

Influence of "Thireomagnile" and "Thyrioton" preparations on the antioxidant status of pregnant cows with symptoms of endotoxycosis

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The purpose of this search was to investigate the influence of "Thireomagnile" and "Thyrioton" on the antioxidant status of cows in the development of endotoxycosis. The experimental part of the work was performed at the Department of Pharmacology and Toxicology of Stepan Gzhytskyj Lviv National University of Veterinary Medicine and Biotechnologies, in the laboratory of Pharmacology and Toxicology of the State Scientific Research Institute of Veterinary Preparation and Feed Additives (Lviv) and in the Ltd. "Barkom", village Yampil of Pustomyty district, Lviv region. To solve the tasks of the research, three experimental groups of 10 pregnant cows of the Ukrainian Black-Spotted Dairy breed were formed in each: control and two experimental. Cows of the control group (K) had characteristic clinical signs of endotoxycosis. Animals of the first experimental group (E₁) were given 10 mL per animal of "Thyroid magnet" at the eighth and ninth months of gestation. The animals of the second experimental group (E₂) were given Thyrioton at a dose of 10 mL per animal in the eighth and ninth months of gestation. As a result of the conducted researches it is found out that in pregnant cows with clinical manifestation of endotoxycosis the inhibition of the activity of the antioxidant protection system and intensification of processes of lipid peroxidation occurs. The use of "Thireomagnile" and "Thyrioton" in cows by the development of endotoxycosis contributed to the increased activity of the antioxidant system, which is indicated by an increase in the activity of glutathione peroxidase, glutathione reductase and glucose-6-phosphate dehydrogenase. The use of "Thireomagnile" and "Thyrioton" to cows in the development of endotoxycosis contributed to the suppression of lipid peroxidation processes, which is indicated by the low level of primary and final products of lipid peroxidation, namely: lipid hydroperoxides and TBA-active products. Better normalizing action on the equilibrium on the activity of the antioxidant system and the intensity of lipid peroxidation was shown by the introduction of "Thyroid magnet" at a dose of 10 cm³ per animal.

Key words: Antioxidant protection system; Pregnant cows; Endotoxycosis; Preparation

Introduction

It is well known that many animal diseases are accompanied by the development of intoxication (Clark et al., 1991; Katholm & Andersen, 1992; Eades, 1993; Andersen, 2003; Chala & Rusak, 2016). The damaging action of endogenous intoxication factors on the organism of cows is concentrated in three main directions, namely: in the form of stoppage of exchange processes due to delay in withdrawal or removal of the final product of exchange; in the form of switching synthetic processes to the production of non-physiological compounds, down to the so-called "lethal synthesis", which leads to the appearance of excessively toxic substances in the internal environment; in the form of damage of cell membranes, which is the most harmful (Culbertson & Osburn, 1980; Boosman et al., 1991; Fabris et al., 2017; Bomko et al., 2018; Klosova et al., 2019). Modern ideas about the mechanism of action of endotoxins on the organism of cows are based on the leading role of antioxidant system in it (Luzhnikov et al., 2007; Gutyj et al., 2017). Antioxidant system of animals protection is a powerful mechanism that prevents the development of so-called oxidative stress and avalanche-free radical and peroxide reactions in the organism (Khariv et al., 2016; Khariv et al., 2017; Gutyj et al., 2019; Rudenko et al., 2019). This system of cells of the animal organism operates through the presence of compounds – antioxidants, which contain a mobile hydrogen atom, which is not very strongly connected to carbon (C-H) or sulfur (S-H) (Lavryshyn et al., 2016). As a result of the reactions of antioxidant molecules and free radicals, antioxidant radicals that are not potent oxidizers are formed and which can not continue the course of free radical oxidation reactions, that is, they break the data circuit. The radicals of

antioxidant molecules are excreted as end products, which are the result of interaction with molecules of other antioxidants (Hariv & Gutyj, 2016; Kiserá et al., 2019; Kushnir et al., 2019; Prysiazhniuk et al., 2019).

Of particular importance for antioxidant protection is the glutathione antioxidant protection system (Sobolev et al., 2018; 2019). The components of this system are the metabolite glutathione and the enzyme link, namely: glutathione peroxidase glutathione reductase and glucose-6-phosphate dehydrogenase. The concerted action of all its components contributes to establish the optimum level of peroxide compounds and preserve antioxidant homeostasis (Gutyj et al., 2016; Martyschuk et al., 2016).

