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METHOD FOR THE PATHOGENETIC PREVENTION AND TREATMENT OF INTOXICATION BY THE PESTICIDE DECIS WITH LIPOIC ACID

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Abstract:

The use of the pesticide insectoacaracide Decis, if the safety rules are not followed, can cause occupational poisoning. According to the results of the presented research on finding antidotes by neutralizing the poison when poisoning with Decis, lipoic acid was used as a pathogenetic prophylaxis and treatment. Lipoic acid, when combined with the pesticide, forms a neutral, non-toxic compound in the form of a Decis + Lipoic acid complex, which leads to the normalisation of disturbed metabolic processes.

Keywords: Pesticide Decis, intoxication, prevention, lime acid, neutralisation, correction.

RELEVANCE.

Decis is an insecticide widely used to protect against pests of wheat, rye, oats, barley, cotton, sunflower, sugar beet, tomato, corn, apple, pear, grapevine, potato [3]. Active ingredient: (S)-3-phenoxy-α-cyanobenzyl ether of (R)-cis-3 (2,2 dibromophenyl)-2,2-dimethyl diclopropofankarboxylic acid). Empirical formula: C22H19Br2NO3. Molecular weight is 505.2. In acute intragastric exposure the LD50 for white rats was 155 mg/kg (according to our data) [5]. Lipoic acid is involved in oxidative decarboxylation of pyruvic acid and other α-keto acids, participates in the regulation of lipid and carbohydrate metabolism, has a lipotropic effect, affects cholesterol metabolism, improves liver function (Lipoic Acid: Vitamin Biochemistry) [2,9].

The main condition for the action of lipoic acid is the disulfide five-membered ring. The reduced form of lipoic acid retains almost all of its activity. The biological activity is related to the configuration of the asymmetric carbon atom. Lipoic acid and its reduced form, octane-6,8-dithiol acid, are active [1]. Lipoic acid has a positive therapeutic effect in poisoning with hepato- and nephrotoxic substances (heavy metal compounds, ethylene glycol). Vitamins B1, B6 and B12, coenzyme A complex, cocarboxylase, as well as lipoic acid are used as lipotropic drugs to prevent accumulation of anaerobic glycolysis products - pyruvic and lactic acids, which stimulate oxidation-reduction process in organism.

One of the most widely used in agriculture is the pesticide Decis, belonging to the pyrethroid group. In the available domestic and foreign literature, there are a significant number of works devoted to the elucidation of its mechanism of action [6]. However, there is an almost total lack of research aimed at finding protective and therapeutic remedies for poisoning by the above preparation. Considering that the widespread use of Decis does not exclude the possibility of both accidental and occupational poisoning, we conducted research to find antidotes by neutralizing the poison in Decis poisoning. In this connection, lipoic acid containing active forms of sulfhydryl groups was used as a pathogenetic prophylaxis and treatment of intoxication by Decis, a representative of pyrethroids [8].

THE AIM OF THE WORK STUDY

Is a method of pathogenetic prevention and treatment by neutralisation of toxic properties and correction of metabolic processes in intoxication by the pesticide Decis with the introduction of lipoic acid.

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MATERIALS AND METHODS OF RESEARCH:

To neutralize the molecules of the pesticide Decis, a representative of the pyrethroid group, and to regulate metabolic processes using lipoic acid.

Experimental studies were carried out with laboratory mongrel male rats weighing 170-190 grams, animals were kept on the usual vivarium diet. The experiments were performed in two series, in acute and chronic experiments consisting of 5 groups. Group 1 animals were given an aqueous emulsion of Decis intragastrically once at a dose of 130 mg/kg (1/84 LD50) (the mixture was prepared as an aqueous solution - emulsion). Group 2 rats were intragastrically injected with a mixture consisting of Decis and lipoic acid at doses of 130 mg/kg and 10 mg/kg (a mixture of Decis 13 mg/100 g and lipoic acid 1.5 mg/100 g per 100 g of animal body weight). Group 3 animals were administered Decis repeatedly at a dose of 7.7 mg/kg for 60 days. Group 4 animals were administered Decis 5 mg/kg intragastrically daily for 60 days. The 5th group of animals served as a control. Subcellular fractions of the liver and small intestine mucosa, biochemical indices of carbohydrate-energetic [4], protein metabolism and nucleic acids - DNA, RNA were studied. Extraction of liver subcellular elements was performed by centrifugation and spectrophotometrically determined the amount of nucleic acids [7].

