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ORIGINAL ARTICLE

Preclinical searches of the preparation Thireomagnile

B. Gutyj[1], Y. Grymak[1], V. Hunchak[1], A. Mysak[1], N. Nazaruk[1], O. Brezvyn[2], I. Hariv[1], A. Shcherbatyy[1], B. Semeniv[1], I. Bushueva[3], V. Parchenko[3], A. Kaplaushenko[3]

[1]Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologies Lviv, Pekarska Str., 50, Lviv, 79010, Ukraine, bvh@ukr.net
[2]State Scientific-Research Control Institute of Veterinary Medical Products and Fodder Additives, Lviv, Ukraine
[3]Zaporizhzhia State Medical University, Zaporozhye, Ukraine
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The article deals with the results of acute and chronic toxicity of the new iodine-lipid preparation Thireomagnile, which contains iodine and magnesium in its composition. This drug is used by cows in recent months of pregnancy to prevent the development of endogenous intoxication. It was found that the preparation Thireomagnile under conditions of intra gastric injection to white mice and rats in different doses did not cause their death. Only a short-term inhibition of white mice and rats due to the injection of the maximum test dose of 5000 mg/kg of body weight was established. During the period of search to determine the chronic toxicity of the drug Thireomagnile, there were no abnormalities in the behavior of the experimental animals. In doses of 1/50 DL_{50} and 1/100 DL_{50}, the With the injection of Thyreomagnet at a dose of 1/20 DL_{50} on the thirty-first day of the experiment, did not affect the results of functional tests, which is associated with the normal functioning of the hepatic tissue and the absence of a negative effect on the animals body. With the injection of Thireomagnile, at a dose of 1/20 DL_{50} on the thirty-first day of the experiment, it was established that against the background of a slight decrease in the body weight of white rats, the weight of the liver was significantly increased by 24.6% in relation to the animals of the control group. In the search of blood hematologic parameters of rats after the intrinsic muscular injection of Thireomagnile at a dose of 1/20 DL_{50}, a tendency was established to decrease the level of hemoglobin, hematocrit, the number of leukocytes, and an increase in the number of erythrocytes. After prolonged injection of the preparation Thireomagnile to the experimental animals, no significant deviations were observed in the evaluation of hemopoiesis and the functional state of the liver in animals. Thireomagnile in doses of 1/50 and 1/100 DL_{50} in serum reduced the level of ALT, in comparison with the rats of the control group. With the injection of Thireomagnile at a dose of 1/100 DL_{50}, the number of leukocytes was significantly increased. By a one-time application on the skin of rabbits, Thireomagnile does not cause damage to the skin in the form of erythema or its edema. On a visual assessment of the conjunctiva, cornea and eyelid eyes of rabbits, it is established that the Thireomagnile preparation causes a slight irritation of the conjunctiva 30 minutes after instillation. Thus, when used externally, Thiromagnet preparation does not have irritating properties. As a result of the conducted searches, the allergenic properties of the Thireomagnile preparation were not revealed. In determining the acute and chronic toxicity of the preparation Thireomagnile, it is established that it belongs to the 4th toxicity class – low-toxic substances, and its DL_{50} for intra gastric injection of laboratory animals (white mice and rats) exceeds 5000 mg/kg of body weight.The received results of researches specify that the preparation Thireomagnile is safe at application for preventive maintenance and treatment of animals at development of an endogenic intoxication.
Key words: pharmacology; toxicology; rats; rabbits; guinea pigs; iodine; magnesium

Introduction

According to the literature, it is known that the conditions for feeding and keeping pregnant cows significantly affect their future offspring (Mainardes and DeVries, 2016; Sheldon et al., 2006; Fabris et al., 2017). Therefore, from the very beginning of pregnancy, the cow must receive the necessary amount of nutrients that provide its need to maintain her own life, develop the fetus and produce milk. As a result of a deficit or excess energy, biologically active substances in diets there is a metabolic disorder in the pregnant cows (van der Drift et al., 2015; Macmillan et al., 2017; Vieira-Neto et al., 2017).

