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## Influence Of Amprolinsile And Brovitacoccid On The Protein Synthesizing Function Of The Liver And Enzyme Activity In Turkey Blood Serum During Eimeria Invasion.

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### ABSTRACT

While parasitizing in the intestinal mucosa, Eimeria releases metabolic products, which have a toxic influence on the various systems and tissues of turkeys. When Brovitacoccid is used for treatment, owing to its antiprotozoal action, it eliminates the action of toxins on the liver and intestinal mucosa. However, the recovery of the protein synthesizing function of the liver occurs 10 days after clinical recovery, but when using Amprolinsile, the restoration of the protein synthesizing function of the liver begins on the 5th day of treatment. During the research on the therapeutic effectiveness of Amprolinsile, in comparison with Brovitacoccid, for spontaneous Eimeria invasion, it was noticed that when using Amprolinsile for treatment, general aminotransferase activity was slightly higher than the normal range, on the 5th day. However, the coefficient of AST/ALT levels was within the normal physiological value range. This indicates that there is a stabilization of permeability of the outer cell membranes of hepatocytes as well as the internal mitochondrial membranes. It was determined that using Amprolinsile to treat turkeys, compared to Brovitacoccid, results in a faster normalization of the protein synthesizing function of the liver, and enzyme activity in blood serum as well.

**Keywords:** pharmacology, Brovitacoccid, Amprolinsile, protein-synthesizing function of the liver, blood serum enzymes, turkeys, Eimeria.

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## INTRODUCTION

Breeding turkeys is a profitable and reliable field of the poultry production. This branch of the meat industry offers the opportunity to produce a significant amount of valuable meat in a short time with minimal labour costs and resource input per production unit. Turkeys have an economically short period of fattening. The average weight of turkeys bred to produce meat typically reaches 13–14 kg, while the weight of a fattened turkey is typically more than 20 kg [1]. Incomplete nutrition, inadequate housing conditions, bacterial infections, helminthosis and protozoan parasite invasion are among the stress factors that influence the physiology of young turkeys and lower the natural resistance of the organism. It has been established that in poultry under 3 months of age, the formation of the natural immune system of the organism is incomplete [1]. That is why there is an urgent need to improve its physiological state with the help of appropriate immunostimulants and immunomodulators [2, 3]. Different immunostimulant preparations are used in the practice of veterinary medicine in order to improve the immune state of animals and poultry, in particular: leucogen, immunoglobulins, thymogen, camazol, etc [4, 5, 6]. The disadvantage of these preparations is that they are introduced parenterally, and it has been established that poultry under 3 months of age cannot tolerate the aforementioned injection without suffering adverse consequences [7, 8]. Herbal medicines are safe and may be administered effectively through their addition to food, they are used to improve the immune state of turkeys. Their immunostimulating activity is not inferior to the same action of animal pharmaceuticals, and the action of herbal medicines appears to be more gradual. [9, 10, 11]. Echinacea and milk thistle are noteworthy herbal preparations that show a high degree of immunostimulating activity. These plants are widely studied and are also administered to humans, however, they have not received sufficient attention to date in the practice of veterinary medicine.

The purpose of this work is to research the influence of Amprolium and fruit of milk thistle on the blood serum enzyme activity of turkeys after the occurrence of Eimeria invasion.

## MATERIALS AND METHODS

Experiments were performed on 458 turkeys spontaneously affected by Eimeria invasion. They were divided into two groups, with 229 animals in each group. Turkeys from the first group were given Amprolinsile at a dose of 2 g/kg of feed (R1). Turkeys from the second group were given Brovitacoccid at a dose of 2 g/kg of feed (R2). Brovitacoccid – it is supplied as a 12.5% premix: amprolium hydrochloride 12.5 g, vitamin A –  $1 \times 10^6$  ME, vitamin K – 200 mg, corn flour up to 100 g (Brovapharma, Ukraine).

