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Metabolic disorders as a factor in pathogenesis of infectious diseases in cattle

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SUMMARY
An important factor affecting the performance of cattle is the satisfaction of animal needs in nutrients, macro- and microelements. High-yielding dairy cows with intense metabolism are especially sensitive to errors in feeding practices, because even minor nutritional or mineral deficiencies cause metabolic disorders leading to immunodeficiency conditions, reduced resistance to infectious agents and raised sensitivity to infections with pathogenic and opportunistic microorganisms. Besides some infections, for example acute respiratory diseases, also result in metabolic disorders, immunosuppression, decrease in the overall resistance of the organism and ultimately in mixed infections. All this is the reason for low efficacy of vaccination against major infectious diseases. The paper presents the results of testing of plant tissue product "Vidoral", developed by the FSBEI HE Ural SAU for prevention of immunodeficiency conditions in cattle, caused by different factors. The product was injected subcutaneously at a dose of 0.025 mL/kg of live weight to cows in late gestation and calves showing mild anemia, low red blood cells counts, leukocytosis, high lymphocyte and monocyte counts and elevated erythrocyte sedimentation rate, which suggest inflammatory processes in the animal body. Fourteen days post injection blood was collected for hematological and biochemical testing. It was demonstrated that the product restores the animal metabolism, improves hematopoiesis and reduces inflammation. It was established that injection of "Vidoral" in combination with vaccination against infectious rhinotracheitis, viral diarrhea, infection with respiratory syncytial virus and parainfluenza-3 virus induced generation of specific antibodies against the abovementioned infections.

Keywords: metabolic disorders, cattle, metabolic immunodeficiency, secondary immunodeficiency, acute bovine respiratory diseases, foot infections in cattle, foot rot, staphylococcal infection, streptococcal infections, pasteurellosis, infectious rhinotracheitis, viral diarrhea, parainfluenza-3, infection with respiratory syncytial virus

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Метаболические нарушения как фактор патогенеза инфекционных заболеваний крупного рогатого скота

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РЕЗЮМЕ
Немаловажным фактором, влияющим на продуктивность крупного рогатого скота, является удовлетворение потребности животных в питательных веществах, макро- и микроэлементах. Особенно чувствительны к погрешностям кормления высокопродуктивные коровы, характеризующиеся высоким обменом веществ. У таких животных даже при незначительном дефиците питательных и минеральных веществ возникают метаболические нарушения, на фоне которых развиваются иммунодефицитные состояния и снижается устойчивость к инфекционным агентам, увеличивается восприимчивость к инфицированию патогенной и условно-патогенной микробиотой. Кроме того, при некоторых инфекциях, например при острых респираторных заболеваниях, также возникают метаболические нарушения, иммуносупрессия, снижается общая резистентность организма, в результате чего развиваются микст-инфекции. Все это является причиной низкой эффективности вакцинации крупного рогатого скота против основных инфекционных заболеваний. В статье представлены результаты испытания иммунометаболического растительно-тканевого препарата «Видорал», разработанного в ФГБОУ ВО Уральский ГАУ с целью профилактики иммунодефицитных состояний крупного рогатого скота различного генеза. Препарат применяли подкожно в дозе 0,025 мл/кг живой массы глубокостельным коровам и телятам, у которых выявили незначительную анемию, эритроцитопению, лейкоцитоз, лимфоцитоз

и моноцитоз, повышенный уровень скорости оседания эритроцитов, что является свидетельством наличия воспалительных процессов в организме животных. Через 14 дней производили отбор крови для проведения гематологических и биохимических исследований. Показано, что препарат нормализует обменные процессы в организме животных, увеличивает гемопоэз, снижает воспаление. Установлено, что введение «Видорала» в сочетании с иммунизацией против инфекционного ринотрахеита, вирусной диареи, респираторно-синцитиальной инфекции и парагриппа типа 3 стимулирует у коров и телят выработку специфических антител к возбудителям указанных инфекций.

Ключевые слова: метаболические нарушения, крупный рогатый скот, метаболический иммунодефицит, вторичный иммунодефицит, острые респираторные заболевания крупного рогатого скота, инфекции дистального отдела конечностей крупного рогатого скота, некробактериоз, стафилококкоз, стрептококкоз, пастереллез, инфекционный ринотрахеит, вирусная диарея, парагрипп-3, респираторно-синцитиальная инфекция

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INTRODUCTION

In today's world, taking into account sanctions from the collective West and counter-sanctions, the food security of the Russian Federation plays an important role. The policy of import substitution allowed domestic producers to significantly increase the volume of produced milk and dairy products.

The profitability of commercial dairy farming depends on three factors:

1) genetic potential of the herd;
2) complete feeding;
3) disease freedom [1–3].