Numerous publications cause significant concern on the development of endogenous intoxication of various etiologies in pregnant animals (Gutyj et al., 2016; Rodríguez et al., 2017). There are several important biochemical mechanisms for the

development of endotoxicosis in animals, one of which is the activation of free radical oxidation (Gutyj et al., 2016). It is known, that pregnancy of animals as a physiological condition is associated with significant energy costs for biosynthetic processes and needs more oxygen and is characterized by an intensification of cellular respiration and, as a consequence, is an oxidative stress (Hariv and Gutyj, 2016; Khariv et al., 2016; Martyshuk et al., 2016; Khariv et al., 2016).

It is established, that in the conditions of development of endogenous intoxication in sterile cows on the 8th and 9th months, the content of triiodothyronine and thyroxine decreases and the level of thyroid-stimulating hormone of the pituitary gland that in the conditions of development of endogenous intoxication in pregnant cows on the 8th and 9th months, the content of triiodothyronine and thyroxine decreases and the level of thyroid-stimulating hormone of the pituitary gland (Hrymak and Hunchak. 2014). Thus, when endogenous intoxication in the pregnant cows the function of the thyroid gland is suppressed, and has an influence on fat, protein and carbohydrate metabolism.

Therefore, for the effective treatment of calf cows with the development of endogenous intoxication it is advisable to use preparation that contain iodine (Hrymak and Hunchak, 2014; Hunchak et al., 2016). In our case, we used the iodine- lipid preparation Thireomagnile, which contains iodine and magnesium.

According to the decree of the Department of Veterinary Medicine "Toxicological control of new animal protection products", approved by the Chief Directorate of Veterinary Medicine of the Ministry of Agriculture and Food of Ukraine of December 16, 1996, each new preparation that is recommended for the treatment of animals must meet the following requirements:

• a new preparation, in comparison with the preparation -analogue, should show high therapeutic efficiency;
• it should not be toxic to animals that use it;
• the preparation or its metabolites should not affect the sanitary quality and nutritional value of livestock products;
• during production and use, the preparation should not cause damage to the environment.

That is why the purpose of the work was to conduct experimental searches on the study of acute, chronic toxicity and pharmacological effects of the iodine lipid preparation Thireomagnile.

Material and methods of research

Research studies due to the parameters of acute and chronic toxicity of Thireomagnile were carried out on laboratory animals. At the first stage, the toxicity parameters were investigated, and at the second stage – the pharmacological properties (irritant and allergenic actions) of the new preparation on the organism of laboratory animals (Fig. 1).

Groups of animal analogs were formed, namely: white mice 2–3 months of age, body weight 19–23 g, white rats 3-4 months of age, body weight 200-230 g, guinea pigs aged 3–4 months, body weight 350–400 g, rabbits aged 5-6 months, body weight 2–2.5 kg. Animals were kept in standard cages under vivarium conditions according to the current "Sanitary requirements for the device, equipment and maintenance of experimental biological clinics (vivaria)", with a stable temperature regime of 18–20 °C. A standard diet was used in the form of a set of concentrated feeds, taking into account the norms of laboratory animals feeding. An adaptation period was 7–8 days. The animals were monitored daily. Acute toxicity of iodine lipid preparation was determined in two stages.

