensive effect in presence of atropine sulphate indicating the peripheral cholinergic effect of the drug (Fig. 9).

A possible interaction with the peripheral cholinergic receptors in the blood vessels and heart were confirmed by absence of the hypotensive effect after pretreatment with peripheral cholinergic receptor antagonist, atropine sulphate.

Spraying of lambda-cyhalothrin on second group of rabbits for 5 successive days in single effective concentration (1mg/40ml) did not produce any harmful effect on blood picture after 1,2,3 and 4 weeks of last spray. Meanwhile, spraying of double effective concentration for 5 successive days on the third group of rabbits produced a significant decrease in erythrocytes , leucocyte counts, Hb% and P.C.V.% with

Table (I) : Effects of lambda- cyhlothrin spray in single effective concentration (1 mg/40 ml) and double effective concentration (2mg/40 ml) for 5 successive days on blood picture of rabbits 1,2,3 and 4 weeks after last spray (n= 10).

Groups	Hb (gm%)	R. B. Cs (10^6/mm^3)	P. C. V. (%)	M. C. V. (cuu)	M. C. H. (μg)	M. C. H. C. (%)	W. B. Cs. (10^3/mm)	Prothrombin time (sec)
Control	13.91±0.02	6.4 ± 0.6	43.7±0.08	74.1 ± 6.8	23.8 ± 1.4	35.8 ± 2.5	8.9±0.6	11.7 ± 0.7
Single effective conc. (1mg/40ml)								
after 1 W	13.8±0.2	6.3 ± 0.6	43.9±2.7	75.2 ± 0.9	23.9 ± 1.3	34.7 ± 4.5	9.1±0.1	10.8 ± 0.8
2W	13.2±0.09	6.6 ± 0.3	42.6±1.3	75.7 ± 0.1	23.2 ± 3.2	35.4 ± 4.6	8.1±1.5	11.3 ± 2.1
3W	12±0.2	6.7 ± 0.3	41±2.9	74.2 ± 4.3	24.7 ± 1.3	34.9 ± 3.6	9.7±1.8	12.1± 2.6
4W	13.6±0.1	5.8 ± 0.2	42±1.7	77.9 ± 2.6	34.3 ± 0.8	36.9± 2.2	7.2±1.1	11.1± 1.6
Double effective conc. (2mg/40ml)								
after 1 W	12.5±0.1	5.8±0.5	39.3±0.7	66.7±6.1	21.4±1.3	32.2±2.3	8.0±0.5	10.5±0.6
2W	10±0.08*	4.6±0.8*	31.4±0.3*	53.7±4.3*	17.1±1.2*	25.8±1.8*	6.4±0.3*	8.4±0.5*
3W	6.3±0.1*	2.7±0.1*	18.8±2.5*	32.1±5.6*	10.3±2.2*	15.5±2.3*	3.8±0.8*	5.1±0.9*
4W	5.7±0.6*	2.4±0.7*	16.9±1.8*	28.9±4.8*	9.3±1.3*	13.1±2.1*	3.4±0.4*	4.6±0.8*

Mean ± SEM * P<0.05

Table (2) : Effects of lambda-cyhalothrin spray in single effective concentration (1 mg/40 ml) and double effective concentration (2mg/40 ml) for 5 successive days on liver function of rabbits 1,2,3 and 4 weeks after last spray (n= 10).

Groups	sAST (u/ml)	sALT (u/ml)	Alakaline phosphatase (u/ml)	Serum bilirubin (u/ml)
Control	17.8±0.1	18.8±0.08	9.6 ± 0.6	0.50 ± 0.01
Single effective conc. (1mg/40ml)				
after 1 W	16.9±0.3	17.2±0.5	9.2 ± 0.7	0.55 ± 0.02
2W	18.8±0.02	17.6±1.6	10.8 ± 2.3	0.61 ± 0.03
3W	17.3±2.5	14.7±5.6	10.1± 3.9	0.82± 0.1
4W	18.9±3.3	18.07±3.6	11.01± 4.1	0.89± 0.4
Double effective conc. (2mg/40ml)				
after 1 W	18.6±0.6	19.1±0.5	10.1±0.2	0.52±0.07
2W	37.2±0.5*	38.3±3.8*	21.7±0.7*	1.6±0.08*
3W	65±6.3*	66.9±5.9*	35.4±2.7*	1.82±0.08*
4W	83.7 ± 7.3	85.9 ± 6.2*	47 ± 5.3*	3.43± 0.7*

Mean ± SEM. * P <0.05

Table (3) : Effects of lambda-cyhalothrin spray in single effective concentration (1 mg/40 ml) and double effective concentration (2mg/40 ml) for 5 successive days on kidney function of rabbits 1,2,3 and 4 weeks after last spray (n= 10).