Preparations were administered with wet forage for 5 days in succession. The third group of healthy turkeys was the control group. In each group, 20 poultry heads were marked with ink, vein blood was taken from under the winglets of these birds and used for biochemical tests. Blood samples were taken before treatment, on the 3<sup>rd</sup> and the 5<sup>th</sup> day of treatment, and on the 5<sup>th</sup> day after clinical recovery (10<sup>th</sup> day of experiment).

The protein synthesizing function of the liver was determined by the total protein level in the blood serum (biuret reaction) and protein fractions (by the electrophoresis method in polyacrylamide gel). 4 ml of biuret reagent was added to 1 ml of the sample. The contents of the tubes were mixed and left for 30 minutes at room temperature. The colour intensity was determined using a spectrophotometer at a wavelength in the range of 540–650 nm or with a photocolormeter, using appropriate filters. Measurements were carried out against a control sample, containing the same components, with the exception of the protein solution. By measuring the optical density of the researched samples and using a calibration graph, the concentration of protein in the research samples was determined.

The method of electrophoresis in polyacrylamide gel – is an established method of protein separation, in which the separation system with polyacrylamide is used as a carrier. The protein content in the sample should be: ~ 150–250 mg for electrophoresis without detergents; ~ 75–100 mg for electrophoresis with detergents.

The activity of aminotransferase in blood serum was determined using the method of Raytman and Frenkel as a modification of the A. Kapetanaki method. As a result of transamination, which occurs under the influence of ALT and AST, oxalic acid and pyruvic acid are formed, and with the addition of 2,4 –

dinitrophenylhydrazine, form coloured hydrazones in an alkaline medium, which have a maximum absorption at a wavelength of 500–560 nm.

The activity of lactate dehydrogenase (LDH) (K.F.1.1.1.27) was determined using the colorimetric method of Shevel and Tovarek [12]. The principle of the method is as follows: L-lactate in an alkaline medium, in the presence of blood serum lactate dehydrogenase and with the addition of NAD, is oxidized to pyruvate. The enzyme activity is established by the amount of pyruvate formed (the level of which is determined using 2,4 dinitrophenylhydrazine) [12].

The activity of glutamate dehydrogenase (GDH) (K.F.1.1.1.28) was determined by enzyme action on glutamic acid at pH 7.6 and a temperature of 37 °C in the presence of nicotine amidadenine dinucleotide [12].

The activity of alkaline phosphatase (ALP) (EC. 3.1.3.1.) was determined by a method that is based on the fact that under the action of the enzyme in blood serum, sodium beta-glycerophosphate is hydrolysed with the release of inorganic phosphorus. Enzyme activity was determined by analysing the amount of phosphorus formed [12].

The activity of blood catalase (K.F.1.11.1.6.) was determined using a method developed by Bach and Zubkova [12]. The principle of the method is based on a reaction where hydrogen peroxide breaks into atomic oxygen and water in the presence of blood catalase.

**RESULTS AND DISCUSSION**

While studying the protein synthesizing function of the liver, it was determined that during the application of Brovitacoccid (R2) for the treatment of sick poultry, on the 3rd and 5th day, the total protein level in the blood serum gradually increased, however, even on the 10th day of the experiment, namely, 5 days after clinical recovery, it did not reach the level of the control group (Table. 1).

**Table 1: The protein content and its fractions in blood serum of turkeys poultts affected with Eimeria invasion, which were treated with Amprolinsile (R<sub>1</sub>) and Brovitacoccid (R<sub>2</sub>) (M ± m; n = 20)**

