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Toxicological Characteristics Of Skimmianine Under Chronic Administration In White Rats

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Abstract: In chronic experiments in laboratory animals, studied toxicological perspective new antidepressants Skimmianine for the treatment of depressive states, an original herbal preparation based on Haplophylum perforatum was created. During 6 months of intragastric administration in animals exposed to all doses of skimmianine, no deviations in the parameters of the functioning of the nervous system were found, therefore, this value is the lowest effective (threshold) dose in a chronic experiment.

Keywords: Skimmianine, chronic experiments, central nervous system, biochemical parameters

1. INTRODUCTION

Scientists of the Institute of Plant Chemistry of the Academy of Sciences of the Republic of Uzbekistan as a result of the development of new antidepressants Skimmianine [1] for the treatment of depressive states created an original herbal preparation based on *Haplophylum perforatum*. In previous experiments, psychostimulating, anxiolytic [2], m-cholinomimetic and low-toxic [3] properties of skimmianine were found. To identify substances with new antidepressant activity, several different models of depression and behavioral assessments were developed in experimental rodent animals [4]. In order to justify and carry out measures aimed at protecting human health and the environment at the stage of production design, as well as in accordance with the requirements of international legislation [6], it is necessary to identify patterns of manifestation of toxic properties of Skimmianine in various indicators for safe production and its further use in medical practice. A special role in conducting such studies belongs to the study of chronic toxicity of the compound in warm-blooded animals, as a result of which the values of threshold and subthreshold doses are established.

The aim of the work was to determine the threshold and inactive doses of Skimmianine in a chronic experiment on white rats.

2. MATERIALS AND METHODS

The experiments were performed on 36 randomized white male rats with an initial weight of 180-200 g. Healthy animals with a clean coat were selected for the experiment after

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intragroup adaptation. The treatment of animals was consistent with the ethical principles of good laboratory practice [7]. Skimmianine (SCM) was injected into the stomach of experimental animals using a needle probe. Distilled water was used as a solvent.

The study of toxic properties was carried out by administering fixed doses of Skimmianine to male white rats for 6 months (5 days a week). The animals were divided into 4 groups of 6 individuals each: I-control and II, III, IV-experimental, exposed to 1/4500, 1/45 and 1/9 of LD_{50} (0.1; 10 and 50 mg / kg, respectively). The control group was administered distilled water in equivalent volumes.

During the experiment, changes in the body weight of animals were recorded. At the end of the experiment, a number of indicators of behavioral activity in the "Open field" installation were studied in rats. After simultaneous decapitation of rats during autopsy, the relative mass coefficients (RMC) of internal organs – heart, kidneys, liver, spleen, thymus, adrenal glands, lungs-were determined. To characterize the functional state of the body of experimental animals, the morphofunctional composition of peripheral blood was studied (hematological analyzer Mythic18, Switzerland), and a number of biochemical parameters of blood serum were also determined (automatic biochemical analyzer Accent 200, Poland).

The results of the studies were processed by conventional methods of variational statistics. When assessing the differences between the groups, the Student's parametric t-test with the Bonferroni correction or the nonparametric Mann-Whitney U-test were used. The critical level of significance when testing statistical hypotheses was assumed to be $p \leq 0.05$.

3. RESULTS

During 6 months of the experiment, no animal deaths were observed in any of the experimental groups. Chronic administration of SCM at doses of 50; 10 and 0.1 mg / kg did not cause significant changes in the condition of experimental animals, also, during the experiment, experimental animals did not differ from the control ones in terms of body weight gain. The functional state of the central nervous system of experimental animals in a chronic experiment was evaluated by the parameters of their behavioral activity. With the introduction of SCM in all doses, statistically significant changes in the behavior of animals of the experimental groups were noted, expressed according to the studied behavioral indicators in a significant increase from control rats both on the 26th day of administration (Table 1) and repeated on the 60th day of administration (Table 1).

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Table-1.Indicators of behavior of white rats when administered skimmianine in a chronic experiment day 26 administration n=6

The comparison group	Indicators					
	pass through sectors	mink reflex	plumbing	grooming	stool	urine
I- control	11,7±5,16	12,17±4,3	1±0,43	0,5±0,43	2,17±2,15	0,8±0,4
II - 0,1 mg/kg	27,7±3,87*	25,8±4,3*	2,7±1,72*	0,3±0,4	2±1,7	0,1±0,4*
III - 10 mg/kg	20,7±6,88*	13,5±5,16	1,7±2,58	0,67±0,43	3,8±2,15	0*
IV - 50 mg/kg	13,7±4,73	10,3±3,8	1±0,43	0,5±0,4	2±1,3	0*

Note. * - differences are statistically significant, $p \leq 0.05$

Indicators of behavior of white rats when administered skimmianine in a chronic experiment day 60 administration n=6

The comparison group	Indicators					
	pass through sectors	mink reflex	plumbing	grooming	stool	urine
I- control	10,2±2,15	8,83±3,44	0,5±0,43	0,17±0,43	1,3±0,43	2,8±1,3
II - 0,1 mg/kg	25,5±5,16*	24±7,3*	2±0,86*	1±0,43*	0,33±0,43*	0,3±0,4*
III - 10 mg/kg	21±3,44*	23±2,58*	1,3±0,43*	1,17±0,43*	0,67±0,43	0,83±0,86*
IV - 50 mg/kg	16±4,3*	18,3±3,1*	1±0,43*	0,67±0,4*	0,5±0,43*	1±0,43*

Note. * - differences are statistically significant, $p \leq 0.05$

Administration of SCM at doses of 0.1, 10 and 50 mg / kg for 6 months did not cause changes in the RMC of internal organs – heart, liver, kidneys, lungs, spleen, and adrenal glands in rats compared to control animals. Macroscopic examination of internal organs also showed that the drug does not cause general pathological and specific destructive changes in the organs and tissues of animals, the state of internal organs in experimental and control rats corresponded to the norm (Table 3).

