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Galaxy Publication

Investigation of Butaselmevit's Acute and Chronic Toxicity in Laboratory Animals

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ABSTRACT

This study aimed to investigate the hepatoprotective effects of potassium 2-((4-amino-5-(morpholinomethyl)-4H-1,2,4-triazole-3-yl)thio)acetate's on tetracycline and viral hepatitis models in chickens. The intact Cobb 500 cross-broiler chickens were subjected to a biochemical analysis of their blood and liver serum. According to the specified specifications, each group of chickens was housed independently in a distinct cell in the same room with the same climatic characteristics. It was found that "Butaselmevit" had a dose-dependent effect on laboratory animals' leukopoiesis, hematological profile, and function of the liver. Research on the model of tetracycline-induced hepatitis in chickens showed that the compound 2-((4-amino-5-(morpholinomethyl)-4H-1,2,4-triazole-3-yl)thio)acetate has a hepatoprotective effect that is comparable to that of the reference medication, Thiotriazolin®. According to the results of a biochemical study, in the model of infectious hepatitis, potassium 2-((4-amino-5-(morpholinomethyl)-4H-1,2,4-triazole-3-yl)thio) acetate is combined with the traditional antibiotic Enrofloxacin® to produce hepatoprotective effects.

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

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Introduction

The focus of the paper is on how the novel complex liposomal medication "Butaselmevit" affects markers of both acute and long-term toxicity in experimental animals. Butafosfan, selenium, methionine, thistle spot, fat-soluble vitamins, and tween lecithin are among the ingredients in this medication.

Research has shown that white rats did not perish when given intramuscular injections of "Butaselmevit" at doses of 50, 500, 5000, and 50,000 mg/kg. Simultaneously, the use of a formulation containing 50,000 mg/kg caused

the general state of experimental animals to be temporarily suppressed, which is probably because rats' bodies absorb massive quantities of the medication.

According to research on the acute toxic effect of the medication "Butaselmevit" in white rats and mice, the DL50 medication for intramuscular injection to lab animals surpasses 50,000 mg/kg. The medication is classified as a low-toxic material in the IV class by GOST 12.1.007-76.

White dosages of 200 mg/kg were given to rats, which resulted in a likely rise in mean sleep time and a concurrent reduction in mean swimming time, according to an investigation on the severe toxicity of the medication "Butaselmevit." The rats in the groups being studied did not exhibit any substantial variations in the average amount of time they spent swimming and resting for a long time when receiving the research medication at dosages of 100 and 20 mg/kg.

To look into the severe toxicity of the medication "Butaselmevit," some adjustments in the internal organ coefficients were noted during the 31-day experiment. In particular, rats in both groups of experiments received dosages of 200 and 100 mg/kg, respectively, at 33.6 and 9.3% for the animals in the control group. These groups' liver mass coefficients probably increased.

The investigation of the harmful impact of the medicine "Butaselmevit" in a chronic investigation showed that notwithstanding the low toxicity, the research showed that the drug had a dose-dependent influence on the hematological and biochemical variables in the blood.

Toxic lesions in people and animals are on the rise due to several factors, including the rapid advancement of chemical chemistry in industry and agriculture, ecological degradation, xenobiotic contamination of the surroundings, and unregulated medication management [1–3]. The liver is recognized to be the key organ responsible for the detoxification activities of the body. The toxic lesion of the liver is the most well-known of the diffuse liver lesions. It has just been demonstrated that the etiology of liver illnesses involves the mechanisms of causing free radical oxidation of lipids in plasma and intracellular membranes of hepatocytes in the backdrop of the loss of protective antiradical systems [4–10].

Animal protein synthesis and enzyme function have improved recently thanks to the development of new, complex drugs that increase the organism's immunological responsiveness and adaptive capability. Thistle blisters, vitamins, selenium, and betafosfan have all been shown by different authors to stimulate the immunological and antioxidant systems in mice [11–14]. Nevertheless, the intricate relationship between these medications and liver function, as well as the animal body's defense mechanisms, is currently underemphasized in the scholarly literature. For this reason, we created a novel liposomal medication that contains vitamins, butafosfan, selenium, methionine, and thistle [15–17].