Indicator	Search group	Research day			
		1st	3rd	5th	10th
General protein	K	59.6 ± 1.3	59.5 ± 1.4	59.3 ± 1.3	59.4 ± 1.2
	R <sub>1</sub>	54.3 ± 1.6*	56.3 ± 1.2*	59.2 ± 1.1	59.5 ± 1.2
	R <sub>2</sub>	54.2 ± 1.6*	55.6 ± 1.3*	56.7 ± 1.1*	56.8 ± 1.3*
Albumines, g/l	K	26.7 ± 1.4	26.2 ± 1.4	26.7 ± 1.3	26.6 ± 1.2
	R <sub>1</sub>	18.7 ± 0.9***	21.4 ± 1.2**	24.7 ± 1.3*	26.6 ± 1.0
	R <sub>2</sub>	18.8 ± 0.8***	20.2 ± 1.3***	22.7 ± 1.2**	23.4 ± 1.2*
Globulin, g/l	K	32.3 ± 1.1	32.3 ± 1.3	32.3 ± 1.2	32.3 ± 1.2
	R <sub>1</sub>	35.7 ± 1.2*	35.6 ± 1.4*	34.5 ± 1.1*	32.5 ± 1.3
	R <sub>2</sub>	35.7 ± 1.2*	35.5 ± 1.4*	34.7 ± 1.1*	34.6 ± 0.7*
Coefficient A/T	K	0.80 ± 0.03	0.81 ± 0.03	0.81 ± 0.03	0.81 ± 0.03
	R <sub>1</sub>	0.51 ± 0.08***	0.60 ± 0.02**	0.72 ± 0.03*	0.81 ± 0.05
	R <sub>2</sub>	0.51 ± 0.08***	0.56 ± 0.04***	0.66 ± 0.03**	0.67 ± 0.04*

The degree of probability: \* P <0.05, \*\* P <0.025, \*\*\* P <0

The inadequate restoration of the total protein level in turkey poultry that were treated with Brovitacoccid is due to the low level of albumin in the blood serum as a result of Eimeria invasion. The albumin level before treatment was 28% lower than the levels normally found in clinically healthy poultry, on the 3rd day – it was 18% and on the 5th day –7% lower than the level of the control group. Also, as it is set out in our experiments, in turkeys affected with Eimeria invasion, the level of globulins in the blood serum was 11% higher than in clinically healthy turkeys. This is caused by the release of proteins into the blood, including globulin fractions, as a result of catarrhal inflammation of the mucous membrane of the small intestine, which is colonized by Eimeria. In the course of the treatment process of turkey poultry, on the 3rd and 5th day, the level of globulin in the blood serum only changed slightly; the value increased by 7% and remained above the

normal level on the 5th day after clinical recovery. Due to the fact that, in the blood serum of turkeys, the level of albumin was low, and the globulin level was high, there was only a small change in the total protein content in the serum.

Therefore, the determination of protein levels in the blood serum of sick poultry, when only total protein content is taken into account without specifying the level of albumin, does not produce an objective assessment of the protein synthesizing function of the liver. An important indicator of the functional state of the liver is the value of the albumin–globulin coefficient (A/T ratio). The lower it is below the optimal level, the greater the extent to which the protein synthesizing function of the liver is reduced. As one can see from Table 1, for turkeys, which were treated with Amprolinsile, the value of the A/T coefficient gradually returned to normal. However, even on the 10th day of the experiment, namely 5 days after clinical recovery, this value remained 21% lower than that of the control group. This is because of the fact that on the 10th day, the globulin level was 7% higher than it was for the control group, and the albumin level was 14% lower than it was for the control group of turkeys. Consequently, the total protein level in the serum was only 5% below the normal index. Our results indicate that for turkeys affected with Eimeria invasion, which are administered with Brovitacoccid, on the 5th day after clinical recovery, the protein synthesizing function of the liver does not completely recover. This is indicated by the low albumin level and inflammation that results from the increased globulin level.

When studying the influence of Amprolinsile on the protein synthesizing function of the poultry liver (R1) affected with Eimeria invasion, it was determined that there is a gradual normalization of total protein content and its fractions in the blood serum. On the 3rd day of treatment, the albumin level increased from  $18.7 \pm 0.9$  g/l to  $21.4 \pm 1.3$  g/l. in the blood serum of the turkeys. However, this result was 22.4 % below the normal value. Therefore, the total protein level in the blood serum increased, but it remained at 5.6% below the control value. It should be noted that the level of globulins in the blood serum of turkeys, which were treated, has essentially remained unchanged compared to the level before treatment. On the 5th day, namely the period of clinical recovery, in turkeys, which were treated with Amprolinsile, the total protein level was the same as in clinically healthy poultry. However, the albumin level was 8.1% lower and the globulin level was 6.8% higher than the values of the control group. Therefore, the value of the A/G coefficient was  $0.72 \pm 0.03$  to  $0.81 \pm 0.03$  ( $P < 0.05$ ) in clinically healthy turkey poultry. On the 10th day, namely 5 days after clinical recovery, the total protein level and its fractions in the blood serum were normalized.