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Table 3.Relative mass coefficients of internal organs of rats with the introduction of SCM in a chronic experiment g / kg

RMC bodies	I-control	II-experimental 0.1 mg / kg	III-experimental 10 mg / kg	IV-experimental 50 mg / kg
Liver	6,8±0,88	7,12±0,6	7,15±1,0	7,3±1,1
renals	1,47±0,13	1,52±0,2	1,58±0,13	1,6±0,2
suprarenal	0,058±0,02	0,06±0,008	0,061±0,01	0,06±0,01
Spleen	0,93±0,1	0,93±0,17	1,05±0,21	1±0,36
Heart	0,7±0,08	0,83±0,13	0,9±0,08	1,0±0,16
light	2,23±0,3	2,2±0,69	2,5±0,3	2,5±0,5
thymus	0,19±0,06	0,15±0,07	0,16±0,03	0,17±0,05

In the future, a study of blood cells was conducted, which showed that SCM in doses of 0.1, 10 and 50 mg / kg does not have a negative effect on the functioning of the "red sprout"system. Similarly, in all experimental groups, the values of platelet parameters corresponded to the control values. Also, no statistically significant changes in the leukogram were found in comparison with the control group of animals (Table 4).

Table-4.Morphofunctional blood parameters of white rats exposed to SCM in a chronic experiment

Indicators	The comparison group			
	I-control	II-experimental 0.1 mg / kg	III-experimental 10 mg / kg	IV-experimental 50 mg / kg
HGB- 10^9 g/l	128,2±15,48	147,3±14,62*	122,5±18,5	116±15,5*
RBC- 10^{12} g/l	7,58±1,35	8,11±0,93*	7,07±1,12*	6,53±1,08*
HCT- %	40,13±5,42	45,6±5,01*	39,3±5,98	35,3±5,4*
MCV- fl.	53,82±2,75	56,32±0,9*	55,82±2,1	54,32±2,7
MCH- pg.	17,05±0,95	18,2±0,43*	17,32±0,65	17,3±0,52

WBC- 10^9 g/l	8,08±1,94	8,72±2,1*	8,83±3,9*	10,01±1,8*
PLT-10^9 g/l	710,7±109,2	680,5±105*	740,83±71,4*	672±225*
MPV-fl.	7,3±0,13	7,72±0,3*	7,9±0,34*	7,68±0,17*
PCT- %	0,525±0,08	0,526±0,09	0,605±0,04	0,493±0,12
PDW	13,6±0,13	13,92±0,34*	13,93±0,26*	13,72±0,34

Note. * - differences are statistically significant, $p \leq 0.05$

In order to assess the toxic effect of the studied compound on the body in a chronic experiment, biochemical parameters of the functioning of internal organs and systems, as well as blood serum of experimental animals, were determined. The studied indicators are integral during toxicological studies and fully reflect both the general state and features of metabolism (protein, carbohydrate and lipid) of laboratory animals exposed to SCM. As the results of the study showed, chronic intragastric administration of SCM in doses of 0.1, 10 and 50 mg / kg reduces cholesterol, but did not lead to a significant deviation of the considered indicators from those registered in the control series (Table 5).

Table-5.Biochemical parameters of blood serum of white rats exposed to chronic SCM exposure

Indicators	The comparison group			
	I-control	II-experimental 0.1 mg / kg	III-experimental 10 mg / kg	IV-experimental 50 mg / kg
Total protein mg/ml	36,1±4,9	43,6±4,5*	40,6±8,7*	41,4±6,4*
Glucose mmol/l	4,74±0,84	5,06±0,89*	4,95±0,43*	5,2±0,53*
AST mmol/L	0,61±0,3	0,7±0,043*	0,73±0,07*	0,79±0,12*
Cholesterol mg/dl	41,7±16,7	34,7±19,9*	23,3±14,5*	23±8,6*
Triglycerides mg/dl	21,65±4,0	22±9,5	21,6±14,45	21,15±5,72
MDA nmol/mg	1,9±0,66	2,0±0,8	1,92±0,8	1,41±0,44*

Note. * - differences are statistically significant, $p \leq 0.05$

4. DISCUSSION

Thus, according to the results of the analysis of laboratory data, there is no pronounced negative effect of SCM in the applied doses on the processes of hematopoiesis, the functional

state of the main organs and systems, including various types of metabolism. On biochemical indicators, it reduces cholesterol levels, and this indicates a hypocholesterolemic effect.

5. CONCLUSION

As shown by the results of the study of chronic toxicity in intragastric intake of white rats, SCM affects the functioning of the nervous system, which is reflected in dose-dependent changes in the behavior of animals in terms of research, motor activity and an increase in the threshold of their excitability. Chronic intragastric administration of Skimmianin to white rats did not have a general toxic effect, estimated by indicators of the functioning of the nervous system, body weight gain, hematological and biochemical parameters, therefore, the value of this level of exposure is the most inactive (subthreshold) dose. During 6 months of intragastric administration in animals exposed to all doses of skimmianin, no deviations in the parameters of the functioning of the nervous system were found, therefore, this value is the lowest effective (threshold) dose in a chronic experiment.

6. REFERENCE

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