Original Article

Study of Acute and Chronic Toxicity of "Butaselmevit" on Laboratory Animals

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Abstract

The purpose of this work is to study the hepatoprotective properties of potassium 2-((4-amino-5- (morpholinomethyl)-4H-1,2,4-triazole-3-yl)thio)acetate on tetracycline and infectious hepatitis models in chickens. Biochemical examination of blood and liver serum was carried out on intact broiler chickens Cobb 500 cross. All groups of chickens were kept separate in different cells in the same room for the same microclimate parameters in accordance with the established requirements. The dose-dependent effect of "Butaselmevit" on leukopoiesis, hematological profile, and functional state of the liver in laboratory animals was established.

As a result of research on the model of hepatitis in chickens caused by tetracycline, established the hepatoprotective effect of potassium compound 2-((4-amino-5-(morpholinomethyl)-4H-1,2,4-triazole-3-yl)thio)acetate, which is not inferior to the referent drug - Thiotriazolin®. Based on the results of the biochemical study, hepatoprotective properties of the combination of the above compound with the antibiotic Saroflox®, combination of potassium 2-((4-amino-5- (morpholinomethyl)-4H-1,2,4-triazole-3-yl) thio) acetate with classical antibiotic Enrofloxacin® on the model of infectious hepatitis.

Keywords: Butaselmevit, Acute and chronic toxicity, Hexenal protection, Rats, Mice

Introduction

The article is devoted to the study of the effect of the new complex liposomal drug "Butaselmevit" on the indicators of acute and chronic toxicity in laboratory animals. The composition of this drug includes butafosfan, selenium, methionine, thistle spot, fat-soluble vitamins, and tween lecithin.

Studies have shown that intramuscular administration of the drug "Butaselmevit" at doses of 50, 500, 5000, and 50000 mg/kg did not lead to the death of white rats. At the same time, the use of preparation with a dose of 50,000 mg/kg caused short-term suppression of the general condition of laboratory animals, which is probably due to the introduction into the body of large quantities of the drug in rats.

In the study of acute toxicity of the drug "Butaselmevit" in white rats and mice, it has been established that the DL50 drug for intramuscular injection to laboratory animals is greater than 50,000 mg/kg. The drug "Butaselmevit" belongs to the low-toxic substances - IV class according to GOST 12.1.007-76.

The study of the chronic toxicity of the drug "Butaselmevit" showed that administration of white doses of 200 mg/kg to rats caused a probable increase in mean sleep time with a simultaneous decrease in the average time of swimming. In

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the long-term use of the study drug at doses of 100 and 20 mg/kg, the average sleep time for helenalin and the meantime of swimming in rats of experimental groups did not differ significantly from the control group.

For the study of chronic toxicity of the drug "Butaselmevit", for 31 days of the experiment, some changes in the coefficients of the internal organs were recorded, namely, the probable increase in the liver mass coefficient in the experimental groups of rats, which were administered the doses at doses of 200 and 100 mg/kg, respectively, at 33.6 and 9.3% for animals in the control group.

In the study of the toxic effects of the drug "Butaselmevit" in a chronic study, it was stated that despite the low toxicity, the study drug caused a dose-dependent effect on the hematological and biochemical parameters of the blood.

Intensive development of chemical chemistry in industry and agriculture, deterioration of the ecological situation, pollution of the environment by xenobiotics, and uncontrolled administration of drugs cause an increase in toxic lesions in humans and animals [1-3]. It is known that the central organ that provides the processes of detoxification of the body is the liver. Among diffuse liver lesions, great attention is paid to the toxic lesion of the liver [4-6]. In recent years, the role in the pathogenesis of liver diseases has been determined in the processes of activation of free radical oxidation of lipids of plasma and intracellular membranes of hepatocytes against the background of depletion of protective antiradical systems [7-10].