The aim of the dairy farming is to increase milk performance of cows, which is achieved by stimulation of metabolic processes in high yielding cows. To obtain high milk yields, the balance in nutrient, macro- and microelement supplies must be gained in the diet of high yielding cows. At the same time, an increase in the cow productivity contributes to a decrease in their overall resistance, which is the reason for a higher susceptibility to infectious pathogens [1–3]. The decrease in resistance occurs due to metabolic disorders in the animal body, leading to immunodeficiency conditions and playing an important role in the pathogenesis of bovine infectious diseases.

MATERIALS AND METHODS

The research was conducted on the basis of the Department of Infectious and Non-Infectious Pathology of the FSBEI HE Ural SAU, and agricultural establishments of the Ural region in 2014–2022.

The object of the study were: intensively farmed cattle; whole blood and serum of animals immunized with the combined HIPRABOVIS® 4 vaccine (Laboratorios Hipra, S. A., Spain), as well as developed in the FSBEI HE Ural SAU plant-tissue product "Vidoral" (patent No. RU 2625022 dated 07/14/2015), which contains:

– "Vivaton" veterinary ammonia-free air-dried drug (TU 112-84-803-3615-001-13) – 10%;
– aloe liquid extract for injection (Reg. No. LP-001319 of 12/02/2011) – 6%;
– ASD-2 fraction (TU 10-19.73-89) – 4%;
– sodium chloride 0.9% – up to 100%.

Serological tests of sera from cows and calves were performed in accordance with the "Guidelines for Laboratory Diagnostics of Viral Respiratory Intestinal Infections of Cattle" [4]. For serological diagnostics the following test kits were used: reagent RBC test kit for serodiagnostics of infection with bovine respiratory syncytial virus (BRSV) by indirect hemagglutination test (IHA); reagent RBC test kit for serodiagnostics of infectious bovine rhinotracheitis (IBR) by indirect hemagglutination test (IHA); reagent test kit for bovine parainfluenza-3 (bPI-3) diagnostics and reagent RBC test kit for serological diagnostics of bovine viral diarrhea (BVD) by indirect hemagglutination test (IHA) produced by OOO "Agrovet" (Russia).

Hematological tests were performed by generally accepted methods. The number of erythrocytes, leukocytes, and hemoglobin was determined during complete blood count [5, 6].

Biochemical parameters of blood from cows and calves were determined using an automated analyzer ChemWell® Combi (Awareness Technology, Inc., USA) and standard reagent kits manufactured by OOO "Vital Diagnostics SPb" (Russia) according to the manufacturer's recommendations. The analysis of protein fractions was performed by agarose gel electrophoresis using Cormay Diagnostics (Poland) diagnostic kits according to the manufacturer's recommendations. Serum bactericidal and lysozyme activity was determined by techniques modified by E. S. Voronin et al. [7].

All experiments were carried out in strict accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes No. 123. (ETS No. 123)

The results of laboratory tests were processed by mathematical statistics methods used in biology and

medicine. The reliability was determined by statistical processing and determination of $M \pm m$ with the calculation of the arithmetic mean (M), standard deviation (δ), standard error of the mean (m), mean percentage error (mp) using the Student's paired t-test. The results were considered reliable at $P \leq 0.05$.

RESULTS AND DISCUSSION

Rumen digestion in cattle is based on the digestion of a large amount of fiber by cellulolytic bacteria. To increase milk yields in many farms, feeding higher-concentrate diets containing an insufficient amount of carbohydrates is used. When feeding higher-concentrate diets is used, the starch fermenting rumen microbiome synthesizes volatile fatty acids, mainly lactic acid, from starch contained in grains. Under normal conditions, lactic acid is converted by the rumen microbiome into propionic acid, used by the liver to synthesize glucose and glycogen. With a significant increase in protein diets and a lack of carbohydrates, a large amount of ammonia is formed in the rumen and the synthesis of propionic acid is inhibited. The acidity of the rumen contents decreases, acidosis develops, which leads to an increase in the amount of amylolytic and lactic acid microflora, cellulolytic and propionic bacteria growth inhibition, an increase in the volatile fatty acid concentration in blood, and thus metabolic acidosis develops [1–3, 8–12]. In addition, rumen acidosis and metabolic acidosis develop when cows are fed mainly preserved acidic feeds, such as silage and haylage [8–11, 13–15].

High yielding cows have an intensive metabolism. When there is a shortage of nutrients in the diets, their lack is compensated by the use of substances from their own body tissues to form embryos and milk, which leads to a decrease in the cow immunobiological status, even in case of minor errors in their feeding and deterioration of keeping conditions. As a result, metabolic immunodeficiency occurs and the overall resistance of the organism decreases [1–3, 12, 16–20], which contributes to the infection of animals with pathogenic and opportunistic microorganisms.