RESEARCH RESULTS.

The intended work is achieved by introducing lipoic acid into experimental animals exposed to the toxic chemical representative of pyrethroids, Decis, to neutralise the poison and correct metabolic processes and restore redox processes, which is ensured by hydrogen electron transfer through the respiratory chain (Fig. 1).pesticide deactivation, by combining the freed hydrogen from the biologically active substance and forming a compound complex. Figure 1 shows how lipoic acid, with the help of dehydrogenase, is converted into octandithiolic acid (the reduced form of lipoic acid), producing 2H from NAD-2H.

Thus, the reduced lipoic acid combining with Decis neutralizes the toxic effect of 2 pesticide molecules, forming a complex compound of Decis with lipoic acid, and improves redox processes with hydrogen supply (lipoic acid and Decis giving one hydrogen atom each to NAD-2H) and leads to normalization of metabolic processes in the tricarboxylic acid cycle

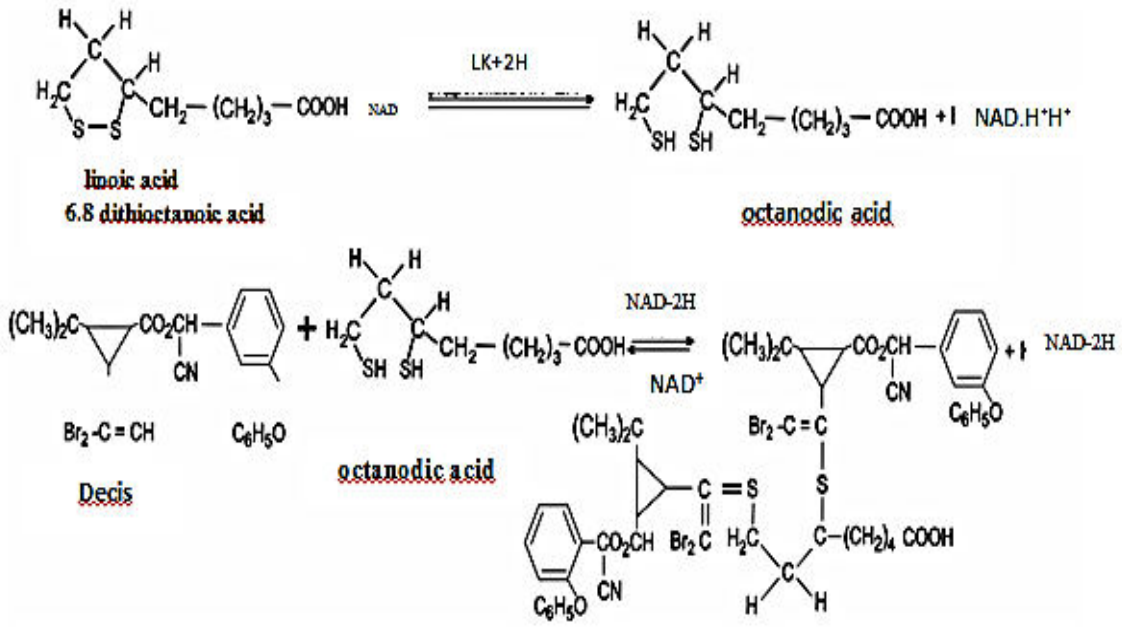

Figure 1: Method of pathogenetic prevention and treatment of intoxication by the pesticide Decis with lime acid.

Our studies confirmed the probability of changes in some parameters of carbohydrate-energy and protein metabolism, enzyme spectrum during intoxication with the pesticide Decis. In order to prevent the adverse effects of pesticides on the body, the use of lipoic acid to neutralise the toxic effect of the pesticide and to correct metabolic processes is of great importance.

