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5% Suspension of Albendazole Echinacea Magenta (Echinacea Purpurea) Toxicometric Evaluation

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ABSTRACT

The acute toxicity of 5% suspension of albendazole Echinacea Magenta (Echinaceapurpurea) was studied when administered orally to outbred white mice. To determine the characteristics of the suspension acute toxicity, it was administered to animals once with varying doses. The general condition and behavior of animals were observed during 14 days. The intoxication symptoms' manifestation and possible death were noticed. The animals' death was observed within five days after the drug administration. The drug's acute toxicity characteristics were as follows: MPD -740 mg/kg of body weight, and LD_{50} – 2960 mg/kg of body weight, LD_{16} -1450,4 mg/kg, LD_{84}– 6050 mg/ kg of body weight. In accordance with Russian State Standard 12.1.007-76, the drug belonged to the class 3 of danger (moderately toxic substance).

Keywords: Toxicity, The Lethal Dose, Anthelmintics, Drug, Mice, Albendazole, Research.

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INTRODUCTION

Drugs ecological safety is of a great importance [1, 2]. Natural products are of great interest in drug discovery, due to their large structural and chemical diversity [3]. Antimicrobial resistance, toxicity and poor immune-system of the host are the major problems encountered in the management of infectious diseases, and require the development of new, more effective and less toxic drugs [4]. To determine the main toxicometric characteristics of the drug substances, means to find out the drugs' scope of influence on the health status of animals and animal source products, which is an integral part of veterinary drugs' pre-clinical testing [1- 10].

In the veterinary medicine, the chemotherapeutic agents with mild irritants, resorptive and cumulative properties related to GOST 12.1 .007-76 to III and IV classes of danger have been the preferred drugs [1-12].

The search, the study and the implementation of new anthelmintic drugs with a low toxicity for animals in combination with selective toxicity

for parasites in small doses, have been promising vectors in the veterinary helminthology.

The 5% suspension of albendazole Echinacea Magenta *(Echinaceapurpurea)* was developed in the laboratory of infectious, non-contagious and parasitic diseases of VNIIOK — branch of the FGBNU «North Caucasian FNAC» (All-Russian Research Institute of Sheep and Goat Breeding — branch of the Federal State Budgetary Scientific Institution «North Caucasian Agrarian Center») along with the scientists of the Drugs Technology Department of the Pyatigorsk State Pharmaceutical Academy [13].

The aim of this research was to identify the main characteristics of toxicometric 5 % suspension of albendazole Echinacea Magenta *(Echinaceapurpurea)*.

METHODS AND MATERIALS

In the laboratory of the Institute (invitro) by the Kerber's method, the 5% suspension of albendazole Echinacea Magenta's *(Echinaceapurpurea)* lethal dose was determined. The research work was carried out in accordance with the ethical standards for the treatment of laboratory animals [14].

For toxicological studies by random sampling, considering the body mass, the clinically healthy, sexually mature, male, nonlinear white mice were picked, and kept in quarantine within 10-14 days.

Throughout the whole experiment, the animals were kept in the identical conditions of feeding and keeping (6-5 mice in each cage, at a temperature of 19-21 °C**,** mixed fodder ration "Vaka" («Вака»), "BIOSPHERA" («БИОСФЕРА», LLC, Russia), at the rate of 15-9 g per individual) in accordance with the applicable rules with free access to water and food. Before the administration of the researched suspension, the animals were on the starvation diet. The drug was administered orally and fractionally. The maximum amount of suspension on one dose was 0.5 ml.

On the first stage, the maximum tolerated dose of the suspension was determined. To achieve this, the mice (males, n=15, weight 17-24g.) were divided into 3 groups, which once were orally given the drug in different doses: 695,6 mg/kg per reactant, 740 mg/kg per reactant, 784,4 mg/kg per reactant.

Then the toxicity for the proposed 5% drug suspension was determined by increasing the doses. 5 groups of animals including 6 heads each was formed out of the thirty male white mice weighing 21-22 g., by random sampling, considering the body mass index. The animals of the first group were administered the suspension at a dose of 740mg/kg per reactant, the second group - a dose 1850mg/kg per reactant, and the third group - a dose 3700mg/kg per reactant, the fourth group - a dose mg/kg per reactant, twice at intervals of an hour and a half, and the fifth group - a dose 7400mg/kg per reactant twice, with an interval of half an hour.