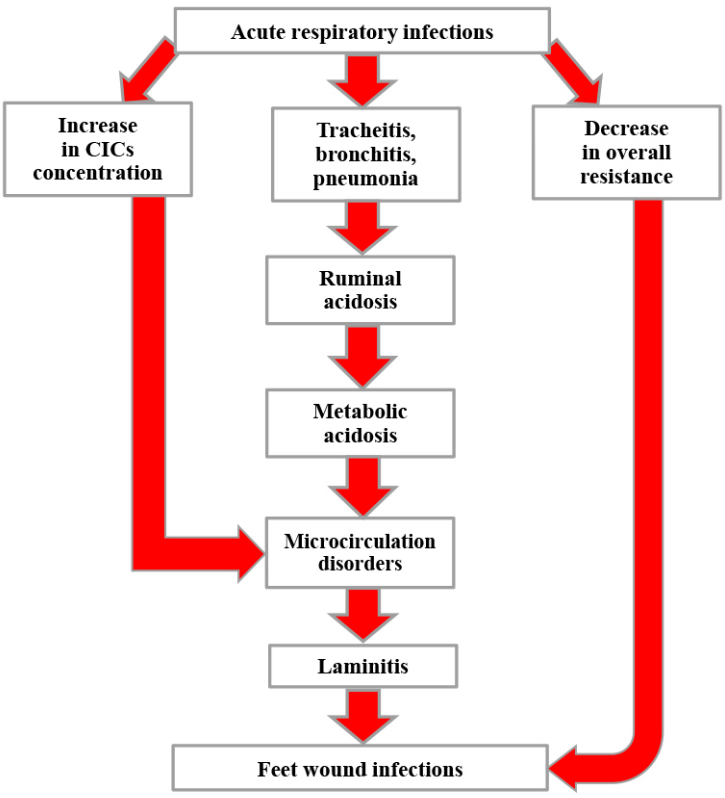

Fig. 1. Effect of acute respiratory diseases on pathogenesis of wound infections of cattle feet

With a deficiency of macro- and microelements in the diets, chronic micronutrient deficiency develops, productivity decreases, secondary immunodeficiency develops in the setting of metabolic disorders, which also leads to a decrease in the body's resistance. With cobalt, copper, zinc, calcium metabolic imbalance, rumination slows down, appetite disappears or is perverted, joints are affected. With an insufficient amount of alkaline and alkaline earth metals in the feed, such as calcium, sodium, magnesium, etc., and an excess of acidic elements, such as phosphorus, chlorine, sulfur, etc., the alkaline reserve capacity of blood decreases, the acid-base balance shifts towards acidosis, which also leads to a decrease in the body's resistance. Deficiency of copper, cobalt and zinc leads to micronutrient deficiency that induce immunosuppression and secondary immunodeficiency [1–3, 19, 20], and increases the animal susceptibility to infectious agents.

At the same time, infectious diseases in some cases may themselves be the root cause of metabolic disorders in cattle. For example, the main pathological factors caused by acute respiratory infections are bronchitis, tracheitis and pneumonia. When the respiratory tract is involved, hypoxia occurs, which leads to endogenous intoxication and ruminal acidosis [21–23]. As a result, vasoactive agents (bacterial endotoxins, histamine, lactic acid) enter the blood [8, 10, 13, 15, 21], due to the simultaneous expansion of arterioles and compression of venules, the vascular endothelium is damaged, blood fluid perfuses from blood vessels into surrounding tissues, blood flow in small blood vessels is disrupted [13, 21].

An important role in malperfusion within the blood microcirculation system is played by circulating immune complexes (CICs), which are "antigen – antibody" complexes. The formation of CICs is one of the factors of the normal immune response to the introduction of an infectious agent into the animal's body. CICs increased concentration, which occurs under a high antigenic load or in the course of pathological processes, related to CICs elimination from the body, due to their high biological activity leads to pathological changes in animal tissues and organs. CICs can be immunostimulating and can be immunosuppressive. The main pathogenic effect of CICs is associated with the complement and neutrophils. Complement-related CICs are chemotactic, inducing the concentration of neutrophils in the lesions; hydrolytic enzymes release from the neutrophils, which destroy the tissues of the body. At the same time, CICs can cause pathological effects regardless of the complement and neutrophils [21, 24]. Low-molecular-weight CICs accumulate in various organs and tissues of the animal body, damage them and cause inflammation. Most often, immune complexes affect the endothelium of blood vessels, renal glomeruli, joints, which is manifested by clinical signs in various, usually small joints [21, 25].