Studies have shown that lipoic acid, by neutralizing, prevents the development of acute

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intoxication and death of animals: out of 9 rats poisoned with Decis at a dose of 130 mg/kg (LD84), 8 animals died, that is 88.9%; in the group of rats that received lipoic acid together with pesticide - only 4 out of 9 animals died, ie, there is a decrease in toxicity of the pesticide by 44.4%. Consequently, in rats that received Decis with lipoic acid, the survival rate of the animals was 55.6%. Group 2 experimental animals were injected daily for 60 days with lipoic acid at a dose of 5 mg/kg, an aqueous emulsion of the pesticide Decis at a dose of 7.75 mg/kg in the stomach. The first experimental group of animals received only the pesticide Decis at the same dose.

Repeated poisoning of animals with the pesticide Decis led to significant changes in the content of nucleic acids in the studied subcellular fractions of the liver and the small intestine mucosa in all terms of the experiment. At the same time, DNA content in the nucleus, liver supernatant and small intestine mucosa decreased reliably in all periods of the study; RNA level in all elements of the liver and small intestine decreased to a significantly greater extent (Table 1).

Lipoic acid preparations administration in chronic pesticide poisoning resulted in normalization of nucleic acids content in the studied liver and small intestine elements or in their approximation to the control data. At the same time, DNA content in the liver homogenate on 30 and 60 days of poisoning increased up to 129,5 and 186%, and RNA content - up to 134 and 195%, respectively. DNA and RNA concentrations were increased by 150.7-196% in the nuclear fractions and by 152% and 182% in the supernatant. In the small intestinal mucosa, the efficiency of changes in RNA content was higher than that of DNA. Repeated intragastric administration of Decis to animals at a dose of 1/20 of LD50 had a significant effect on protein content in subcellular fractions of liver and small intestine mucosa, and the level in mitochondria, nucleus and supernatant significantly decreased on days 30 and 60. In the small intestinal mucosa, the protein content decreased, but to a slightly lesser extent (Table 2)

Table 1.
Effects of lipoic acid (LA) on nucleic acid content acids in subcellular fractions of the liver and small intestine mucosa on exposure to Decis

Researh day	**Group**	**Liver**			**The mucous membranes of the small intestine**
		homogenate	**kernel**	**supernatant**	
DNA					
30	Control	4,02±0,24	3,52±0,31	4,65±0,31	3,28±0,28
	1	2,51±0,3***	2,27±0,16***	2,82±0,30***	2,01±0,18***
	2	3,25±0,26	3,42±0,31*	4,31±0,44	3,26±0,27*
60	1	2,47±0,23***	2,33±0,12**	2,48±0,48**	1,91±0,27**
	2	4,60±0,42***	3,86±0,45*	4,51±0,43**	2,73±0,28
RNA					
30	Control	5,40±0,42	5,37±0,42	5,28±0,47	4,28±0,34
	1	3,85±0,56*	3,51±0,29**	3,56±0,26*	3,15±0,35***
	2	5,19±0,61	5,38±0,46**	5,76±0,48***	4,82±0,41*
60	1	2,79±0,47***	2,98±0,35***	2,94±0,31***	1,95±0,12***
	2	5,43±0,42***	4,64±0,48**	4,91±0,30**	3,84±0,39***

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*Note: significance * - when comparing group 1 with control; * - P<0.05; ** - P<0.01; *** - P<0.001; significance * - when comparing group 2 with group 1: * - P<0,05; ** - P<0,01; *** - P<0,001.*

The application of lipoic acid in repeated poisoning with pesticide Decis for 60 days resulted in increased content of total protein in subcellular fractions of the liver and small intestine. Concentration of protein in liver homogenate in animals of group 2 by 30 and 60 days increased by 136 and 126,4%, as compared with animals poisoned without bioactivator administration. In other liver fractions the increase on 30 and 60 days was 124,5 and 144%, and in the mucous membrane of the small intestine of poisoned rats, after injection of lipoic acid, the number of proteins increased by 119 and 122%. Consequently, when poisoned with Decis, application of bioactivator - lipoic acid led to normalization of protein level in subcellular fractions of the liver and small intestine mucosa or brought it closer to the indicators of the control group.