Groups	Creatinine (mg%)	Blood Urea Nitrogen (mg%)	Uric Acid (mg%)
Control	1.09±0.14	28.4±0.9	0.78 ± 0.16
Single effective conc. (1mg/40ml)			
after 1 W	1.08±0.13	28.3±0.8	0.80 ± 0.06
2W	1.51±0.18	30.35±1.35	0.90 ± 0.22
3W	1.67±0.42	28±0.75	0.70± 0.31
4W	1.64±0.35	29±2.3	0.81± 0.32
Double effective conc. (2mg/40ml)			
after 1 W	2.94±0.32*	31.8±1.5*	2.7±0.51*
2W	3.76±0.24*	46.2±2.6*	3.81±0.11*
3W	6.7±1.2*	48.8±3.8*	5.7±0.21*
4W	8.6 ± 1.3*	53.7 ± 5.4*	8.8 ± 0.35*

Mean ± SEM. * P <0.05

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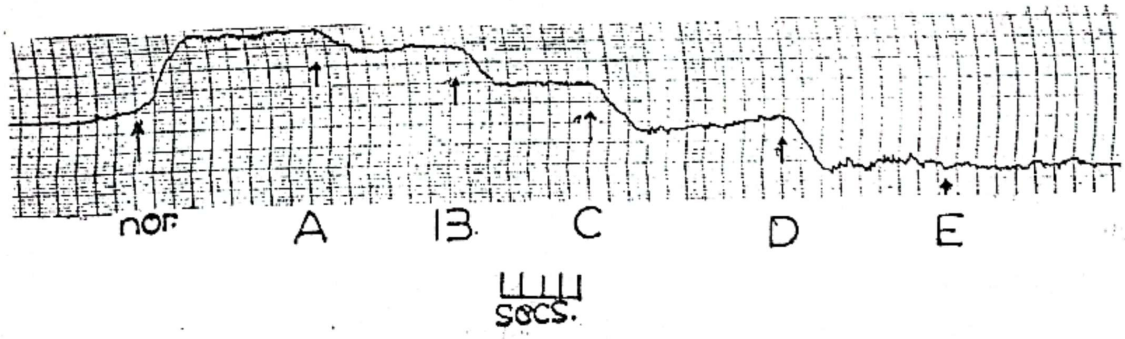

Fig. (1) : Effects of different concentrations of lambda- cyhalothrin on isolated rat thoracic aorta .