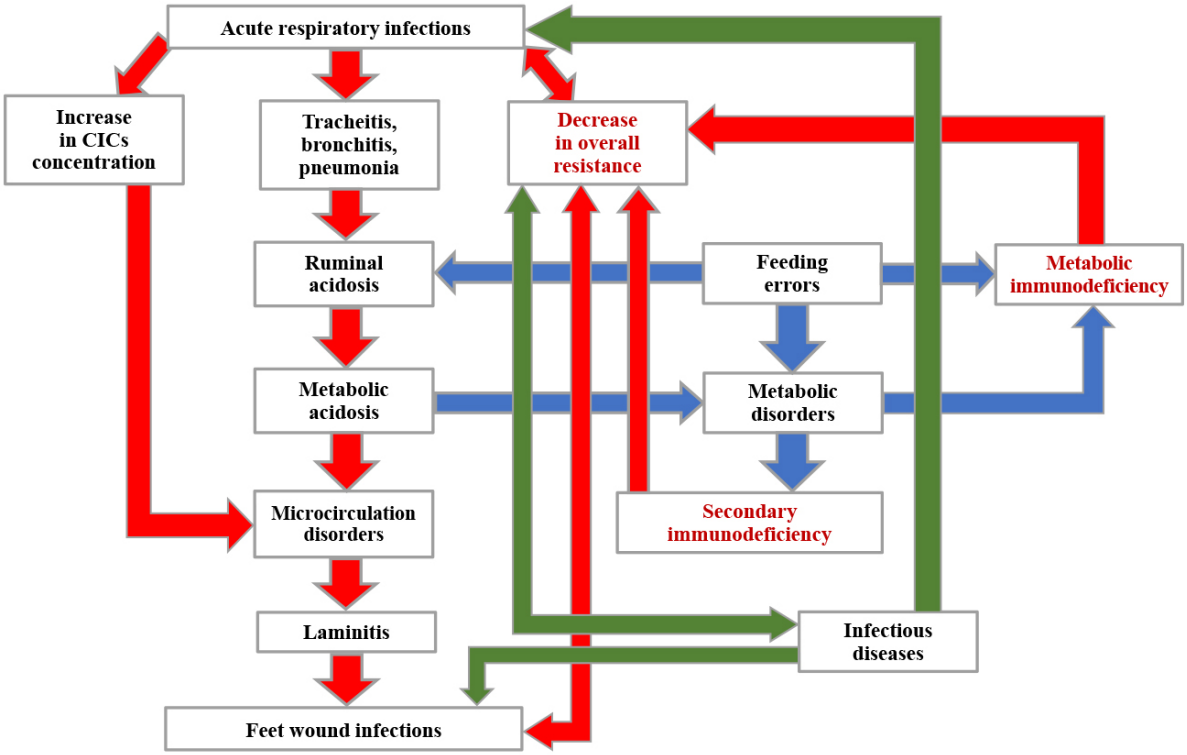

Fig. 2. Effect of metabolic disorders on pathogenesis of infections in cattle

In cattle, the small vessels of feet are most susceptible to damage, this leads to inadequate nutrient supply to foot skin and hooves, then laminitis develops, while the hoof horn is weakly keratinized and cannot resist aggressive mechanical and chemical environmental factors [13, 15]. Damaged hooves are the gateway of infection with necrobacteriosis pathogen like *Fusobacterium necrophorum*, staphylococcosis pathogen *Staphylococcus* spp., streptococcosis pathogen *Streptococcus* spp. and other pathogens [13, 15, 21, 23, 26]. In addition, mixed infection can occur due to restricted overall resistance of the body, which is observed both during respiratory pathology [2, 3, 27] and during foot pathologies [26]. The effect of acute respiratory viral infections on the pathogenesis of bovine foot wound infections is shown in Figure 1.

Calves born from cows, suffering from metabolic disorders during pregnancy are weakened, they have fatty liver disease, diseases of kidneys, spleen and lymph nodes [1, 9, 13], they are more susceptible to infections.

In high yielding cows, metabolic disorders occur year-round, with the peak reported during the first months after calving [1–3].

The effect of metabolic disorders on the pathogenesis of cattle infections is shown in Figure 2.

Metabolic disorders and resulting immunodeficiency in cows are important factors in the low effectiveness of vaccination against cattle infections [1–3] due to insufficient response of the animal's immunity to vaccines.

To prevent immunodeficiency conditions of various genesis in cattle the FSBEI HE Ural SAU developed an immunometabolic plant-tissue drug "Vidoral" [28].

The effect of the "Vidoral" on the hematological and biochemical blood parameters of second lactation cows (n = 5), which had slight anemia, erythropenia, leukocytosis, lymphocytosis and monocytosis, their erythrocyte sedimentation rate (ESR) was higher than normal, which suggested the inflammatory processes in the animals. The drug was injected to cows once subcutaneously at a dose of 0.025 mL/kg of live weight and after 14 days blood was sampled for testing. The results are shown in Tables 1 and 2.

An increase in the hemoglobin content in the cow blood 14 days after the injection of the plant-tissue drug "Vidoral" by 5.7% and the number of erythrocytes by 22.2% to the level of physiological norm suggests hematopoiesis stimulation, and a decrease in the rate of erythrocyte sedimentation by 3.4 times to reference values is the evidence of improvement in metabolic processes and a decrease in inflammatory reactions in the animals. The number of leukocytes in the cow blood decreased by 21.2% to the physiological norm, which suggests the anti-inflammatory effect of "Vidoral", the number of basophils decreased by 37.8%, and eosinophils – by 22%, which is a explained by decreased allergic reactions in the animals caused by allergens of various genesis. Besides, the anti-inflammatory properties of the studied drug are evidenced by a decrease in the number of neutrophils by 14.4%, of immature neutrophils – by 58.8%, of rod-shaped neutrophils – by 18.3%, of segmented neutrophils – by 4.3%, of lymphocytes – by 7%, of monocytes – by 16.1%.