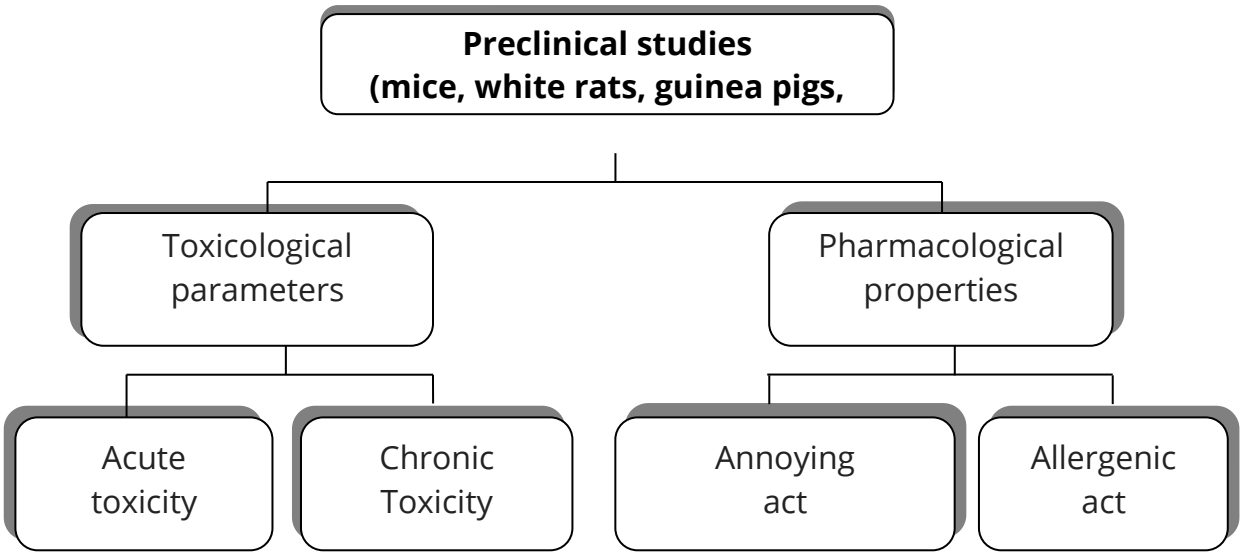

Fig. 1. Scheme for the determination of toxicological and pharmacological properties of Thireomagnile

At the first stage – for white mice and rats, a dose of 50, 500 and 5000 mg/kg of body weight of the animal was taken. For each dose, 3 laboratory animals were used. At the second stage, the laboratory animals were injected with the preparation at the maximum dose of 5000 mg/kg of body weight. Experience in two repetitions of 6 animals in each. The preparation was tested with intragastric injection to animals. Observation of laboratory animals was conducted for 14 days.

The behavior of animals, their appearance, the state of the coat, visible mucous membranes, clinical signs (temperature, pulse, respiration), the presence of signs of poisoning, the time of death of animals and the like were taken into account. When carrying out long-term experiments on the study of chronic toxicity, white rats were injected intramuscularly with the test preparation at different doses for 30 days. Four groups of analogical animals were formed, identical in number (6 in each) and body weight (180–190 g). The first group, which served as the control, was injected a 0.9% of solution of sodium chloride, and the rats of the experimental groups (I1, I2, I3) – Thireomagnile in doses 1/100, 1/50, 1/20 DL_{50}. On the thirty-first day of the study, euthanasia of rats was performed with light ether anesthesia, while taking blood for hematological and biochemical studies (Hrymak et al., 2015; Gutyj et al., 2016; Gutyj et al., 2017).

Mathematical processing of research results was processed statistically using the Statistica 6.0 software package. The results of mean values were considered statistically significant at * – $P < 0.05$ (ANOVA).

Results

Under conditions of intragastric injection of various doses of the search preparation to white mice and rats, the death of animals did not occur. Their general state was satisfactory, the reflexes were preserved, the response to sound and tactile stimuli was adequate, changes in behavioral reactions are not determined. Short-term inhibition of white mice and rats for the injection of a maximum dose of 5000 mg/kg of body weight is associated with manipulation of laboratory animals, giving them a significant amount of the preparation and a little restorative character.

The same results were obtained with repeated injection to the laboratory animals of the preparation in a dose of 5000 mg/kg. The data of the searches are presented in Tables 1 and 2.