For turkeys affected by Eimeria invasion and treated with Brovitacoccid (R2), the gradual normalization of aminotransferase and phosphatase activities in the blood serum is observed (Table 2). For this group, ALT enzyme activity on the 3rd day remained 2 times higher than for the control group. It decreased slightly on the 5th day; however, even on the 10th day it was 19% higher than the normal value. In comparison, the AST activity in the blood serum of infected turkeys on the 3rd day was 62% higher, and on the 5th day it was 55% higher than in the control group.

**Table 2: The enzyme activity in serum of turkeys affected with Eimeria invasion which were treated with Amprolinsile (R<sub>1</sub>) and Brovitacoccid (R<sub>2</sub>) (M ± m; n = 20)**

Indicator	Search group	Research day			
		1st	3rd	5th	10th
AST, mmol/l	K	54.4 ± 2.3	53.4 ± 3.6	56.5 ± 3.5	56.4 ± 3.2
	R <sub>1</sub>	94.7 ± 2.4***	83.6 ± 2.1***	73.1 ± 3.1**	60.4 ± 3.0
	R <sub>2</sub>	91.7 ± 2.4***	86.5 ± 3.2***	87.5 ± 2.2***	62.5 ± 2.8
ALT, mmol/l	K	19.6 ± 1.4	19.4 ± 2.3	19.6 ± 2.8	19.6 ± 3.0
	R <sub>1</sub>	42.6 ± 2.6***	30.5 ± 2.7***	26.3 ± 2.1**	21.5 ± 2.4
	R <sub>2</sub>	42.6 ± 2.6***	40.3 ± 2.5***	38.5 ± 2.5***	23.4 ± 3.0*
Coefficient of AST/ALT	K	2.76 ± 0.02	2.69 ± 0.02	2.85 ± 0.02	2.84 ± 0.02
	R <sub>1</sub>	2.22 ± 0.05***	2.26 ± 0.04**	2.77 ± 0.03	2.79 ± 0.03
	R <sub>2</sub>	2.22 ± 0.05***	2.14 ± 0.04*	2.27 ± 0.04**	2.68 ± 0.04
LDH, mmol/l	K	573.4 ± 15.2	585.6 ± 24.8	581.8 ± 22.0	579.4 ± 18.6
	R <sub>1</sub>	643.7 ± 23.0*	630.7 ± 16.5*	631.4 ± 14.7*	561.4 ± 13.5
	R <sub>2</sub>	643.7 ± 13.1*	631.6 ± 17.5*	679.3 ± 15.2*	589.5 ± 14.6

GGT. mmol/l	K	74.5 ± 2.1	75.6 ± 2.5	75.3 ± 3.6	74.6 ± 2.4
	R <sub>1</sub>	96.6 ± 2.5***	89.1 ± 1.7*	80.8 ± 2.0	77.6 ± 2.4
	R <sub>2</sub>	96.6 ± 2.5**	90.4 ± 2.0*	87.3 ± 3.2*	82.4 ± 3.5*
LF. mmol/l	K	231.6 ± 17.2	235.5 ± 16.1	234.4 ± 12.7	235.3 ± 13.3
	R <sub>1</sub>	122.9 ± 13.4***	193.5 ± 13.6**	205.5 ± 13.6**	226.3 ± 13.5
	R <sub>2</sub>	122.9 ± 13.4***	161.3 ± 14.2***	190.7 ± 15.4**	198.7 ± 15.7*
KT. mmol/l	K	343.6 ± 22.4	343.8 ± 24.6	349.4 ± 16.7	344.1 ± 22.4
	R <sub>1</sub>	255.9 ± 24.6***	246.9 ± 13.8**	333.4 ± 18.2	352.8 ± 13.8
	R <sub>2</sub>	255.9 ± 25.7***	283.9 ± 23.5**	308.6 ± 18.6*	315.9 ± 17.7*