It was found that the lysozyme activity of cow serum increased by 2.1 times, the bactericidal activity of serum – by 6.3 times, which is a result of an increase in overall resistance of the cows. The concentration of α-globulins in the cow sera increased by 52.7%, which indicates the improvement of the pancreas function. The concentration of β-globulins increased by 7.2%, γ-globulins – by 7.6%, protein – by 3 times, which indicates the improvement of protein metabolism. "Vidoral" contributed to the increase in carotene concentration by 7.4 times, which

Table 1
Changes in hematological parameters of cow blood after using "Vidoral"

Parameter	Standard	Before drug administration	After 14 days of drug administration
Hemoglobin, g/L	99–129	94.30 ± 0.83	99.66 ± 0.48*
ESR, mm/h	0.5–1.5	2.82 ± 0.26	0.83 ± 0.26
Erythrocytes, million/mm	5.0–7.5	4.28 ± 0.13	5.23 ± 0.15*
Leukocytes, thousand/mm	4.6–12.0	14.02 ± 0.24	11.05 ± 1.22
Basophils, %	0–2	3.33 ± 0.02	2.07 ± 0.38
Eosinophils, %	3–8	9.42 ± 0.16	7.34 ± 1.32
Neutrophils, %	20–35	46.26 ± 0.31	39.62 ± 1.39
Immature neutrophils, %	0–1	1.14 ± 0.20	0.47 ± 0.25
Rod-shaped neutrophils, %	2–5	6.18 ± 0.16	5.05 ± 0.45
Segmented neutrophils, %	20–35	37.04 ± 0.36	35.46 ± 0.54
Lymphocytes, %	40–75	82.14 ± 0.63	76.36 ± 1.46
Monocytes, %	2–7	8.74 ± 0.16	7.33 ± 0.26

* data are reliable: $P \leq 0.05$.

Table 2
Changes in biochemical parameters of cow blood after using "Vidoral"

Parameter	Standard	Before drug administration	After 14 days of drug administration
Lysozyme activity, %		11.18 ± 0.26	23.43 ± 2.73*
Bactericidal activity, %		6.70 ± 0.16	42.50 ± 2.24*
Albumins, g/L	25–35	24.42 ± 0.11	24.67 ± 1.72
α-globulins, g/L	12–20	8.65 ± 0.26	13.21 ± 1.90
β-globulins, g/L	10–16	9.98 ± 0.31	10.70 ± 0.38
γ-globulins, g/L	25–40	23.20 ± 0.32	24.96 ± 0.25*
Protein, g%	6.8–9.0	12.40 ± 0.49	37.10 ± 13.23
AST, nkat/L	80–120	41.60 ± 0.76	44.92 ± 0.22*
ALT, nkat/L		31.80 ± 0.74	13.06 ± 6.11
Urea, mol/L	3.6–9.0	4.74 ± 0.14	4.72 ± 0.12
Glucose, mmol/L	3.11–4.89	2.34 ± 0.01	2.37 ± 0.01
Bilirubin, μmol/L	0–12	5.29 ± 0.02	5.18 ± 0.08
Total lipids, g/L		3.51 ± 0.03	3.53 ± 0.04
Carotene, μmol/L	0.5–2.0	0.07 ± 0.01	0.52 ± 0.08*
Calcium, mmol/L	2.0–3.0	2.73 ± 0.02	2.77 ± 0.02
Phosphorus, mmol/L	1.29–2.77	1.05 ± 0.02	1.08 ± 0.02
Alkaline phosphatase, U/L	28–233	251.54 ± 2.78	248.44 ± 5.02
Cholinesterase, U/L		519.76 ± 1.41	520.32 ± 1.16
Amylase, U/L	0–34	17.32 ± 0.65	18.21 ± 0.52*
GGT, U/L		21.44 ± 0.43	21.62 ± 0.16
α-HBDH, U/L		533.08 ± 1.25	524.37 ± 6.57
LDH, mmol/L		939.74 ± 5.48	896.49 ± 27.32

* data are reliable: $P \leq 0.05$.

suggests an increase in the overall resistance of the animal organism. A decrease in the concentration of lactate dehydrogenase (LDH) in the cow sera by 4.6% indicates improvement of liver, kidney, and pancrease functions.

The effect of the plant-tissue drug "Vidoral" on seroconversion when using the combined HIPRABOVIS® 4 vaccine against IBR (caused by bovine herpesvirus-1, BHV-1), bPI-3, BVD, BRS infection was tested in second lactation cows 2 months before the expected calving. For this purpose, four of 10 cows were formed: in first two groups the cows were with a low background antibody level to bPIV-3, BHV-1, BVDV, and BRSV (Experimental Group No. 1 and Control Group No. 1) and in the other two groups the cows were with a high background antibody level to BRSV (Experimental Group No. 2 and Control Group No. 2). Animals of all groups were twice immunized with HIPRABOVIS® 4 vaccine with a 14 day-interval. "Vidoral" was administered subcutaneously to cows of experimental groups No. 1 and 2 on vaccination days at a dose of 0.025 mL/kg of live weight; the drug was not injected to animals of control groups No. 1 and 2. The results are given in Table 3.