Table 1. The toxicity of the preparation Thireomagnile on white rats

Number of animals	The dose of the preparation mg/kg	Number of dead animals		
		Total	%	average time
3	50	0	0	0
3	500	0	0	0
3	5 000	0	0	0
6	5 000	0	0	0

During the research period in animals, the clinical signs of toxic effects of Thireomagnile in the studied doses by us is not established. The general condition of the experimental animals was the same as in the control group. Feeding and water consumption were within normal limits. Feces were without deviations from normal consistency and odor. The reaction of animals to sound and tactile stimuli is adequate.

Table 2. The indices of toxicity of the preparation of Thireomagnile on white mice

Number of animals	The dose of the preparation mg / kg	Number of dead animals		
		Total	%	average time
3	50	0	0	0
3	500	0	0	0
3	5 000	0	0	0
6	5 000	0	0	0

So, the preparation Thireomagnile in accordance with GOST 12.1.007-76 refers to low-toxic substances – 4 classes of toxicity. Its DL_{50} for intragastric injection to laboratory animals (white rats and mice) exceeds 5000 mg/kg body weight.

During the period of searches to determine the chronic toxicity of the preparation Thireomagnile, there were no abnormalities in the behavior of the experimental animals. The results of the hexenal and floating samples, which were carried out after the end of the injection of the preparation in a chronic experiment, ndicate that a statistically significant increase in sleep time with a simultaneous decrease of average time was in the animals of the third research group (Table 3). These changes indicate a violation of the detoxification function of the liver and general inhibition on the body caused by prolonged injection of Thireomagnile at a dose of 1/20 DL_{50}. The preparation in doses of 1/50 DL_{50} and 1/100 DL_{50} did not affect the results of functional tests, which is due to the normal functioning of the hepatic tissue and the absence of a negative effect on the animal organism of the third and fourth research groups.

Table 3. The results of the functional tests (M ± m, n = 20)

Group of animals	Dose of the preparation	Hexenal sample	Sample with swimming
		Average time of sleep, min.	Average swimming time, min.
1	control	28.8 ± 1.66	12.84 ± 1.51
2	1/20 DL_{50}	36.4 ± 1.45*	9.05 ± 1.29*
3	1/50 DL_{50}	31.0 ± 0.60	11.19 ± 1.75
4	1/100 DL_{50}	29.7 ± 1.85	13.11 ± 1.69

On the thirty-first day of the experiment, with the injection of Thireomagnile at the maximum studied dose (1/20 DL_{50}) we noted that against the background of a slight decrease in the body weight of white rats, the weight of the liver was significantly increased by 24.6% ($P < 0.01$) relative to the animals in the control group. After an insignificant recovery period (5–6 days), the weight of the liver of rats in group I2 approximated the mass of animals that did not receive the preparation (K) (Table 4).

Table 4. The coefficients of the mass of the internal organs of white rats on the thirty-first day for the study of chronic toxicity Thireomagnile (M ± m, n = 6)

Internal organs	Doses of the preparation			
	Conrol	1/20 DL_{50}	1/50 DL_{50}	1/100 DL_{50}
Lungs	8.5 ± 0.31	9.4 ± 1.39	8.3 ± 0.35	9.3 ± 0.65
Liver	33.2 ± 0.49	48.0 ± 2.72**	31.1 ± 0.70*	29.6 ± 0.45*
Right kidney	3.3 ± 0.18	3.6 ± 0.19	3.4 ± 0.14	3.2 ± 0.25
Left kidney	3.6 ± 0.16	3.8 ± 0.12	3.3 ± 0.18	3.2 ± 0.14
Heart	3.4 ± 0.13	3.7 ± 0.32	3.7 ± 0.29	3.5 ± 0.38
Spleen	5.5 ± 0.28	5.7 ± 0.30	4.9 ± 0.32	5.0 ± 0.30

In the search of blood hematological parameters of rats after intramuscular injection of Thireomagnile in a dose of 1/20 DL_{50}, a tendency to decrease the level of hemoglobin, hematocrit, leukocyte count and increase in the number of red blood cells was established (Table 5).