Table 2.
Effects of lipoic acid (LA) on total protein levels in subcellular fractions of liver and small intestine mucosa in Decis pesticide poisoning

Researh day	**Group**	**Liver**				**Small intestine**
		homogenate	**mitochondrie**	**kernel**	**supernatant**	
30	control	12,47±1,10	13,27±0,78	12,71±0,82	13,73±0,99	9,97±0,91
	1 - Decimus	9,28±0,59**	9,73±1,00*	9,04±0,89**	9,81±0,35**	7,63±0,73
	2 - Decis + LC	12,61±0,55**	12,11±0,52^	11,94±0,92*	12,75±0,47	9,03±0,54
60	1 - Decis	9,35±0,40*	8,04±0,65***	7,71±0,73**	9,20±0,52**	8,33±0,47
	2 - Decis + LC	11,82±0,38**	11,35±0,52**	11,11±0,50*	11.43±0,49*	10.18±0,94

*Note: significance * - when comparing group 1 with control; * - P<0.05; ** - P<0.01; *** - P<0.001; significance * - when comparing group 2 with group 1: * - P<0,05; ** - P<0,01; *** - P<0,001.*

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Thus, chronic poisoning with pesticide Decis causes changes in content of nucleic acids - DNA and RNA, total protein in subcellular fractions of liver and small intestine mucosa.

As a result of the study for the first time quite typical disorders of carbohydrate-energetic metabolism, expressed in the accumulation of pyruvic and lactic acids, changes in the intensity of oxygen consumption with phosphorylation, due to violations of the functional activity of enzymes in liver mitochondria involved in the metabolism of tricarboxylic acid cycle (glutamate, malatehydrogenases and cytochromoxidase) were revealed. The characteristic changes in carbohydrate metabolism indicate increased anaerobic glycolysis and disturbances in the rate of redox processes. The daily introduction of the bioactivator lipoic acid into the stomach of the animals leads to a significant normalisation of the redox process (Table 3). The table shows that when rats were treated with pesticide Decis, the lactic and, especially, pyruvic acid content in liver during 60 days increased from 44 to 142,4% compared with control and resulted in reduced activity of glutamate dehydrogenase (GDH), succinate dehydrogenase (SDH), malate dehydrogenase (MDH) and cytochrome oxidase (COX).

Comparison of the results of studied enzymes with results of bioenergetics substrate studies showed that in Decis poisoning, impairment of liver mitochondria functional status was manifested by inhibition of tricarboxylic acid cycle enzymes activity, resulting in accumulation of pyruvic and lactic acids in liver. The use of lipoic acid in the biosurfactants studied increased the activity of redox enzymes and decreased the levels of lactic and pyruvic acids.

Table 3
Effects of lipoic acid on liver carbohydrate-energetic parameters in Decis poisoning

Research day	Group	**Acid**		**Enzyme activity, µmol/g.h.**			
		lactic, µmol/g	**ruvic acid, µmol/g**	**GDG**	**SDG**	**MDG**	**TSHO**
30	control	4,27±0,17	187,5±15,8	15,47±0,84	87,5±3,41	49,8±3,51	1,38±0,07
	Decis	4,70±0,16**	2677,0±13,6*	10,69±1,36*	41,75±4,05**	30,3±3,339**	0,65±0,05**
	Decis + LC	4,51±0,12	157,3±13,8**	14,1±0,85*	84,0±3.35***	41,27±3,00*	0,87±0,09*
60	Decis	4,85±0,11	252,3±13,7**	8,94±1,7***	44,0±4,26***	29,04±2,95**	0,73±0,05
	Decis + LC	4,61±0,19	209,4±14,0*	13,43±1,19**	76,2±0,42**	39,68±3,82*	0,82±0,08

*Note: significance * - when comparing group 1 with control; * - P<0.05; ** - P<0.01; *** - P<0.001; significance * - when comparing group 2 with group 1: * - P<0,05; ** - P<0,01; *** - P<0,001.*