In cows with low background antibody levels to BRSV (Experimental Group No. 1 and Control Group No. 1) had high background antibody titers to bPIV-3, BHV-1, and vice versa.

When using the plant-tissue product "Vidoral" in Experimental Groups No. 1 and 2, 10–14 days before calving, the levels of specific antibodies to bPIV-3 virus increased by 1.2 and 2.7 $\log_2$, respectively. In Experimental Group No. 1 and Control Group No. 1, 10–14 days before calving, the titers of bPIV-3 antibodies were at the same level, while in animals with low background bPIV-3 antibody levels in Experimental Group No. 2 the titer was 0.62 $\log_2$ higher than in Control Group No. 2, and 1.0 $\log_2$ higher than in Experimental Group No. 1 and Control Group No. 1.

The number of antibodies to BHV-1 in cow sera of Experimental Groups No. 1 and 2 increased by 1.5 and 1.3 $\log_2$, respectively. In groups with high background BHV-1 antibody levels (Experimental Group No. 1 and Control Group No. 1), 10–14 days before calving, the antibody titers were identical, while their level in Experimental Group No. 2 was higher than in Control Group No. 2 by 0.12 $\log_2$.

Ten – fourteen days before calving, when the plant-tissue product "Vidoral" was used in Experimental Groups No. 1 and 2, the level of antibodies to BVDV increased by 3.5 and 1.4 $\log_2$, respectively, the number of antibodies in Experimental Group No. 1 and Control Group No. 1 was at the same level, moreover, antibody titers in Experimental Group No. 2 were higher than in Control Group No. 2 by 0.72 $\log_2$.

When using "Vidoral" as an immunometabolic drug 10–14 days before calving in Experimental Groups No. 1 and 2, the titers of BRSV antibodies increased by 4.2 and 2.6 $\log_2$, while in Control Groups No. 1 and 2 only by 2.6 and 2.0 $\log_2$, respectively. In animals with low background antibody levels to BRSV in Experimental Group No. 1, the antibody titer was 1.6 $\log_2$ higher than in Control Group No. 1. In experimental group No. 2 with a high background level of BRSV antibodies, the antibody titer was 1.2 $\log_2$ higher than that of Control Group No. 2.

Thus, the use of the plant-tissue product "Vidoral" together with HIPRABOVIS® 4 vaccine stimulates seroconversion in late gestation cows to bPIV-3, BHV-1, BVDV and BRSV, in general, the titers of antibodies to these viruses

in both experimental groups were higher than the level of antibodies in the corresponding control groups.

The next stage of the study was to analyze the effect of "Vidoral" product on hematological and biochemical blood parameters of 30-day-old calves, in which minor anemia, erythrocytopenia and leukocytosis, increased ESR levels had been observed, which suggested inflammatory processes in the animals.

The plant-tissue drug "Vidoral" was administered to calves (n = 5) once subcutaneously at a dose of 0.025 mL/kg of live weight. Before the application of the tested product, as well as 14 days after, blood was sampled from calves for testing. The results are given in Tables 4 and 5.

It was found that 14 days after the injection of "Vidoral", the concentration of hemoglobin in the blood of calves increased by 2.5%, the level of erythrocytes increased to the physiological norm (by 15.5%), which indicates stimulation of hematopoiesis and erythropoiesis.

Improvement of metabolic processes and reduction of inflammatory reactions in the calves is supported by a 2.2-fold decrease (to the physiological norm) of the erythrocyte sedimentation rate, by 7.4% – of the leukocyte number, by 27% – of the of basophil numbers, by 2.9% – of the number of neutrophils, by 41.7% – of immature neutrophils, by 7.4% of rod-shaped neutrophils, by 2.9% – of segmented neutrophils and by a 5.7% increase in the number of monocytes. The number of eosinophils decreased by 11.5%, which indicates a decrease in allergic reactions of various genesis in the calves.

Fourteen days after the use of the plant-tissue product "Vidoral", the lysozyme activity of the calf serum increased by 1.3 times, the bactericidal activity – by 1.15 times, the amount of carotene – by 2.3 times, which indicates an increase in the body's resistance. Improvement of protein metabolism is evidenced by an increase of albumin content by 4.4%, α-globulins – by 3.6%, β-globulins – by 10.4%, γ-globulins – by 4.7% and protein concentration – by 8% (within the physiological norm) in calf sera. The hepatoprotective effect of "Vidoral" is supported by an increase in the concentration of aspartate aminotransferase by 2.2%, alanine aminotransferase – by 10%, urea – by 10%, bilirubin – by 2 times. Improvement of fat metabolism is evidenced by a 14% increase in the total lipid content. An increase in the calcium content in calf sera by 25.4% and phosphorus by 26.8% indicates the improvement of mineral metabolism.