The degree of probability: \* P < 0.05, \*\* P < 0.025, \*\*\* P < 0.01

On the 10th day the activity of AST in turkeys, which were treated with Brovitacoccid, was 11% higher than it was for healthy turkeys. The low value of the coefficient of AST/ALT during the experiment indicates the high activity of ALT and AST in the blood serum, AST has a slightly lower activity level. Even during the clinical recovery of turkeys, which were treated with Brovitacoccid, the value of the coefficient of AST/ALT was  $2.68 \pm 0.04$  units against  $2.84 \pm 0.02$  units for the control group, which indicates that the activity of ALT normalizes more slowly than AST activity. This points to the fact that the occurrence of substantial damage to cell membranes of hepatocytes and the mitochondrial membrane, caused by Eimeria toxins. As a result of the increased permeability of cell membranes in the blood serum of sick turkeys, LDH activity was at 12% and GGT was at a level 30% higher than it was for the clinically healthy poultry. Reduced activity of these enzymes in the blood serum of turkeys occurred gradually on the 3rd and 5th day of treatment. The normalization of enzyme activity on the 5th day after clinical recovery indicates the process of the restoration of the functional and morphological state of the liver. It was found that the activity of catalase was low— 34% lower than in clinically healthy poultry. Considering that at the time of clinical recovery of turkey poultry (5th day) and 5 days after recovery (10th day) the number of red blood cells was still significantly reduced; this might be an explanation for the reduction in the activity of turkey blood catalase after treatment with Brovitacoccid, respectively by 13% and 9%.

In the treatment of turkeys, affected with Eimeria invasion, the use of Amprolinsile (R1) produced a rapid normalization of enzyme activity in the blood serum. It was found that in the blood serum of turkeys, the aminotransferase activity, on the 3rd day of treatment, remained at a high level. AST was at 56.6% and ALT at 57.2% higher than in clinically healthy poultry. The enzyme activity decreased significantly on the 5th day and normalized on the 10th day of the experiment, namely 5 days after the clinical recovery of the poultry. The value of the coefficient of AST/ALT gradually levelled out and on the 10th day, the aminotransferase ratio in the blood serum of the turkeys was within normal physiological values.

Through the research described above we found that during the Eimeria invasion of turkeys, Amprolium shows a high therapeutic efficiency when the treatment is combined with milk thistle fruit [9]. Brovitacoccid – it is supplied as a 12.5% premix: amprolium hydrochloride 12.5 g, vitamin A –  $1 \times 10^6$  ME, vitamin K – 200 mg, corn flour up to 100 g (Brovapharma, Ukraine). Amprolium is an antiprotozoal analogue of thiamine. Within the Eimeria organism, Amprolium blocks the metabolism of glucose-6-phosphate dehydrogenase, which leads to disorders in carbohydrate metabolism and the destruction of the parasites. Considering the fact that, in the small intestine, which is colonized by Eimeria parasites, the destruction of the epithelial cells of the mucosa occurs [15–17]. This leads to catarrhal inflammation and, as a result, Eimeria toxins delay blood clotting. That is why vitamin K is included in the preparation of Brovitacoccid, which promotes hemocoagulation, and vitamin A which stimulates the regeneration of the epithelium of the mucous membranes. During protozoan invasions, the immune system is suppressed, causing secondary immunodeficiency in poultry. In these animals, the protozoan invasion is complicated by viral and bacterial microflora. In our previously conducted research on non-infected turkeys it was established that Brovitacoccid, even in a therapeutic dose (2 g/kg feed), suppresses the immune systems of poultry.