Therefore, the purpose of our work was to investigate the influence of "Thyroid magnet" and "Thyrioton" on the antioxidant status of cows in the development of endotoxycosis.

Material and Methods

The experimental part of the work was performed at the Department of Pharmacology and Toxicology of Stepan Gzhytskyj Lviv National University of Veterinary Medicine and Biotechnologies, in the laboratory of Pharmacology and Toxicology of the State Scientific Research Institute of Veterinary Preparations and Feed Additives (Lviv) and in Ltd "Barkom", village Yampil of Pustomyty district, Lviv region. To solve the tasks of the research, three search groups were formed 10 pregnant cows of Ukrainian Black-Spotted Dairy breed in each: control and two experimental. Cows of the control group (K) had characteristic clinical signs of endotoxycosis. Animals of the first experimental group (E₁) were given 10 mg per animal of "Thireomagnile" at the eighth and ninth months of gestation (Gutyj et al., 2018). The animals of the second experimental group (E₂) were given "Thyrioton" at a dose of 10 mL/animal in the eighth and ninth months of gestation.

Blood for analysis was taken from the jugular vein at ninth and eighth months of gestation.

The activity of glutathione peroxidase (GP) and glutathione reductase (GR) was investigated in serum – by the method of V.V. Lemeshko; glucose-6-phosphate dehydrogenase (G-6-FDG) - according to the method of N.Z. Baquezetal; the level of TBK-active products - according to Y.N. Korobeynikov; the content of lipid hydroperoxide (GPL) – according to the method described by V.V. Myronchuk (Vlizlo, 2012).

Analysis of the research results was performed using the Statistica 6.0 software package. The probability of differences was evaluated by Student's T-test. P-values for the significance of mean values determined using ANOVA were considered *P < 0.05, **P ≤ 0.01, and ***P ≤ 0.001.

Results and Discussion

The intensity of the course of free radical processes in the organism of cows depends on the concentration of oxygen in the tissues, as well as enzyme and non-enzyme protection systems. The accumulation of free radicals and active oxygen species in the organism of cows is a potential prerequisite for the development of oxidative stress, which plays a leading role in the development of endotoxycosis. Therefore, in normal-functioning systems, free radicals and peroxide compounds are prevented by the system of antioxidant protection of the animal organism, which finely regulates lipoperoxidation responses in cellular structures.

In the formation of the antioxidant effect, the glutathione system of antioxidant protection of the organism plays an important role formed by glutathione, glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase and etc.

As a result of the searches, the lowest activity of glutathione peroxidase was in the control group of cows, which were characterized by clinical signs of endotoxycosis. Thus, at the eighth month of pregnancy, it was 20.5 ± 1.02 GSH min⁻¹ mg⁻¹ proteins, and at the 9th month it was 19.5 ± 1.15 GSH min⁻¹ mg⁻¹ proteins (Table 1).

Table 1. Influence of "Thireomagnile" and "Thyrioton" on the activity of glutathione system in the organism of cows with the development of endotoxycosis, M ± m, n = 10.

Months of calving	Groups of animals	Glutathione peroxidase, nmol GSH/min/mg protein	Glutathione reductase, nmol NADPH/min/mg protein	Glucose-6-phosphate-dehydrogenase, nmol NADPH/min /mg protein
8	K	20.5 ± 1.02	2.4 ± 0.16	59.1 ± 2.62
	E ₁	25.4 ± 0.77**	3.0 ± 0.10**	64.7 ± 1.72
	E ₂	24.7 ± 0.69**	2.7 ± 0.08	63.4 ± 2.09
9	K	19.5 ± 1.15	2.0 ± 0.14	58.5 ± 2.58
	E ₁	27.2 ± 0.90***	3.7 ± 0.15***	66.4 ± 2.41*
	E ₂	25.1 ± 1.10**	3.1 ± 0.09***	63.8 ± 1.53