In order to increase the adaptive capacity and immunobiological reactivity of the organism, strengthening protein synthesis and enzyme function in animals in recent years, with the success of using new complex drugs. Separate authors have established the stimulating effect of thistle blisters, vitamins, selenium, and betafosfan on the activity of antioxidant and immune systems in animals [11-14]. However, the complex application of these drugs to liver function and the protective systems of the animal body at present in the scientific literature is not sufficiently highlighted. That is why we developed a new liposomal drug, which includes: butafosfan, selenium, methionine, thistle, and vitamins [15-17].

It is known that all new drugs, before entering serial production, on the market of veterinary medicines, must undergo appropriate toxicological testing with the clarification of the parameters of acute and chronic toxicity in laboratory animals in the long term of its introduction into the body [18, 19].

With this in mind, objective toxicological control accelerates the development of new highly effective veterinary drugs, prevents possible metabolic disorders, the structure of individual organs and tissues, the emergence of side effects, and long-term consequences, and creates the preconditions for determining the optimal dosages, methods and timing of use, ways and time of withdrawal from the body [20-22].

The purpose of the work was to determine the parameters of acute and chronic toxicity of the complex liposomal preparation "Butaselmevit" and to determine the degree of its mortality for laboratory animals.

Materials and Methods

Experiments on the study of acute toxicity of the drug "Butaselmevit" were performed on 48 white rats, 2-3 months old, weighing 160-180 g, and 48 white mice 2-3 months old, weighing from 19-21 g. The product was injected intragastrically and intravenously. laced test animals once. The drug was administered to white mice and rats in the following doses: 50, 500, 5000, and 50000 mg/kg. For each dose, 6 laboratory animals were used.

After the introduction of the drug observation of laboratory animals was conducted for 14 days. On the first day of the experiment, the animals were under constant surveillance. The following indicators were taken into account: general condition, appearance, peculiarities of animal behavior, intensity and character of mobile activity, presence of a vessel, coordination of movements, reaction to external stimuli (tactile, sound, light), state of hair, visible mucous membranes, relation to feeding, respiration rate, time of occurrence and nature of intoxication, its severity and course.

Chronic toxicity was studied on 40 white rats weighing 90-110 g. For research on the principle of analogs, 4 groups were formed, each of 10 rats. The first (I) group of animals that served as control was administered isotonic sodium chloride solution at a dose of 6 ml/kg m.t. Animals of the other three groups were given Butazelmevit in doses: Group II (D_1) - 200 mg/kg (ten times the therapeutic), Group III (D_2) - 100 mg/kg (five times therapeutic) and IV group (D_3) - 20 mg/kg (therapeutic). In a chronic study, the drug "Butaselmevit" was administered to rats for 30 days at the above doses.

For 31 days from the start of the drug on 5 white rats from each group, the determination of the detoxifying function of the liver was carried out using a hexenal test [23]. To this end, laboratory animals were intraperitoneally injected with a 1% solution of hexenal at a dose of 45 mg/kg. Then the average sleep time was recorded from the moment when the animal took a side position.

At the same time, the other 5 rats were tested for swimming by M. L. Rylova [24]. To experiment, a glass aquarium was used. The pillar of water in the aquarium is 50 cm. The water temperature is + 12- + 13 ° C. Animals of experimental groups attached a load (metal weavers) - 5% of body weight. Before the experiment, the rat was weighed and attached to the tail corresponding to its weight load. Then it was allowed to swim at the same time with animals of experimental and control groups of approximately the same weight. It was

observed that the animals constantly floated. The indicator of working capacity is the time during which the animal can stay on the water. The animals were swimming until they were completely lowered to the bottom. After that, the laboratory animals were digested and digested, and body mass factors were determined, as compared to the control group, morphological and biochemical studies were performed according to generally recognized methods.

The obtained results were statistically processed by the method of variation statistics with the definition of average values of values and average error. The probability of differences between the mean values during the analysis was estimated using Student's criterion (t). The difference between the values was considered probable, when the probability difference was: P <0,05 - *, P <0,01 - **, P <0,001 - ***.