The effect of the plant-tissue product "Vidoral" on seroconversion when using the HIPRABOVIS® 4 vaccine was studied on 20–25-day-old calves. For this purpose, four groups of calves were formed: Experimental Group No. 1 (n = 10) and Control Group No. 1 (n = 10) consisted of normotrophic calves, Experimental Group No. 2 (n = 7) and Control Group No. 2 (n = 10) consisted of hypotrophic calves. "Vidoral" was injected twice (5 days before vaccination and on the day of vaccination) to calves of Experimental Group No. 1 subcutaneously at a dose of 0.025 mL/kg of live weight, and three times to Experimental Group No. 2 (10, 5 days before vaccination and on the day of vaccination) at the same dose. The drug was not injected to the calves of Control Groups No. 1 and 2. The titers of antibodies to BHV-1, BVDV, bPIV-3 and BRSV in calves of all groups were determined after 7, 14 and 28 days. The results are given in Table 6.

Table 3
Effect of plant tissue product "Vidoral" on seroconversion to bPIV-3, BHV-1, BVDV and BRSV in late gestation cows

Group	Antibody titers, $\log_2$			
	background level	in 14 days	in 28 days	10–14 days before calving
bPIV-3				
Experimental group No. 1	8.72	8.66	9.65	9.94*
Control group No. 1	8.68	8.64	9.65	9.94
Experimental group No. 2	8.28	9.56	10.86	10.94*
Control group No. 2	8.27	8.714	9.32	10.32
BHV-1				
Experimental group No. 1	8.77	9.42	9.90	10.27*
Control group No. 1	8.37	9.41	9.89	10.27
Experimental group No. 2	6.95	7.53	8.21	8.25*
Control group No. 2	6.91	7.13	7.78	8.13
BVDV				
Experimental group No. 1	6.93	8.83	10.24	10.44*
Control group No. 1	6.91	8.82	10.24	10.44
Experimental group No. 2	7.06	7.68	8.29	8.50*
Control group No. 2	6.91	7.49	7.71	7.78
BRSV				
Experimental group No. 1	4.32	6.02	7.02	8.49*
Control group No. 1	4.32	5.32	6.32	6.91
Experimental group No. 2	5.91	6.49	7.91	8.49*
Control group No. 2	5.32	5.91	6.91	7.32

* data are reliable: $P \leq 0.05$.

Table 4
Changes in hematological parameters of calf blood after using "Vidoral"

Parameter	Standard	Before "Vidoral" use	14 days after "Vidoral" use
Hemoglobin, g/L	99–129	96.98 ± 0.88	99.44 ± 0.21*
ESR, mm/h	0.5–1.5	2.74 ± 0.19	1.24 ± 0.26
Erythrocytes, million/mm	5.0–7.5	4.38 ± 0.15	5.06 ± 0.24*
Leukocytes, thousand/mm	4.6–12.0	14.260 ± 0.362	13.20 ± 0.35
Basophils, %	0–2	3.04 ± 0.25	2.22 ± 0.07
Eosinophils, %	3–8	10.48 ± 0.64	9.28 ± 0.42
Neutrophils, %	20–35	40.22 ± 0.91	39.04 ± 1.06
Immature neutrophils, %	0–1	0.72 ± 0.07	0.42 ± 0.10
Rod-shaped neutrophils, %	2–5	5.64 ± 0.16	5.22 ± 0.10
Segmented neutrophils, %	20–35	36.92 ± 0.30	35.86 ± 0.36
Lymphocytes, %	40–75	78.06 ± 0.61	77.28 ± 0.68
Monocytes, %	2–7	5.62 ± 0.71	5.94 ± 0.53

* data are reliable: $P \leq 0.05$.

It was found that when using the plant-tissue product "Vidoral" 28 days after vaccination in Experimental Group No. 1, the bPIV-3 antibody titers increased by 2.85 $\log_2$, in Control Group No. 1 – by 2.64 $\log_2$, in Experimental Group No. 2 – by 3.33 $\log_2$ in Control Group No. 2 – by 2.63 $\log_2$; BHV-1 antibody titers in Experimental Group No. 1 increased by 2.61 $\log_2$, in Control Group No. 1 – by 2.29 $\log_2$, in Experimental Group No. 2 – by 2.51 $\log_2$, in Control Group No. 2 – by 2.06 $\log_2$; BVDV antibody titers in Experimental Group No. 1 increased by 1.42 $\log_2$, in Control Group No. 1 – by 1.03 $\log_2$, in Experimental Group No. 2 – by 2.25 $\log_2$, in Control Group No. 2 – by 2.01 $\log_2$; BRSV antibody titers in Experimental Group No. 1 increased by 3.0 $\log_2$, in Control Group No. 1 – by 1.09 $\log_2$, in Experimental Group No. 2 – by 2.39 $\log_2$, in Control Group No. 2 – by 0.74 $\log_2$.