The study of liver mitochondria revealed an adverse effect of Decis at a toxic dose on the functional system of oxidative phosphorylation, which was manifested by a decrease in respiration rate, oxidative phosphorylation of tricarboxylic acid cycle substrates, α-ketoglutaric acid and succinate. The data obtained suggest that, when intoxicated with Decis, the amount of endogenous substrates changes, against the background of a shift in the intensity of respiration and oxidative phosphorylation. In Decis-poisoned animals, administration of lipoic acid resulted in enhanced respiration in liver mitochondria and resulted in respiratory control values and ADP/O ratio of substrates, α-ketoglutaric acid and succinate, being close to normal. Repeated administration of the pesticide Decis to animals caused accumulation of under-oxidized products of lactic and pyruvic acids in the liver. The activity of transaminases of other amino acids in all elements of liver cells decreased on the 30 and 60 days of the experiment, while bioactivator application increased and approached to the control group of animals. Similar phenomena occurred in the mucosa of the small intestine when poisoned with Decis. The intensity of α-ketoglutaric acid reamination of the studied amino acids was reliably decreased when animals were repeatedly poisoned with Decis.

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When lipoic acid was administered, the activity of these transaminases increased and reached that of the control group (Table 4).

Consequently, introduction of lipoic acid into the stomach of pesticide-poisoned animals causes activation of the intensity of amino acid reamination - histidine, tyrosine, tryptophan and phenyl alanine with α-ketoglutaric acid in homogenate, mitochondria, liver supernatant and small intestine mucosa.

Table 4
Peculiarities of the effect of lipoic acid on liver and small intestine mucosal transaminase activity in Decis poisoning

Subject	**Research day**	Group	**Transaminase activity, μmol/g.h.**			
			histidine	**tyrosine**	**tryptophan**	**phenylalanine**
homogenate		control	8,14±0,89	6,97±0,62	7,11±0,58	6,25±0,50
		1	4,50±0,9**	2,98±0,29***	3,27±10,5***	2,91±0,70***
	30	2	7,41±0,74*	6,02±0,59**	6,84±0,53***	5,89±0,72*
	60	1	44,6±0,71*	3,74±0,54***	4,33±0,56**	4,24±0,60*
		2	7,14±0,58*	6,97±0,50***	6,73±0,70**	6,94±0,51**
mitochondria		control	6,24±0,43	7,22±0,66	7,16±0,58	6,17±0,42
		1	3,65±0,60*	3,12±0,41**	3,74±0,57***	3,42±0,65***
	30	2	6,08±0,64*	5,89±0,49**	6,84±0,44**	6,84±0,41***
	60	1	4,12±0,49**	4,37±0,68**	4,43±0,78*	4,07±0,58**
		2	7,41±0,58***	6,84±0,44**	6,68±0,40*	6,71±0,63**
supernatant		control	7,38±0,68	7,54±0,53	6,73±0,65	8,25±0,74
		1	4,12±0,64**	3,74±0,53***	3,93±0,59**	4,78±0,69**
	30	2	6,89±0,43**	6,52±0,49**	6,78±0,44***	6,52±0,58*
	60	1	4,31±0,57***	4,18±0,62***	4,37±0,69***	4,18±0,56***
		2	6,40±0,92*	6,35±0,53**	6,57±0,80	5,89±0,65
small intestine mucosa		control	6,89±0,55	7,03±0,50	6,77±0,78	7,22±0,54
		1	3,98±0,52**	3,72±0,77**	4,03±0,78*	4,37±0,32***
	30	2	6,71±0,63*	6,90±0,47**	6,58±0,49*	7,11±0,44**
	60	1	4,18±0,62*	3,80±0,73***	5,32±0,73*	3,99±0,73**
		2	6,30±0,52*	6,73±0,75**	6,72±0,48	6,21±0,69*

*Note: significance * - when comparing group 1 with control; * - P<0,05; ** - P<0,01; *** - P<0,001; significance * - when comparing group 2 with group 1: * - P<0,05; ** - P<0,01; *** - P<0,001.*

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CONCLUSIONS:

1. As a result of the carried out researches in experimental animals at intoxication by pesticide Decis, changes of some parameters of carbohydrate-energetic, protein and nucleic acid metabolism, enzyme spectrum and oxidative phosphorylation have been revealed.

2. In order to prevent adverse effects of pesticide Decis, for correction of metabolic processes in the body, the use of lipoic acid is of great importance. Lipoic acid, when combined with the pesticide, forms a neutral, non-toxic compound in the form of "Decis + lipoic acid" complex.

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