Results and Discussion

Under the condition of intramuscular injection of "Butaselmevit" at doses of 50, 500, 5000, and 50000 mg/kg, the death of white mice was not recorded. However, in the first minutes after the administration of the drug, the reaction of the animals of the experimental groups was the same as that of the control group, that is, the reaction was solely to stress after the appropriate intervention. Further, short-term inhibition of laboratory animals was prescribed in the maximum dose.

Thus, the drug "Butaselmevit" belongs to the 4th grade according to GOST 12.1.007-76 - low-toxic substances, where DL50 for its intragastric administration and intramuscular injection to laboratory animals (white mice and rats) is greater than 50,000 mg/kg.

After experimenting on the study of chronic toxicity of the drug "Butaselmevit", the death of rats was not established. The results of functional tests determined after the last administration of the drug in a chronic study are presented in **Table 1**.

Table 1. Results of the functional tests (M±m, n=5)

Group	Dose, mg/kg	Hexenal Sample	Swim test
		Average sleeping time, min	Average swimming time, min
1	Control	28,6±1,62	12,8±1,49
2	200	36,4±1,60**	9,0±1,30**
3	100	31,0±0,85	11,3±1,62
4	20	29,6±1,39	13,1±1,35

Note. Differences are probable compared with similar indicators in animals of the control group - P <0.05 - *, P <0.01 - **, P <0.001 - ***

The effect of the drug "Butaselmevit" on the antitoxic function of the liver was studied by the hexenal test, which is based on the ability of various chemicals to influence the duration of hexenal sleep in laboratory animals, and as it is known, hexenal is completely metabolized in the liver.

From the data presented in **Table 3**, we see that in animals of 2 group, which was administered a dose of 200 mg/kg, an increase in mean sleep time was observed with a simultaneous decrease in the meantime of swimming (P <0.05). These changes indicate a violation of the detoxifying function of the liver and the overall depressant effect on white rats caused by the long-term administration of the drug "Butaselemvit" at a dose of 200 DL50. For a long-term administration of the dosage at doses of 100 and 20 mg/kg, the mean sleep time for hexenalin and the meantime of swimming of rats in experimental groups did not differ significantly from the control group, where, accordingly, it fluctuated within the 3rd group 31.0 ± 0, 8 min and 11.3 ± 1.62 min, whereas in the 4th group - 29.6 ± 1.4 min and 13.11 ± 1.35 min.

Thus, the study drug at doses of 100 and 20 mg/kg did not affect the results of functional tests, which is associated with the normal functioning of the liver tissue and the absence of adverse effects on the organism of animals of groups 3 and 4.

For the study of chronic toxicity of the drug "Butaselmevit" on the 31st day of the experiment, some changes in the coefficients of the internal organs **(Table 2)** were found. In particular, a probable increase in the liver mass coefficient in the experimental rats was observed, which was administered at doses of 200 and 100 mg/kg, respectively, at 33.6 and 9.3% relative to the control group. The lung mass ratio in rats fed a dose of 200 mg/kg increased by 13.3%. For the introduction of the drug "Butaselmevit" at doses of 200 and 100 mg/kg, the heart rate of rats increased accordingly by 8.8%. The weight of the spleen was the highest in the animals of the first experimental group, which was 5.7 ± 0.20 versus the control 5.4 ± 0.24.

Table 2. The coefficients of the mass of the internal organs of white rats at 31 days for the study of chronic toxicity of the drug «Butaselmevit» (M±m, n=6)

Internal organs	Dose			
	Control	200 mg/kg	100 mg/kg	20 mg/kg
Lungs	8,3±0,36	9,4±1,12	8,1±0,39	8,5±0,62
Liver	33,3±0,46	44,5±2,75***	36,4±0,54**	33,0±0,45
Right kidney	3,2±0,18	3,6±0,15	3,2±0,10	3,0±0,15
Left kidney	3,6±0,20	3,8±0,18	3,3±0,14	3,2±0,11
Heart	3,4±0,12	3,7±0,25	3,7±0,23	3,5±0,22
Spleen	5,4±0,24	5,7±0,20	4,9±0,32	5,0±0,36

Consequently, the results of the conducted studies showed that the administration of "Butaselmevit" to rats at doses of 200 and 100 mg/kg over 30 days had a greater effect on the functional state of the liver than on other internal organs.