After the drug administration, the general condition of the rodents was observed for 14 days. The integral indices of intoxication were analyzed (the consumption of water and food, activity and mobility, response to the external stimuli, paying attention to the condition of the coat, fixing the time of death of the animals).

Toxicometric assessment of the lethal dose was calculated by the following formula [15, 16]:

$$LD_{50} = LD_{100} - \frac{E_{ZD}}{n} \qquad (1)$$

E – the sum of the products ZD;

D – the interval between adjacent doses;

Z – the arithmetic mean of the number of animals, which have died under the influence of every two adjacent doses;

n – the number of animals in the group.

To determine the correlation between median lethal dose and the intermediate doses, the dependence between frequencies of deaths and increment dosages was determined graphically [13, 14].

The standard deviation was calculated according to the Gaddam's formula [13, 14]:

$$S = \frac{\sqrt{Ksd}}{n} \qquad (2)$$

K = 0,564;

d –the average of the intervals between the doses;

THE RESULTS

In the first experiment, the group of animals received the drug in a dose of 695,6 mg/kg per reactant. There were no signs of deviations of integral indicators. The individuals of the second and the third groups received the drug at doses of 740 mg/kg and 784,4 mg/kg per reactant; respectively, the signs of the onset of toxic effects were registered (the periods of excitation were followed by the inhibition). 14 days after the administration of the suspension, the maximum tolerated dose of the suspension was found out. LD_0 for the white mice was 740mg/kg per reactant.

This dose was defined as the initial one to assess the toxicity of the drug in the incremental doses. The results have been presented in table 1.

Table 1. Determing the 5% suspension of albendazole with tincture Echinacea Magenta *(Echinaceapurpurea) acute toxicity of on white mice, n=30*

Dose, mg/kg	740	1850	3700	5550	7400
Survived	6	3	2	1	0
Died	0	3	4	5	6
Z	1.5	3.5	4.5	5.5	
D	1110	1850	1850	1850	
ZD	1665	6475	8325	10175	

Thus, in the first experimental group, the suspension administration at a dose of 740mg/kg mice death was not registered. Within 48 hours, the signs of animals' intoxication were registered including: lethargy, inactivity and refusal to eat. In the second experimental group, the suspension administration at a dose of 1850 mg/kg killed 3 of the six specimens (one mouse died after 48 hours, 2 mice on the fifth day). In the third group, the dose of 3700 mg/kg killed 4 mice out of 6 (two animals died after 24 h after the administration, and two mice, in 48 h), and the dose of 5550mg/kg killed five mice of the 6 (three specimens of 6 died after 24 h, and 2 mice died after 48 h). In the fifth group, after the administration of the suspension to the maximum dose of 7400mg/kg, general depression, reduced the reaction to the seizure of the cell, and convulsions were registered; mouse dug into the litter and died. The data on the deaths of mice which received different doses of the suspension have been presented in table 2.

Table 2. Data on the deaths of mice which received different doses of the suspension *n=30*

Drug dose mg/100 g	Dose mg/kg body weight per reactant	The dose per mouse ml	The number of mice involved in the experiment n=50			% mortality	Days of death
			Total in experiment	survived	died		
14.8	740	0.1	6	6	0	0	0
37	1850	0.8	6	3	3	50	5
74	3700	1.5	6	2	4	66.7	4
111	5550	2.3	6	1	5	83.4	2
148	7400	3.1	6	0	6	6.84	1

In mice with the administration of the suspension in toxic doses (1850mg-5550мг/kg) after 30-40 min, piloerection, rapid breathing, narrowing of palpebral fissures, excitation, tremor, gradually turning into attacks of clonic convulsions were registered, which were repeated at the intervals of different durations, and they either caused death or gradual recovery of the vital functions of the animal organism.

Thus, in the acute experiment, the deaths of animals were registered within five days after the drug administration.