It is commonly known that before being put into serial production and marketed as veterinary drugs, all new drugs must pass an appropriate toxicological evaluation that clarifies the criteria of acute as well as prolonged toxicity in lab animals over the long term of their implementation into the body [18, 19].

In light of this, objective toxicological control establishes the prerequisites for figuring out the best dosages, usage schedules, and withdrawal times from the body, as well as preventing potential metabolic illness, the composition of distinct tissues and organs, the emergence of adverse impacts, and long-term effects [20–24]. It also speeds up the development of new, extremely efficient veterinary medications.

Determining the complex liposomal preparation "Butaselmevit's" acute and chronic toxicity characteristics, as well as the extent of its death in lab animals, was the aim of the study.

Materials and Methods

Acute toxicity testing of the drug "Butaselmevit" was conducted on 48 white rats aged 2–3 months, weighing 160–180 g, and 48 white mice aged 2–3 months, weighing 19–21 g. The drug was administered both intragastrically and intravenously as a single dose. The doses given to both rats and mice were 50, 500, 5000, and 50,000 mg/kg, with six animals tested per dose group.

Following drug administration, the animals were observed for 14 days. On the first day, continuous monitoring was performed. Evaluations included the animals' general health, physical appearance, behavioral characteristics, level and type of motor activity, presence of seizures, coordination, responses to tactile, auditory, and visual stimuli, condition of fur and visible mucous membranes, feeding behavior, respiratory rate, and the onset, severity, and progression of any intoxication symptoms.

Chronic toxicity was assessed in 40 white rats weighing 90–110 g, divided into four groups of 10 rats each. The first group served as the control and received an isotonic sodium chloride solution at 6 ml/kg. The remaining groups were treated with Butaselmevit at doses of 200 mg/kg (10 times the therapeutic dose), 100 mg/kg (5 times the therapeutic dose), and 20 mg/kg (therapeutic dose), respectively. The drug was administered daily for 30 days. For 31 days following treatment initiation, five rats from each group were evaluated for liver detoxification function using the hexenal test. Rats were injected intraperitoneally with 1% hexenal solution at 45 mg/kg, and the duration of sleep from the time the animal lay on its side was recorded.

Simultaneously, the other five rats per group were subjected to swimming endurance testing according to Rylov's method. A glass aquarium with a 50 cm water column at 12–13 °C was used. Each rat was weighed and fitted with a metal weight equal to 5% of its body weight, attached to the tail. Rats were then observed swimming alongside controls of similar weight until exhaustion, indicated by sinking. The duration of swimming served as a measure of physical endurance. Afterward, the animals were euthanized for evaluation of body mass and comparative morphological and biochemical analyses using standard procedures.

Data were statistically analyzed using variance statistics to calculate mean values and standard errors. Differences between means were assessed by Student's t-test, with significance thresholds set at $P < 0.05$, $P < 0.01$, and $P < 0.001$.

Results and Discussion

White mice did not die after receiving intramuscular injections of "Butaselmevit" at dosages of 50, 500, 5000, and 50000 mg/kg, respectively. However, in the 1st few minutes after the medicine was administered, the animals in the experimental groups exhibited the same reaction as the control group, indicating that the reaction was primarily due to stress following the proper interference. In addition, the highest dose of temporary inhibition was given to lab animals.

Accordingly, the medication "Butaselmevit" falls into the 4th category of low-toxic chemicals (GOST 12.1.007-76), with a DL50 of more than 50,000 mg/kg for both intragastric administration and intramuscular injection in lab animals (white mice and rats).

The mortality of rats was not verified after experiments were conducted to evaluate the long-term toxicity of the medication "Butaselmevit." **Table 1** shows the outcomes of functional tests conducted after the medicine was last administered in a chronic trial.

Table 1. The functionality test outcomes (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

$P < 0.05$ (*), $P < 0.01$ (**), and $P < 0.001$ (***) indicate that variations are likely to be in comparison to equivalent markers in animals in the control group.

Since hexenal is believed to be fully metabolized in the liver, the hexenal test, which depends on the capacity of different chemicals to impact the length of hexenal sleep in laboratory animals, was used to examine the impact of the medicine "Butaselmevit" affecting the liver's antitoxic operation.