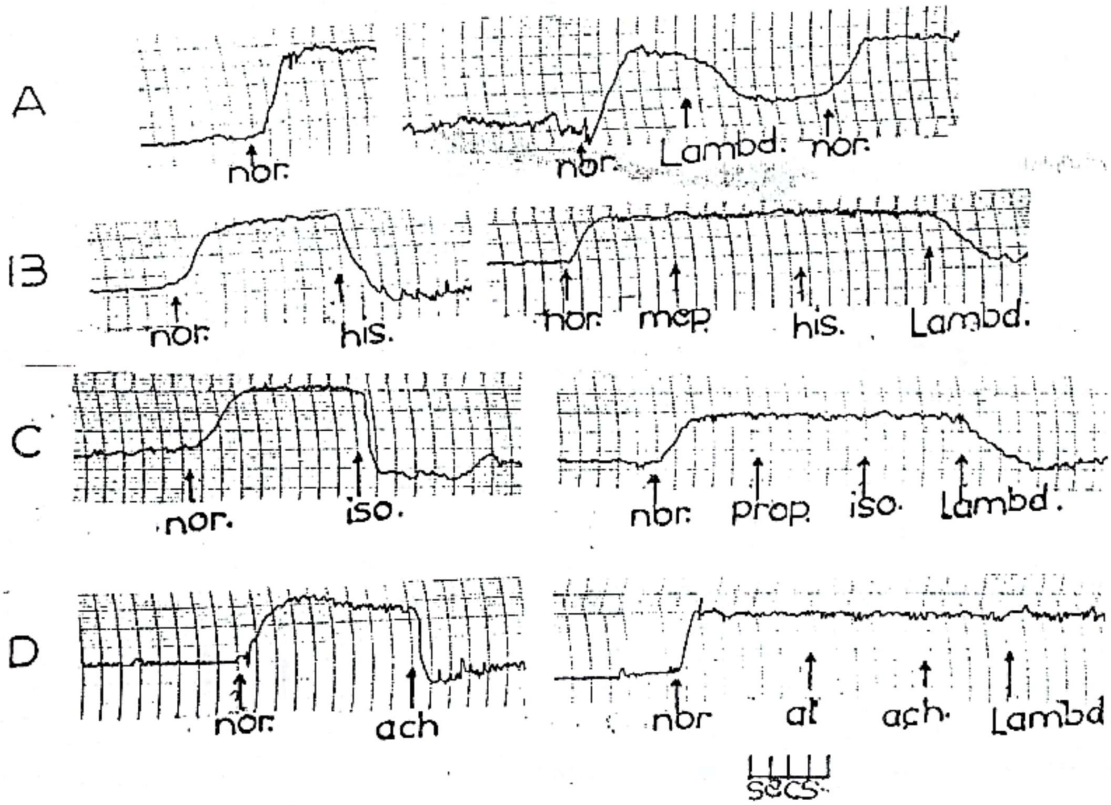

Fig. (2) : The site of action of lambda-cyhalothrin on the rat thoracic aorta .
(A) The alpha - blocking activity . (B) The histaminic activity.
(C) The beta - stimulant activity (D) The cholinergic activity

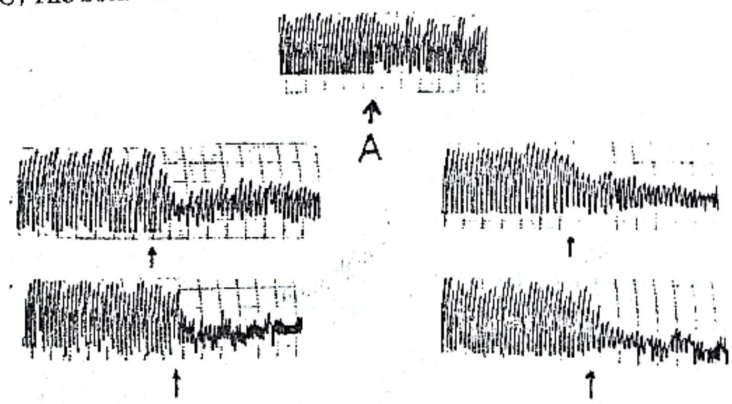

Fig. (3) : The response of isolated perfused rabbit's heart to different concentrations of lambda-cyhalothrin.

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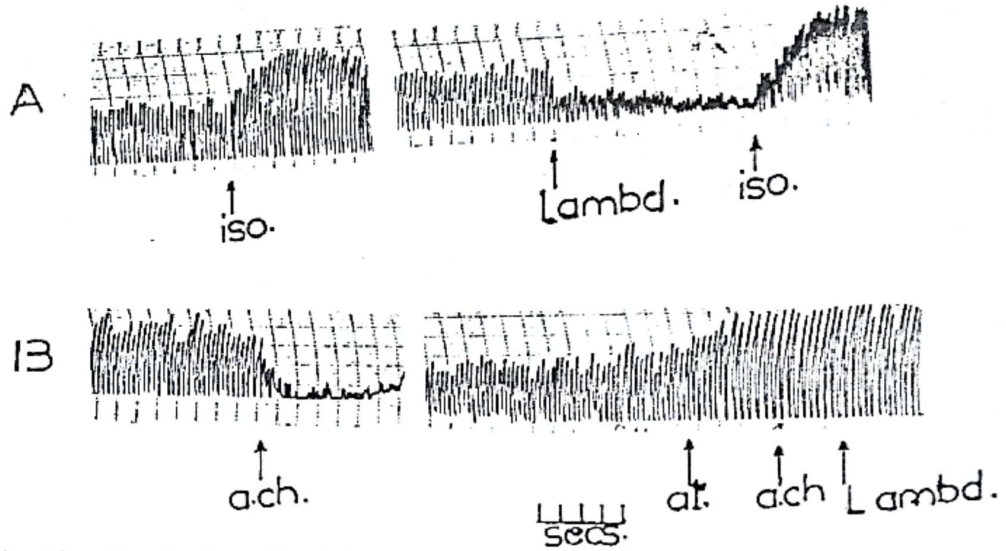

Fig. (4) : The site of action of lambda - cyhalothrin on perfused rabbit's heart.
(A) The alpha - blocking activity . (B) The cholinergic activity.