The results of the experiment the LD50 was calculated (1).

$$LD_{50} = 7400 - \frac{26640}{6} = 2960\text{mg/kg}$$

The found dependence, while incrementing the dose in the range from LDo to LD50, and further from LD50 to LD100 was used to identify the intermediate doses (in the middle of the interval and the next located ones, which was confirmed by the statistical findings based on the graphic data of the parent population), and has been presented in Figure 1.

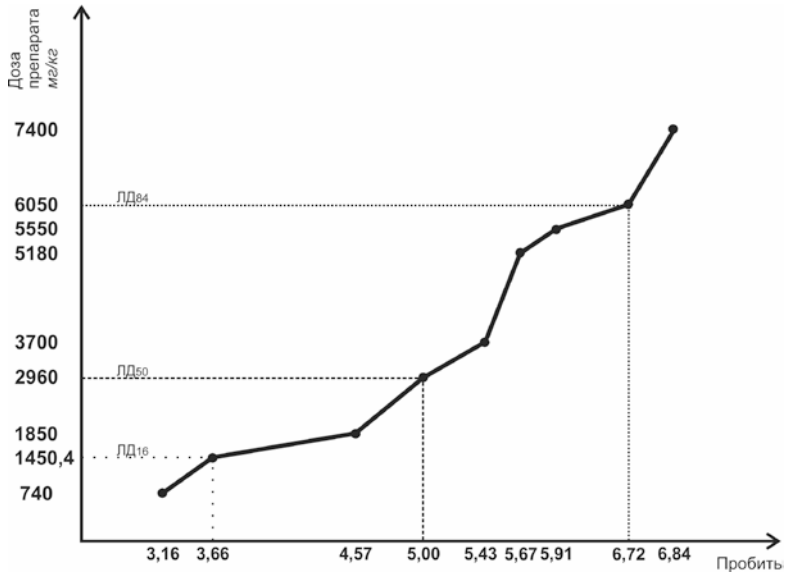

Fig. 1. The curve "dose-effect" of 5% suspension of albendazole with tincture Echinacea Magenta *(Echinaceapurpurea)* was introduced to white mice, n=30.

While increasing the dose by 22% (intercal 1450,4 mg/kg and 1850mg/kg), the lowest percentage of the animals' death rate increase was observed.

In dosages of between 3700mg/kg and 5180mg/kg (exceeding the dosage from the previous value by 28%), an abrupt increase in the animals' death rate was observed, which was fading between dosages 5180mg/kg and 6050mg/kg, and then again, abruptly increased in the interval between 6050mg/kg and 7400mg/kg (exceeding the dosage of 18% from the previous value), indicating the heterogeneous nature of the increasing doses' effects on the laboratory animals.

The standard deviation was determined by the Gaddam's formula (2):

s = (LD84 - LD16)/2 = (6050-1450,4)/2=5324,2 mg/kg.

$$S = \frac{\sqrt{0.56 * 5324.2 * 67.2}}{6} = 183.2 \text{ mg/kg}$$

Thus, LD_{50} considering the standard error, in 2960±183,39 mg/kg of body weight suggested that the drug, according to the classification (GOST 12.1 .007-76) was a moderately hazardous compound (class 3).

As a result of the suspension of albendazole administration in incremental doses, the basic toxicometric characteristics of the 5% suspension of albendazole Echinacea Magenta *(Echinaceapurpurea)*, were found out, and have been presented in Table 3

Table 3. The characteristics of 5% suspension albendazole Echinacea Magenta *(Echinaceapurpurea)* acute toxicity after a single dose (mg/kg).

Method of administration	Toxicity characteristics					S_{LD50}
	LD_0	LD_{16}	LD_{50}	LD_{84}	LD_{100}	
Peroral	740	1450.4	2960	6050	7400	±183.39

CONCLUSION

In this experiment, LD_{50} considering the standard error, was equal to 2960±183,39 mg/kg of the body weight of the mice. Therefore, the 5% suspension of albendazole with the immunostimulant, according to the conventional classification (Russian State Standard 12.1.07-76) could be considered as a low-toxic substance (III hazard class).

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