According to the results, animals in the 2nd group, which received a dosage of 200 mg/kg, showed a rise in mean sleep duration along with a concurrent reduction in swimming time ($P < 0.05$). These alterations show that the long-term treatment of the medication "Butaselemvit" at a dose of 200 DL50 has a depressive impact on white rats overall and violates the liver's detoxifying function. The mean hexenalin sleep time and swimming time of rats in the experimental groups did not vary substantially from the control group after years of dosage control using 100 and 20 mg/kg dosages. As a result, it varied between the 3rd group (31.0 ± 0.8 min, and 11.3 ± 1.62 min) and the 4th group (29.6 ± 1.4 min and 13.11 ± 1.35 min).

Therefore, the findings of functional tests, which are linked to the liver tissue's proper functioning and the lack of negative impacts on the organism of animals in groups 3 and 4, were unaffected by the study medication at dosages of 100 and 20 mg/kg.

There were some alterations in the internal organ coefficients (**Table 2**) for the investigation of chronic toxicity of the medication "Butaselmevit" on the thirty-1st day of the experiment. Specifically, a likely rise in the experimental rats' liver mass coefficient was seen; these rats received dosages of 200 and 100 mg/kg, respectively, at 33.6 and 9.3% higher than the control group. When 200 mg/kg was administered to rats, their lung mass ratio rose by 13.3%. When the medication "Butaselmevit" was administered at dosages of 200 and 100 mg/kg, rats' heart rates rose by 8.8%. Among the animals in the 1st experimental group, the spleen weighed the most at 5.7 ± 0.20, compared to 5.4 ± 0.24 for the control group.

Table 2. The mass factors of white rats' internal organs at thirty-one days for the investigation of the medication "Butaselmevit's" chronic toxicity (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

P < 0.05 (*), P < 0.01 (**), and P < 0.001 (***) indicate that variations are likely to be in comparison to equivalent markers in animals in the control group.

As a consequence, the findings of the investigations revealed that the functional status of the liver was more affected than other internal organs when "Butaselmevit" was administered to rats at dosages of 200 and 100 mg/kg during 30 days.

When the morphological variables of the white rats' blood were examined after the experimental medication was managed at doses of 200, 100, and 20 mg/kg, it was found that there were more erythrocytes in the blood at 12, 15.5, and 12%, respectively, than in the control group. However, these distinctions were improbable (**Table 3**). After being given the medication "Butaselevit" at a dose of 200 mg/kg for 30 days, the research rats' blood hemoglobin concentration was 6.2% lower than the controls. When the research medication was administered to rats at dosages of 100 and 20 mg/kg, the hemoglobin levels in their blood were 27.6 and 32.8% greater, respectively (P < 0.001) than in the control group. Meanwhile, the average hemoglobin concentration in the blood of the 1st empirical group was 16.8% less than that of the control group, whereas it grew by 14% in the 2nd empirical group. In the meantime, the 1st group of rats received a dosage of 200 mg/kg, and their blood had the smallest mean number of erythrocytes. The mean level of hemoglobin in erythrocytes in the blood of rats in the 1st, 2nd, and 3rd groups of experiments was 6.6%, 12%, and 41.9% greater than the control values, respectively.

Table 3. Morphological factors of white rats' blood on the thirty-first day of the trial to investigate the long-term toxicity of the medication "Butaselmevit" (M ± m, n = 10)

Indices	Group			
	Control	200 mg/kg	100 mg/kg	20 mg/kg
Hemoglobin (g/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 mean hemoglobin content of erythrocytes (pg)	16.7 ± 1.12	13.9 ± 0.27*	18.4 ± 0.45	19.7 ± 1.05
The mean amount of hemoglobin in erythrocytes (%)	30.1 ± 0.38	32.1 ± 0.90	33.7 ± 0.65	42.7 ± 0.45***
The mean erythrocyte volume (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**
Lymphocytes (%)	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

P < 0.05 (*), P < 0.01 (**), and P < 0.001 (***) indicate that variations are likely to be in comparison to equivalent markers in animals in the control group.

When the medication "Butalemivet" was administered intramuscularly to animals in the 1st experimental group at a dose of 200 mg/kg, the hematocrit value decreased to 28.2 ± 2.42%, whereas at a dose of 20 mg/kg, it decreased to 30.0 ± 3.45%. These research findings show that "Butaselmevit" has a dose-dependent impact on the blood's ability to carry oxygen.