The use of "Thyrioton" to the experimental animals contributed to the increase activity of glutathione peroxidase in the serum of experimental group D₂ on the eighth month of gestation by 20.5%, on the ninth – by 28.7% relatively to the indicators of the control group. The use of "Thireomagnile" to the experimental animals contributed to a more reliable increase in the activity of the investigated enzyme in serum than in experimental group E₂. Thus, on the eighth month of pregnancy, the activity of glutathione peroxidase in the serum of the experimental group E₁ was increased by 23.9% relatively to the control group of animals. The maximum activity of the investigated enzyme in the serum was at the ninth month of pregnancy and accordingly was 27.2 ± 0.90 nmol GSH min⁻¹ mg⁻¹ proteins. In addition to glutathione peroxidase activity, research on glutathione reductase activity is important as these two enzymes are involved in glutathione oxidation and reduction. The activity of glutathione reductase in the serum of cows of the control group for the development of endotoxycosis ranged from 2.4 ± 0.16 – 2.0 ± 0.14 nmol NADPH min⁻¹ mg⁻¹ proteins. With the introduction of "Thireomagnile" and "Thyrioton" to cows of the experimental groups for the development of endotoxycosis, the activity of glutathione reductase during the whole period of research was increased. Thus, at the eighth month of pregnancy, enzyme activity was increased by 25.0% and 12.5%, respectively, in the serum of the experimental groups E₁ and E₂. At the ninth month of pregnancy, there was a greater activity of glutathione reductase in the serum of the experimental group of animals, which were injected "Thireomagnile", accordingly, it was 3.7 ± 0.15 nmol NADPH min⁻¹ mg⁻¹ of protein, whereas in the experimental group of animals E₂ – 3.1 ± 0.09 nmol NADPH min⁻¹ mg⁻¹ protein.

To investigate the influence of endotoxigenesis in cows on glucose catabolism in erythrocytes, the activity of the enzyme G-6-FDG, which catalyzes the initial stage of the pentose phosphate pathway, was analyzed. Glucose is known to be the major energy substrate in erythroid blood cells, and the intermediate products of catabolism of this monosaccharide affect the oxygen transport properties of hemoglobin.

In this regard, the dynamics of said enzyme in the blood makes it possible to characterize the level of energy supply of erythrocytes and other links of their functional activity. The results of searches of the influence of endotoxigenesis development in cows of the control group on glucose-6-phosphate dehydrogenase activity in the blood of cows indicate that this indicator is decreasing throughout the experiment, and at the 9th month of gestation it was $58.5 \pm 2.58 \text{ nmol NADPH min}^{-1} \text{ mg}^{-1}$ of protein. It is known that glucose-6-phosphate dehydrogenase determines the overall level of conversion of monosaccharides in the pentose phosphate shunt, which is metabolically linked to the functioning of the glutathione system.

In the reactions of the pentose phosphate pathway, the formation of the NADPH-cofactor of glutathione reductase, an important enzyme of the antioxidant system, occurs.

Therefore, the results obtained for the inhibition of glucose-6-phosphate dehydrogenase indicate a decrease in the activity of glucose catabolism by pentose phosphate and, accordingly, a decrease in the intensity of NADP recovery in erythrocytes of animals with the development of endotoxigenesis. Probably, the established effect can play a role in the metabolic disorders of the state of the antioxidant protection system and the functional characteristics of erythrocytes.

The use of "Thyrioton" to cows in the development of endotoxigenesis contributed to the increased activity of the enzyme glucose-6-phosphate dehydrogenase throughout the experiment. Compared with the control group of animals, who were not treated, enzyme activity was increased by 7.3% at eighth months of gestation and reached $63.8 \pm 1.53 \text{ nmol NADPH min}^{-1} \text{ mg}^{-1}$ of protein at nine months.

The best effect on the activity of glucose-6-phosphate dehydrogenase in the blood of cows was the use to cows of the experimental group E₁ "Thireomagnile", as indicated by the results of the searches shown in Table 1. Thus, the enzyme activity at the eighth month of gestation was $64.7 \pm 1.72 \text{ nmol NADPH min}^{-1} \text{ mg}^{-1}$ of protein, ie, increased by 9.5% compared to the control group. The highest enzyme activity was at the ninth month of gestation.

Thus, the use of "Thireomagnile" and "Thyrioton" contributed to the increase the activity of the enzyme system of antioxidant protection of cows organism, preventing the development of oxidative stress resulting from the development of endotoxigenesis. Our searches have also revealed the intensification of POL in the blood of calves. It is known that uncomplicated pregnancy of animals as a physiological condition is associated with significant energy costs for biosynthetic processes, requires more oxygen and is therefore characterized by intensification of cellular respiration and, as a consequence, is oxidative stress. According to the literature, the whole period of cow gestation is accompanied by the activation of POL.