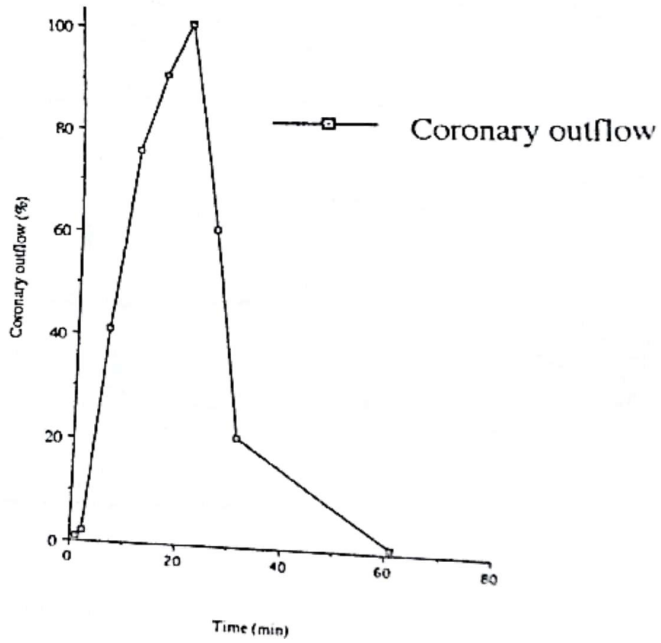

Fig. (5) : The effect of lambda-cyhalothrin on the coronary outflow .

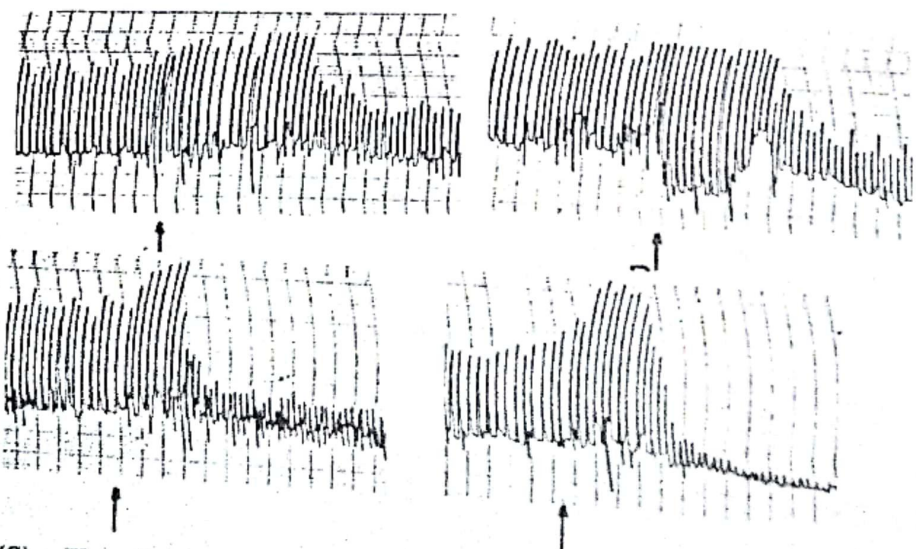

Fig. (6) : The effect of different concentrations of lambda- cyhalothrin on isolated rat phrenic nerve diaphragm preparation .