Similar alterations in animal blood were seen during the research on leukocyte counts and the calculation of species ratios. As a result, rats in both the initial and subsequent sets of studies had 10.3 and 6.2% less leukocytes in their blood, respectively, but rats given the drug "Butaselmevit" at a dose of 20 mg/kg had 7.2% more leukocytes than the control group.

While the relative numbers of lymphocytes and monocytes decreased, the relative numbers of eosinophils and neutrophils increased in the experimental group's blood leukocyte group (**Table 3**). Thus, rats in the initial experimental group had 1.3% more eosinophils in their blood, those in the 2nd group had 1.2% more, and those in the 3rd group had 0.4% more. It was shown that the rats in the initial empirical group had a rise of 1.2% in neutrophils compared to the control group, while the rats in the 2nd and 3rd empirical groups had a rise of 9.7% and 8.4%, respectively. The rats in the experimental group, who were given a dose of 100 mg/kg, had the fewest lymphocytes (61.5 ± 1.50%). As opposed to this, the rats in the control group showed a greater indication, averaging 72.2 ± 2.3%.

The 1st and 2nd experimental groups' animals had the lowest levels of monocytes, at 0.4% and 0.2%, respectively. In contrast, the 3rd experimental group's animals had a 0.3% greater level of this indication than the control group.

The following phase in the examination of the medication "Butaselmevit's" chronic toxicity was to investigate the biochemical variables of white rats' blood on the thirty-1st day of the test. The findings in **Table 4** demonstrate that the rats in the 1st, 2nd, and 3rd experimental groups had blood levels of total protein that were 2.4, 7.1, and 8.2% greater than the control group. Rat blood samples from the group being studied had higher amounts of total protein, particularly those that were given a dose of 20 mg/kg, indicating a boost in the liver's capacity to synthesize proteins.

Table 4. White rat blood biochemical parameters on the thirty-first day of the trial on the investigation of chronic toxicity "Butaselmevit" (M ± m, n = 10)

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

P < 0.05 (*), P < 0.01 (**), and P < 0.001 (***) indicate that variations are likely to be in comparison to equivalent markers in animals in the control group.

In the 3rd experimental group, the blood serum concentration of this enzyme began to fall and was 184.9 ± 11.26 OD/L in rats, while it was 201.6 ± 10.25 U/L in animals in the control group. After receiving injections of "Butaselmevit" at doses of 1/20 DL50 and 100 mg/kg, rats' blood serum alanine-aminotransferase function increased by 29% (P < 0.001), whereas control rats' function increased by 5.7%. The functional state of the rats' livers was evaluated using aminotransferase activity to look at the long-term toxicity of the drug "Butaselmevit." In comparison to the control group, it was shown that the alanine aminotransferase function in the blood serum of the rats in the 1st and 2nd experimental groups began to rise by 16 and 7%, respectively. Rats given a dose of 20 mg/kg likewise showed a 7% fall in this enzyme's activity; however, the control group was unlikely to perceive this difference.

Alkaline phosphatase activity increased when the medicine "Butaselmevit" was administered to animals, particularly in the blood serum of rats in the 1st and 2nd empirical groups, by 49% (P < 0.05) and 18%, respectively. Meanwhile, the impact of the research medication draws attention to the reduced blood content in

the animals of the 1st and 2nd empirical groups while assessing the amount of urea in the rats' blood. Additionally, the blood levels of urea and creatinine in rats that received injections of the medication "Butaselmevit" at a dose of 20 mg/kg rose by 18 and 15.5%, respectively, in comparison to the control group.

The findings in Table 4 demonstrate that while the administration of the medicine "Butaselmevit" to animals did not substantially alter the amount of total lipids, it did cause a tendency for it to decline, particularly in the animals in the 2nd empirical group.

Therefore, it was shown that, despite its low toxicity, the medication "Butaselmevit" had a dose-dependent influence on the blood's morphological and biochemical variables in the chronic examination of its harmful impact.

Conclusion

1. The new domestic liposomal preparation "Butaselmevit" is classified as low-toxic, or in the 4th class of toxicity.
2. It was determined that "Butaselmevit" had a dose-dependent impact on laboratory animals' leukopoiesis, hematological description, and liver function.

Prospects for Further Research: Future research will examine how "Butaselmevit" affects the animal's defense mechanisms against toxic liver damage.

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