Table 5. Hematologic indices of the blood of white rats on the 31st day of the experiment of chronic toxicity search Thireomagnile (M ± m, n = 24)

Indices	Group			
	K	1/20	1/50	1/100
Hemoglobin, g/l	76.4 ± 5.33	70.4 ± 4.11	93.1 ± 6.25	93.1 ± 3.10
Erythrocytes, T/l	4.1 ± 0.30	5.4 ± 0.32	5.3 ± 0.50	5.4 ± 0.27
Hematocrit,%	32.1 ± 1.98	28.4 ± 2.17	36.1 ± 3.70	28.0 ± 3.65
Leukocytes, g/l	3.6 ± 0.70	3.4 ± 1.29	3.6 ± 1.31	4.1 ± 1.58**

So, with the injection of Thireomagnile at a dose of 1/100 DL_{50}, the number of leukocytes was significantly increased.
With the injection of Thireomagnile at a dose of 1/100 DL_{50}, in the serum of the rats, the level of alkaline phosphatase was relatively high, respectively, 2.1 times higher than in the rats of the control group. Thireomagnile at a dose of 1/100 DL_{50}, in the serum was reduced the level of ALT, in comparison with the rats of the control group, simultaneously significantly was increased the level of ASAT in animals of group II (Table 6).

Table 6. Biochemical blood indices of white rats on the 31st day of the experiment on the search of chronic toxicity Thireomagnile (M ± m, n = 24)

Indices	Group of animals			
	Control	1/20 DL_{50}	1/50 DL_{50}	1/100 DL_{50}
Total protein, g / l	8.3 ± 0.22	8.7 ± 0.58	8.9 ± 0.26	9.0 ± 0.37
Alkaline phosphatase, unit/liter	155.5 ± 20.5	327.2 ± 25.5*	185.9 ± 47.1	174.7 ± 19.05
AlAT, u/l	70.7 ± 5.54	54.0 ± 6.10	56.4 ± 6.63	55.1 ± 7.77
ASAT, u/l	203.4 ± 9.50	286.9 ± 8.94*	203.9 ± 20.14	184.3 ± 34.20
Total lipids, g/l	8.5 ± 1.05	8.1 ± 2.72	7.4 ± 0.52	8.3 ± 0.78
Urea, mmol/l	6.1 ± 0.25	4.7 ± 0.28	4.8 ± 0.20	7.3 ± 0.43
Creatinine, mmol/l	107.7 ± 13.5	107.1 ± 7.4	115.9 ± 11.9	129.7 ± 10.4

In this way, we state, that after prolonged injection of the preparation Thireomagnile to the experimental animals, there were no significant deviations in the evaluation of hematopoiesis and the functional state of the liver, and the increase in the activity of individual indicators at a dose of 1/20 DL_{50} had a short-term and restorative character, which characterizes the search preparation as low-toxic.

The results of the experiment on the study of the irritant effect of the preparation Thireomagnile on the skin integument of rabbits are given in Table 7. According to the data obtained for a single application for the skin integument of rabbits at a deposition density of 0.020 to 0.12 ml/cm^2, the preparation Thireomagnile does not cause damage to the skin in the form of erythema or its edema.

Table 7. Characteristics of the local irritant effect of the preparation Thireomagnile with a single exposure to the skin of rabbits

Density of application, ml/cm^2	The observed effect		The average severity of manifestations			
			erythema		edema	
	group 1	group 2	group 1	group 2	group 1	group 2
0,020	0/6	0/6	0	0	0	0
0,040	0/6	0/6	0	0	0	0
0,060	0/6	0/6	0	0	0	0
0,080	0/6	0/6	0	0	0	0
0,100	0/6	0/6	0	0	0	0
0,120	0/6	0/6	0	0	0	0

It is established, that in 30 minutes after the application of the drug the irritant effect was weak, in 60 minutes - there was no irritating effect.