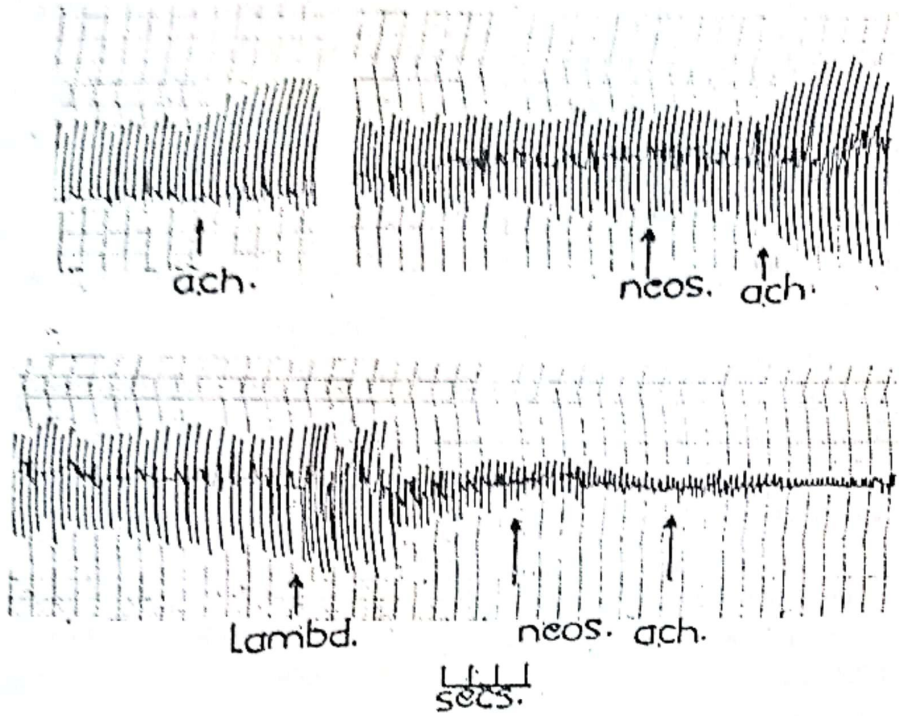

Fig. (7) : The site of action of lambda-cyhalothrin on isolated rat phrenic nerve diaphragm preparation. Notice that Neostigmine did not reverse the action of the drug.

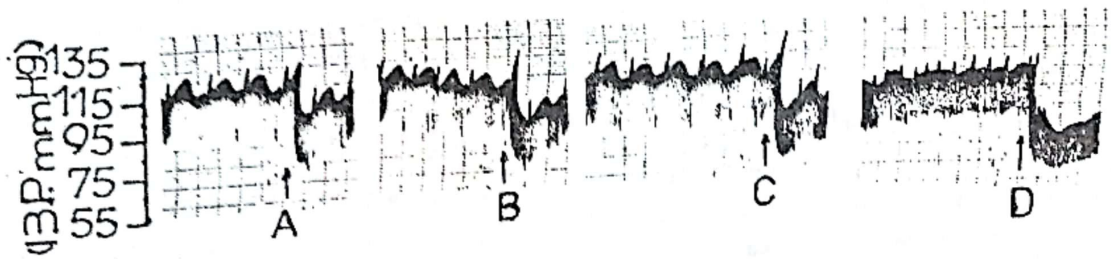

Fig. (8) : The effect of different concentrations of lambda- cyhalothrin on the blood pressure of dogs.

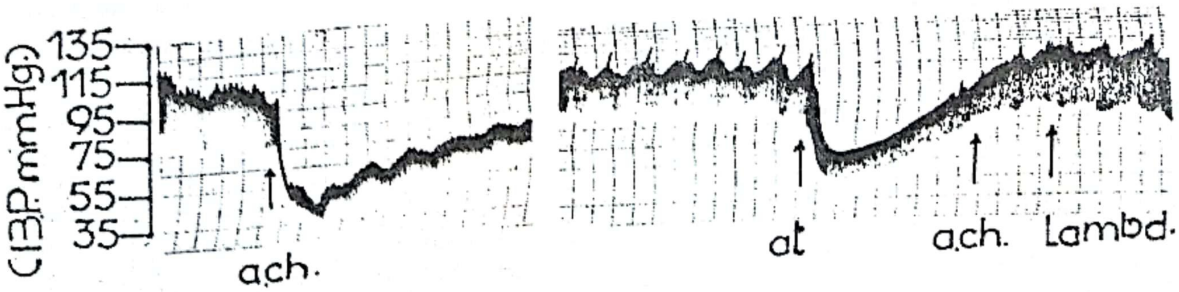

Fig. (9) : The site of action of lambda-cyhalothrin on the blood pressure of dogs. Notice the cholinergic activity of the drug.

a significant prolongation of prothrombin time after 2,3 and 4 weeks of last spray (Table1).

These data concised with that of [20] who reported that oral administration of lambda-cyhalothrin in rats greately affect the blood picture , producing decrease in erythrocyte counts , Hb% and P. C. V. % . They suggested that changes which happened after administration of lambda - cyhalothrin might be due to liver and spleen damage.