Changes in the relative homeostasis of the internal environment against the background of oxidative stress in combination with low adaptive capacity of animals contribute to the development of hypoxic condition, activation of the whole link of neuroendocrine reactions that lead to impaired metabolic processes in the organism. Primary products of POL – hydroperoxides – are rather unstable compounds that undergo further oxidation to form more stable by-products, among which TBA-active products occupy a key place. Monitoring of the processes course of lipid peroxidation showed that in the blood of cows of the control group K₁ level of lipid hydroperoxides at the eighth and ninth months of gestation was high and accordingly fluctuated within 389.5 ± 12.99 – $410.5 \pm 13.75 \text{ E} \times 1000 \text{ mL}^{-1}$.

The content of TBA-active products in the blood of cows of control group K was at eighth months of gestation $5.8 \pm 0.22 \text{ nmol/cm}^3$, and at the ninth this indicator was increased by 12.1% and fluctuated within $6.5 \pm 0.26 \text{ nmol/cm}^3$. Increasing the level of TBK-active products reflects the activation of peroxide processes. The changes we have detected in the processes of lipid peroxidation indicate that there is a shift in intrauterine programming of the systems, that control the basic constituents of this process, namely: the presentation of the substrate (free fatty acids) and the activity of the antioxidant system of organism protection (Table 2).

Table 2. Influence of "Thireomagnile" and "Thyrioton" on the level of products of POL in the blood of cows with development of endotoxigenesis, $M \pm m$, $n = 10$.

Months of calving	Groups of animals	Lipid hydroperoxide, $\text{E} \times 1000/\text{cm}^3$	TBK-active products, nmol/cm^3
8	K	389.5 ± 12.99	5.8 ± 0.22
	E ₁	$241.4 \pm 9.36^{***}$	$4.4 \pm 0.14^{***}$
	E ₂	$256.4 \pm 10.95^{***}$	$4.9 \pm 0.12^{**}$
9	K	410.5 ± 13.75	6.5 ± 0.26
	E ₁	$239.4 \pm 11.56^{***}$	$4.1 \pm 0.18^{***}$
	E ₂	$260.5 \pm 10.42^{***}$	$4.7 \pm 0.24^{***}$

Parenteral injection of "Thireomagnile" and "Thyrioton" to the cows of experimental groups allowed a significant reduction compared with the animals in the control group, the blood content of lipid hydroperoxides and TBA-active products at the eighth and ninth months of pregnancy. The content of lipid hydroperoxides in the blood of cows of the experimental group E₁ on the eighth month of gestation was decreased by 34.2%, and on the ninth – by 36.5% relatively to the control group of cows. In addition, a decrease in the level of lipid hydroperoxides was observed in the experimental group of cows E₂, that is, in animals that were injected with "Thireomagnile" hus, on the eighth month of pregnancy, this indicator fluctuated within $241.4 \pm 9.36 \text{ E} \times 1000 \text{ mL}^{-1}$, and on the ninth month of pregnancy, the level of lipid hydroperoxides reached the limits of physiological values and, compared with sick animals, it was decreased by 41.7%. The data obtained indicate that the injection of "Thireomagnile" and "Thyrioton" to cows increase the activity of the antioxidant system of blood and are able to effectively reduce the content of POL products, that under conditions of stress caused by the development of endotoxigenesis, has a positive influence on the physiological properties of the organism.

Conclusions

1. As a result of the conducted research we have established that in pregnant cows with clinical manifestation of endotoxemia comes inhibition of the activity of the antioxidant protection system and strengthening processes of lipid peroxidation;
2. The use of "Thiromagnile" and "Thyrioton" to cows in the development of endotoxemia contributed to the increased activity of the antioxidant protection system, indicated by an increase in the activity of glutathione peroxidase, glutathione reductase and glucose-6-phosphate dehydrogenase;
3. The use of cows in the development of endotoxemia "Thiromagnile" and "Thyrioton" contributed to the suppression of lipid peroxidation processes, as indicated by the low level of primary and final lipid peroxidation products, namely: lipid hydroperoxides and TBA-active products;
4. Better normalizing effect on equilibrium on activity of antioxidant system and the intensity of lipid peroxidation was demonstrated by the introduction of a 10 cm³ "Thiromagnile" per animal.

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