After application of the preparation Thireomagnile to the conjunctiva of the eye, the clinical state of the rabbit organism remained within physiological values, that is, no changes in body temperature, the number of respiratory movements and the pulse rate were established.

A visual assessment of the conjunctival condition, cornea and eyelids of rabbits showed that the preparation Thireomagnile causes mild irritation of the conjunctiva 30 minutes after instillation (Table 8).

Table 8. The influence of Thireomagnile on conjunctiva, cornea and eyelids of rabbit eyes

Time of test	Rabbit No. 1		Rabbit No. 2		Rabbit No. 3	
	Evaluation in баллах	Annoying effect	Score in points	Annoying effect	Evaluation in баллах	Annoying effect
Before the introduction	0	Absent	0	Absent	0	Absent
In 30 minutes.	2	Weak	2	Weak	2	Weak
In 1 hour	0	Absent	0	Absent	0	Absent
In 2 hours	0	Absent	0	Absent	0	Absent
In 3 hours	0	Absent	0	Absent	0	Absent
In 4 hours	0	Absent	0	Absent	0	Absent
In 5 hours	0	Absent	0	Absent	0	Absent
In 6 hours	0	Absent	0	Absent	0	Absent

Consequently, when used externally, Thireomagnile does not have irritating properties.

The next step was to determine the allergenic properties of the Thireomagnile preparation.

Conjunctival test. Guinea pigs (n = 6) were once injected intradermically into right auricle 0.05 ml of Thireomagnile. The control animals (n = 6) were injected with sterile saline solution. In 12 days, 1 drop of Thireomagnile (experiment), saline solution (control) was instilled in the conjunctival sac. The test showed no conjunctival reaction of sensitized and intact guinea pigs in 1 and 24 hours for instillation of the preparation (Table 9).

Swelling of the paws. A separate injection of the Thireomagnile preparation subcutaneously to guinea pigs (n = 6) of 0.1 ml did not cause edematic paw reaction (Table 9). As a result of the conducted searches, the allergenic properties of the Thireomagnile preparation were not revealed.

Table 9. The frequency of detection of hypersensitivity in guinea pigs after intradermal injection of Thireomagnile after conjunctival test and edema

Groups	Conjunctival test		
	0	In 1 hours	In 24 hours
Thireomagnile	6/6	0/6	0/6
Physis solution	6/6	0/6	0/6
		Paw edema	
Thireomagnile	0/6	6/6	0/6
Physis solution	0/6	6/6	0/6

Discussion

For a normal course of pregnancy, cows need to have a certain hormonal background in their bodies that would contribute to a better current of pregnancy (Hrymak et al., 2015). In violation of the hormonal balance in the body of cows, especially progesterone and estrogen, the contractile function of smooth muscles, the contractile function of smooth muscles is violated, in the future can lead to postpartum complications and deterioration of the reproductive ability. To restore the balance between these hormones in the body of pregnant cows in the practice of veterinary medicine the preparation "Glutam 1M" is applied, which includes sodium glutamate and sodium chloride. It is used by cows on the 260–262th day of pregnancy at a dose of 20 ml once a day (Hrymak and Hunchak, 2014).

During the course of pregnancy, cows are affected by various factors, including the supply of the mother's body with vitamins. For this purpose, cows from the seventh month of pregnancy receive multivitamin preparations, one of which is thetravite (Hrymak et al., 2015). It contains vitamins A, D_3, E and F. These vitamins affect a number of biochemical processes occurring in organs and tissues, normalizing their course (Gutyj et al., 2016).