Thus, the use of the plant-tissue product "Vidoral" together with HIPRABOVIS® 4 vaccine stimulates seroconversion in calves to bPIV-3, BHV-1, BVDV and BRSV, in general, the titers of antibodies to these viruses in both experimental groups were higher than the level of antibodies in the corresponding control groups.

The results obtained allow to conclude that the use of the plant-tissue product "Vidoral" in combination with vaccination of late gestation cows and calves against acute respiratory viral infections provides pronounced stimulation of immunometabolic processes, which is a necessary ground for seroconversion to bPIV-3, BHV-1, BVDV and BRSV.

CONCLUSION

Studies have shown that unbalanced diets, a lack of macro- and microelements in feeds, as well as some acute infectious diseases (for example, acute respiratory diseases) provoke metabolic disorders in cattle, which lead to a decrease in overall resistance and immunodeficiency conditions, increased susceptibility to infectious pathogens and, as a consequence, the development of infections, including mixed infections.

The developed immunometabolic plant-tissue product "Vidoral" improves metabolic processes in cows and calves, increases hematopoiesis, reduces inflammation and induces the production of specific antibodies to bPIV-3, BHV-1, BVDV and BRSV after vaccination with the HIPRABOVIS® 4 vaccine.

Table 5
Changes in biochemical parameters of calf blood after using "Vidoral"

Parameter	Standard	Before "Vidoral" use	14 days after "Vidoral" use
Lysozyme activity, %		15.28 ± 0.25	19.82 ± 0.81*
Bactericidal activity, %		29.62 ± 0.12	34.06 ± 0.34*
Albumins, g/L	25–35	16.38 ± 0.51	17.10 ± 0.63
α-globulins, g/L	12–20	16.20 ± 0.34	16.78 ± 0.31
β-globulins, g/L	10–16	8.50 ± 0.14	9.38 ± 0.22
γ-globulins, g/L	25–40	23.70 ± 0.17	24.82 ± 0.06*
Protein, g%	56–78	57.28 ± 1.29	61.90 ± 1.51
AST, nkat/L	80–120	43.56 ± 0.70	44.50 ± 0.56*
ALT, nkat/L	8–37	5.46 ± 0.16	6.00 ± 0.10*
Urea, mol/L	3.6–9.0	2.50 ± 0.14	2.76 ± 0.05
Glucose, mmol/L	3.11–4.89	1.50 ± 0.15	1.62 ± 0.18
Bilirubin, μmol/L	0–12	0.30 ± 0.03	0.61 ± 0.19
Total lipids, g/L		2.34 ± 0.02	2.67 ± 0.11*
Carotene, μmol/L	0.5–2.0	0.34 ±0.02	0.78 ± 0.20
Calcium, mmol/L	2.0–3.0	1.26 ± 0.01	1.58 ± 0.09*
Phosphorus, mmol/L	1.29–2.77	0.67 ± 0.01	0.85 ± 0.05*
Alkaline phosphatase, U/L	28–233	265.89 ± 16.08	268.36 ± 15.69
Cholinesterase, U/L		447.06 ± 14.03	453.62 ± 8.60
Amylase, U/L	0–34	26.76 ± 1.08	27.46 ± 0.91
GGT, U/L	5–36	15.14 ± 0.47	15.88 ± 0.26*
α-HBDH, U/L		308.56 ± 3.16	309.66 ± 2.63
LDH, mmol/L	300–800	529.36 ± 1.51	533.50 ± 1.54

* data are reliable: $P \leq 0.05$.

Table 6
Effect of plant tissue product "Vidoral" on seroconversion to bPIV-3, BHV-1, BVDV and BRSV in calves

Group	Antibody titers, $\log_2$			
	background level	in 7 days	in 14 days	in 28 days
bPIV-3				
Experimental group No. 1	8.82	10.04	11.06	11.67*
Control group No. 1		9.83	10.87	11.46
Experimental group No. 2	8.63	10.33	11.31	11.96*
Control group No. 2		9.95	10.71	11.26
BHV-1				
Experimental group No. 1	8.34	8.82	9.72	10.95*
Control group No. 1		8.59	9.06	10.63
Experimental group No. 2	8.21	8.93	9.55	10.72*
Control group No. 2		8.82	9.42	10.27
BVDV				
Experimental group No. 1	7.25	7.61	8.17	8.67*
Control group No. 1		7.40	7.56	8.28
Experimental group No. 2	7.16	8.06	8.55	9.41*
Control group No. 2		7.51	7.85	9.17
BRSV				
Experimental group No. 1	5.32	6.32	7.37	8.32*
Control group No. 1		5.64	6.32	6.41
Experimental group No. 2	5.39	6.13	7.32	7.78*
Control group No. 2		5.49	5.91	6.13

* data are reliable: $P \leq 0.05$.

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