In determining the morphological parameters of the blood of white rats for the administration of the study drug at doses of 200, 100, and 20 mg/kg, an increase in the number of erythrocytes in the blood was detected, respectively, at 12, 15.5 and 12% compared with the control group, but the differences were unlikely **(Table 3)**. The hemoglobin content in the blood of experimental rats, which was administered the drug "Butaselevit" at a dose of 200 mg/kg for 30 days, was 6.2% lower than control. At the same time, in rats treated with the study drug at doses of 100 and 20 mg/kg, hemoglobin levels in blood were 27.6 and 32.8% higher respectively (P <0.001) than in control animals. At the same time, in the blood of animals in the first experimental group, the average hemoglobin content was 16.8% less relative to the control, whereas in the rats of the second experimental group it increased by 14%. At the same time, the average concentration of hemoglobin in erythrocytes in the blood of rats of the first, second and third experimental groups was greater than the control values by 6.6, 12, and 41.9%, respectively. The average volume of erythrocytes was the smallest in the blood of the rats of the first experimental group, which was administered a dose of 200 mg/kg.

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Indices	Group			
	Control	200 mg/kg	100 mg/kg	20 mg/kg
Hemoglobin, /l	96,6±5,63	90,6±4,23	123,3±2,10***	128,3±2,50***
Erythrocyte, l	5,8±0,40	6,5±0,42	6,7±0,60	6,5±0,37
Hematocrite	32,1±2,11	28,2±2,42	36,6±3,70	30,0±3,45
Colour index	0,71±0,05	0,58±0,05	0,76±0,03	0,76±0,04
The average level of hemoglobin in erythrocytes, pg	16,7±1,12	13,9±0,27*	18,4±0,45	19,7±1,05
The average concentration of hemoglobin in erythrocytes, %	30,1±0,38	32,1±0,90	33,7±0,65	42,7±0,45***
The average volume of erythrocytes, mkm3	55,3±1,10	43,4±2,05***	54,6±1,47	46,2±3,17**
Leucocytes	9,7±0,76	8,7±1,32	9,1±1,35	10,4±1,62
Eosinophils %	4,6±0,65	5,9±1,11	5,8±1,15	4,2±0,69
Neutrophil %	21,4±2,20	22,6±1,84	31,1±2,05**	29,8±2,35**
Limphocytes%	72,2±2,30	70,1±3,03	61,5±1,50***	63,9±1,25**
Monocytes%	1,8±0,40	1,4±0,70	1,6±0,70	2,1±0,31

Intramuscular administration to animals of the first experimental group of the drug "Butalemivet" at a dose of 200 mg/kg resulted in a decrease in the value of hematocrit to 28.2 ± 2.42%, whereas the dose of 20 mg/kg - to 30.0 ± 3.45%. The results of these studies indicate the dose-dependent effect of "Butaselmevit" on the oxygen-transport function of the blood.

Similar changes in the blood of animals were recorded in the study of the number of leukocytes and the determination of the ratio of their species. Thus, the number of leukocytes in the blood of the rats of the first and second experimental groups was 10,3 and 6,2% less, respectively, and in animals that were administered the drug "Butaselmevit" at a dose of 20 mg/kg, by 7,2% higher than in control.

In the blood leucocyte blood group of experimental groups, there was an increase in the relative number of eosinophils, and neutrophils and, conversely, a decrease in the relative number of lymphocytes and monocytes **(Table 3)**. Thus, in the blood of rats of the first experimental group, the number of eosinophils increased by 1.3%, in the second - by 1.2%, and in the third experimental group - by 0.4%. Regarding the determination of the number of neutrophils, it was found that in the rats of the first experimental group they increased by 1.2%, whereas in the second experimental group - by 9.7%, and the third - by 8.4% relative to the control animals in the animals. The number of lymphocytes was the lowest in the experimental group of rats, which was administered a dose of 100 mg/kg, whereby it was 61.5 ± 1.50%, whereas in the control group rats this indicator was higher and accordingly was 72.2 ± 2, 3%.