Vitamin A in the mother's body affects the activity of tissue respiration enzymes, oxidative phosphorylation processes and the exchange of minerals, in particular calcium salts. Retinol is involved in the formation and functioning of the thymus gland, spleen, lymphoid tissue of the fetus (Lavryshyn et al., 2016). 30–50% of retinol in the colostrum, as well as in the liver of newborn calves is due to its mobilization from the liver of cows. This explains the low level of vitamin A and carotene in the blood plasma of cows in the prenatal and post-natal periods.

Vitamin E promotes the normal course of pregnancy and fetal development, prevents the threat of termination of pregnancy, impaired function of the gonads. The mechanism of pharmacological action of vitamin E on the animal body is that it prevents the oxidation of fats, fatty acids and sterols. It is involved in the improvement of microcirculation, promotes the maturation of germ cells, fetal development (Shcherbatyy et al., 2017).

The important role of vitamin D3 in the regulation of immune system functions is indicated by the presence in the active forms of the vitamin of the corresponding receptors. The main biological role of vitamin D is the effect on the metabolism of calcium and phosphorus in the body of animals, starting from intestinal absorption, distribution in tissues and ending with excretion (Huberuk et al., 2016; Gutyj et al., 2017; Todoriuk et al., 2017).

Vitamin F is a group of unsaturated fatty acids that stimulate the assimilation of fats by the cover epithelium, strengthening the lipotropic effect of choline and promoting the transformation of cholesterol into a soluble form that is easily excreted from the body. This vitamin is referred to limiting vitamins, because it is not synthesized in animals. Vitamin F deficiency in the body of animals is characterized by growth retardation, reproductive damage and changes in hemodynamics (Lavryshyn et al., 2016; Gutyj, 2016; Sobolev et al., 2017).

With the aim of reducing fetal pressure on the maternal organism and preventing metabolic processes in cows, an effective treatment regimen was developed, which included feeding cows of artificial Carlsbad salt, enriched with cobalt and injecting an iodine preparation and Thetravite. Iodilipid preparation on the seventh month of pregnancy of cows was injected twice a month for 15 ml per animal with simultaneous application of Thetravite in a dose of 5 ml. Respectively, iodilide preparation was prepared according to the following procedure: sunflower oil was heated to +140 °C in a dose of 350 ml. With cooling to 50 °C, it was poured into sterile glassware and 70 ml of a 5% alcohol solution of iodine, respectively, was added. Within 3–4 days, this mixture was vigorously shaken three to four times a day. During this period, iodine passes to the fat base, and at the bottom there is a clear liquid. The top layer of the mixture was used to inject cows. When applying this treatment regimen to the cows in the seventh month of pregnancy, they did not notice excessive swelling of the external genitalia, breast, and there were no edema of the ventral abdominal wall, which are characteristic for the development of endogenous intoxication (Hrymak et al., 2015).

The data available in the literature and the results of our searches indicate the important role of iodine and magnesium in the regulation of metabolic processes. The progress achieved in recent years in the study of the biological role of iodine and magnesium on metabolism, physiological functions and various aspects of the productivity of farm animals has ensured the wide use of preparations containing magnesium and iodine in veterinary medicine and animal husbandry in order to prevent and treat pathologies caused by development of endotoxicosis.

Conclusions

In determining the acute toxicity of the preparation Thireomagnile it is established that it belongs to low-toxic substances - the 4th toxicity class, its DL_{50} is more than 5000 mg/kg of body weight for the intragastric injection to laboratory animals (white mice and rats).
According to the dynamics of hematological and biochemical blood indices in laboratory animals, it is set up that a prolonged (30 days) injection of Thireomagnile in a dose of 1/20 DL_{50} causes an increase in the serum of the activity of alkaline phosphatase and AcAT by 16.5% ($P < 0.05$) and 41.1% ($P < 0.01$), respectively, which is short-term and restorative. On application to the skin and mucous membranes the preparation does not show irritating and allergenic effect.

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