Spraying of lambda-cyhalothrin in single effective concentration 1 mg /40 ml) for 5 successive days on rabbits had no effect on liver and kidney function parameters . Meanwhile, spraying of double effective concentration (2 mg/40 ml) induced a significant elevation of sAST , sALT , alkaline phosphatase and total bilirubin (Table 2) and significant rise in blood urea nitrogen, creatinine and uric acid (table , 3) after 1,2,3 and 4 weeks of last spray, respectively. The results indicate that lambda -cyhalothrin in its double effective concentration might produce degenerative changes of liver and kidney.

Our results are in agreement with [5] who reported that lambda-cyhalothrin in its therapeutic concentration did not produce adverse effects after clinical examination and analysis of different biochemical parameters in blood and serum samples of animals exposed to the drug.

It could be concluded from our results that lambda-cyhalothrin (Icon, ICI)[R] , the most recent pyrethroidal insecticide , stimulated the peripheral cholinergic receptors in smooth and cardiac muscles with a transient hypotensive effect, so atropine might be the most effective treatment , if any adverse effects happened due to lambda-cyhalothrin inhalation, or ingestion . The drugs could be sprayed safely in its single effective concentration and care must be taken with the double effective concentration which has harmful effects on blood , liver and kidney function.

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بعض التأثيرات الجانبية لمركب اللامبدا - سايهالوثرين (أيكون ١ ئى)
المبيد الحشري البيروثرويدى الجديد

جمال أمين شمس ، عبدالعليم فؤاد عبدالعليم ، محمد السيد جبر ، طه عبدالفتاح محمد
قسم الفارماكولوجى - كلية الطب البيطرى - جامعة الزقازيق - مصر

لقد إتضح من هذه الدراسة أن مركب اللامبدا - سايهالوثرين يسبب تأثيرا مثبطاً على قوة وعدد ضربات القلب المعزول من الأرانب ولقد وجد أن هذا المركب له تأثيراً مثبطاً على الشريان الأورطى المعزول من الفئران وأن هذا التأثير يشابة فعل الأسيتيل كولين على الأوعية الدموية والقلب وله أيضاً تأثير مثبطا على عضلة الحجاب الحاجز فى الفئران ولقد ثبت عدم فاعلية النيوستجمين على هذه العضلة فى وجود مركب اللامبدا - سايهلوثرين . كما أن المبيد الحشرى يسبب هبوطاً مؤقتاً فى ضغط الدم وأن هذا التأثير مشابهاً أيضاً لفعل الأسيتيل كولين ولقد وجد أيضاً أن رش هذا المركب فى تركيزة المؤثر كمبيد حشرى ليس له تأثيرات ضارة على صورة الدم فى الأرانب بينما رش ضعف التركيز يؤدى إلى تغيرات واضحة فى صورة الدم ومنها الأنخفاض الملحوظ فى نسبة الهيموجلوبين وعدد كرات الدم الحمراء والبيضاء وزيادة ملحوظة فى فترة البروثرومبين .

ولقد وجد أيضاً أن المركب فى تركيزة المؤثر كمبيد حشرى ليس له تأثيرات ضارة على وظائف الكبد والكلى فى الأرانب ولكن فى ضعف جرعته يسبب أرتفاعاً معنوياً فى نشاط خميرة الاسترات أمينو ترانسفيريز والالاتين أمينو ترانسفيريز والفوسفاتيز القاعدى والصفراء وأيضاً يسبب أرتفاعاً معنوياً فى نسبة الكرياتينين وحمض اليوريك واليوريا مما يدل على أن هذا المركب يسبب تغيرات تحطيمية فى خلايا الكبد والكلى فى الأرانب المرشوشة بضعف الجرعة المؤثرة (٢مجم / ٤٠ملل) لمدة خمس أيام متتالية .

ومن هذه الدراسة يمكن أستنتاج أن استخدام مركب اللامبدا - سايهالوثرين فى تركيزة المؤثر كمبيد حشرى (١مجم / ٤٠ ملل) تكون آمنه أما زيادة التركيز يؤدى إلى تأثيرات ضارة على الدم والكبد والكلى . ولذا فإنه يجب حماية الإنسان والحيوان من التعرض للتركيزات العالية من المركبات البيروثرويدية .