The lowest amount of monocytes was in animals of the first and second experimental groups, respectively, at 0.4 and 0.2%, whereas in the third experimental group, this indicator was higher by 0.3% relative to the control group.

The next stage in the study of chronic toxicity of the drug "Butaselmevit" was the study of biochemical parameters of the blood of white rats on the 31st day of the experiment. From the data presented in **Table 4**, we see that the level of total protein in the blood of the rats of the first, second and third experimental groups increased by 2.4, 7.1, and 8.2%, respectively, with respect to control. Increasing the level of total protein in rat blood in experimental groups and, especially, those who were administered a dose of 20 mg/kg,

indicates an increase in protein sintezation function of the liver of these animals.

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Indices	Groups			
	Control	200 mg/kg	100 mg/kg	20 mg/kg
Total protein, g/l	8,5±0,20	8,7±0,56	9,1±0,31	9,2±0,45
ALP, units/l	157,8±21,8	235,8±22,8*	186,3±30,2	171,1±16,23
AlT, units/l	70,4±5,42	81,9±6,13	75,3±5,73	65,3±6,95
AsT , units/l	201,6±10,25	260,3±9,76***	213,1±14,65	184,9±11,26
Total lipids, g/l	8,3±1,00	7,9±1,87	7,2±0,56	8,1±0,85
Carbamide, mmol/l	6,1±0,33	4,7±0,30**	4,8±0,34**	7,2±0,43
Creatinine, mmol/l	107,8±15,1	106,9±8,7	113,8±10,6	124,5±10,9

The functional state of the liver of rats for the study of chronic toxicity of the drug "Butaselmevit" was studied in the activity of aminotransferases. It was established that the activity of the alanine aminotransferase in the blood serum of rats of the first and second experimental groups tended to increase by 16 and 7%, respectively, in comparison with the control animals in animals. At the same time, in rats, which were administered a dose of 20 mg/kg, the activity of this enzyme decreased by 7%, but the difference in control was unlikely. Attention is drawn to an increase of 29% ($P < 0.001$) of alanine-aminotransferase activity in the blood serum of rats, which were injected with the drug "Butaselmevit" with a dose of 1/20 DL50, and a dose of 100 mg/kg - by 5.7% on control. The activity of this enzyme in the blood serum of rats in the third experimental group tended to decrease and amounted to 184.9 ± 11.26 Od / L, whereas in animals in the control group, this indicator was 201.6 ± 10.25 U / L.

Introduction to animals of the drug "Butaselmevit" led to an increase in the activity of alkaline phosphatase, especially in the blood serum of rats of the first and second experimental groups, respectively, on 49 ($P < 0.05$) and 18%. At the same time, when determining the level of urea in the blood of rats, the effects of the study drug attract the attention of its lower content of blood in the animals of the first and second experimental groups. Together with this, in animals, which were injected with the drug "Butaselmevit" at a dose of 20 mg/kg, the level of urea and creatinine in the blood increased by 18 and 15.5%, respectively, relative to the control group.

From the data presented in **Table 4**, we can see that the introduction of animals to the drug "Butaselmevit" did not significantly affect the content of total lipids, but led to a tendency to decrease, especially in animals of the second experimental group.

Thus, in the study of toxic effects of the drug "Butaselmevit" in the chronic study, it was stated that, despite the low toxicity, the study drug caused a dose-dependent effect on the morphological and biochemical parameters of the blood.

Conclusion

1. The new domestic liposomal preparation "Butaselmevit" belongs to the 4th class of toxicity, that is, to low-toxic substances.
2. The dose-dependent effect of "Butaselmevit" on leukopoiesis, hematological profile, and functional state of the liver in laboratory animals was established.

Prospects for Further Research: In the future, it is planned to study the effect of "Butaselmevit" on the protective systems of the animal's body for toxic liver injuries.

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