Considering the immunosuppressive effect of Brovitacoccid, we have developed a treatment method for turkeys, in which Amprolium is used together with the fruits of thistle – 2 g/kg of feed for both preparations over 5 days in succession. The high therapeutic efficacy of milk thistle fruit is owed to the action of the complex of flavolignans known as Silymarin. These flavolignans hinder excessive lipid peroxidation and protect cell membranes from aggressive forms of oxygen; due to this fact a preparation which contains milk thistle fruit shows a high level of hepatoprotective and antioxidant action. The second essential component of

thistle fruit is a wide range of vitamins that are present at high levels. In particular, vitamin C (ascorbic acid) activates the synthesis of antibodies – immunoglobulin classes IgA and IgM. Furthermore, vitamin C strengthens the activity of the active ingredient, enhances immune function and increases the nonspecific immunity of an organism against bacterial infections. Vitamin K, which is also a portion of the thistle content, provides stable blood coagulation [13], and microelements of copper, iron and cobalt which are involved in erythropoiesis [12]. Vitamin A and E facilitate a quick regeneration of the intestinal epithelium [14, 18, 19]. As a result of detailed research on the pharmacodynamics of Amprolium and fruit of milk thistle, for the treatment of poultry affected with Eimeria, we have developed the preparation Amprolinsile. This product contains amprolium – an anti-Eimeria remedy, and Silymarin – an antioxidant, hepatoprotective and immunostimulatory remedy. Amprolinsile – is a preparation, a mixture of amprolium hydrochloride and milled fruit of milk thistle, intended to be used for prophylaxis and treatment of protozoonosis in poultry, as well as treating mixed parasitic invasions. Instead of synthetic vitamins A and K, it contains milled fruit of thistle, which contains natural vitamins A, K, E, B-group vitamins and microelements such as: copper, cobalt, iron and others; this results in a more complex and enhanced pharmacological effect of the Amprolinsile preparation. The replacement of synthetic vitamins A and K with fruit of thistle lowers the cost of the preparation and simplifies its production.

In this study, close attention was paid to the protein synthesizing function of the liver of turkeys, affected with Eimeria invasion, which were treated with Brovitacoccid and Amprolinsile. We have concluded that there are valid reasons for the application of Brovitacoccid, due to its antiprotozoal action and the fact it eliminates the effect of toxins on the liver and intestinal mucosa, however, the recovery of protein-synthesizing function of the liver only occurs on the 5th day after clinical recovery. While using Amprolinsile the restoration of protein-synthesizing function of the liver occurs the 5th day of treatment. During the research on enzyme activity in blood serum together with the study of the therapeutic efficacy of Amprolinsile, compared to Brovitacoccid during spontaneous Eimeria invasion, we come to the conclusion, that for the group treated with Amprolinsile, on the 5th day, the general activity of aminotransferase was slightly higher than the normal values. However, the coefficient of AST/ALT levels was within normal physiological values. This indicates that there is a stabilization of permeability of the outer cell membranes of hepatocytes and internal mitochondrial membranes. In turkeys, which were treated with Amprolinsile, the enzyme activity was normalized in the blood serum by phosphorylation; this could be concluded from the levels of GGT- on the 5th day and LDH –on the 10th day of the experiment. These are intracellular enzymes, and their activities in blood serum depend on the permeability of cell membranes. The activity of catalase in the blood serum of treated turkeys was normalized on the 5th day, that is the period of clinical recovery, and the activity of alkaline phosphatase was normalized on the 5th day after the clinical recovery of the turkeys. Catalase protects hepatocytes from aggressive forms of oxygen, formed by the cleavage of phospholipids. The activity of alkaline phosphatase in the blood serum of turkeys provides information about the morphological state of the intestinal mucosa. The improved normalization of liver enzymes in the blood serum of turkeys, treated with Amprolinsile, compared to treatment using only Brovitacoccid, is due to the presence of thistle fruit, which contains the flavolignan Silymarin, which shows a hepatoprotective effect and restores the integrity of the cell membranes of hepatocytes.

### CONCLUSION

When Brovitacoccid is used for treatment, owing to its antiprotozoal action, it eliminates the action of toxins on the liver and intestinal mucosa. However, the recovery of the protein synthesizing function of the liver occurs 10 days after clinical recovery, but when using Amprolinsile, the restoration of the protein synthesizing function of the liver begins on the 5th day of treatment. It was determined that using Amprolinsile to treat turkeys, compared to Brovitacoccid, results in a faster normalization of the protein synthesizing function of the liver, and enzyme activity in blood serum as well.

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