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Original research

Effectiveness of the drug Kolidev 8M (powder for oral use) for the treatment of bacterial infections in decorative birds and European fallow deer

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Abstract. Clinical tests of the commercial veterinary drug Kolidev 8M (powder for oral use) manufactured by «DEVIE» LLC (Ukraine) were conducted for the treatment of bacterial infections in 3-month-old pheasants, 30-day-old peacocks and young European fallow deer (2-3 months old). Obtained data were compared with the efficacy of the analogous drug Kolin 5. The effectiveness of the drugs was determined by the indicators of preservation, morbidity, and blood clinical and biochemical parameters. Clinical studies of the drug Kolidev 8M were carried out at the Hunting Farm «Bars», Kostopil district and the aviary of the personal peasant farm in the Rivne district. Using recommended doses of the drug Kolidev 8M according to the scheme proposed by the manufacturer ensured the preservation of pheasants at the level of 85.7%, but 100.0% of European peacocks and fallow deer survived. Kolidev 8M did not cause hemo-, immuno- and nephrotoxicity effects; on the contrary, it helped restore immune reactivity to physiological levels and eliminate signs of endotoxicosis in their bodies. Based on the results of our research, it was established that the veterinary drug Kolidev 8M (powder for oral use) has a bactericidal effect on gram-negative microorganisms *Escherichia coli, Enterobacter spp., Pasteurella multocida* and *Salmonella enteritidis*, which cause damage to the digestive and respiratory systems of pheasants, peacocks and European fallow deer, and does not cause resistance in bacteria.

Keywords: veterinary pharmacology; colistin sulfate; antibacterial therapy; therapeutic efficacy; pheasants; peacocks; ruminant ungulates.

Ефективність застосування препарату Колідев 8М (порошок для перорального застосування) на декоративній птиці та ланях європейських при лікуванні бактерійних інфекцій

Анотація. Проведено клінічні випробування виробничої серії ветеринарного препарату Колідев 8М (порошок для перорального застосування), виробництва ТОВ «ДЕВІЕ» (Україна), на фазанах 3-місячного віку, павичах 30 добового віку та молодняку ланей європейських (2-3)-місячного віку у порівнянні з препаратом-аналогом Колін 5, при лікуванні бактерійних інфекцій. Ефективність дослідного препарату визначали за показниками збереженості, захворюваності та клініко-біохімічними показниками крові декоративної птиці та ланей європейських. Клінічні дослідження препарату Колідев 8М на тваринах і птиці здійснювали в умовах Мисливського господарства «Барс» Костопільського району та вольєра ОСГ Рівненського району Рівненської області. Застосування препарату Колідев 8М (порошок для перорального застосування) у приписаних дозах та схемах забезпечувало збереженість поголів'я фазанів на рівні 85,7 %, а павичів і ланей європейських на 100,0 %. Препарат не викликав гемо-, імуно- і нефротоксичного впливу, але сприяв відновленню імунної реактивності до фізіологічного рівня та усуванню ознак розвитку ендотоксикозу в їхньому організмі. За результатами проведених досліджень було встановлено, що ветеринарний препарат Колідев 8М володіє бактерицидною дією на грамнегативні мікроорганізми *Escherichia coli*, *Enterobacter spp.*, *Pasteurella multocida* і *Salmonella enteritidis*, які викликають ураження травної та респіраторної системи у фазанів, павичів та ланей європейських, та не викликає резистентності.

Ключові слова: ветеринарна фармакологія; колістіна сульфат; антибактеріальна терапія; терапевтична ефективність; фазани; павичі; жуйні копитні

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Introduction

The breeding of peacocks and pheasants for ornamental purposes, as well as for the settlement of hunting grounds as the game, has recently become increasingly widespread in Ukraine and around the world. The relevance of the issues of keeping and breeding of wild ungulates, in particular the European fallow deer, is currently beyond doubt, as it is closely connected with the economic efficiency of hunting and game farming, the main purpose of which is to obtain animals with high trophy characteristics of horns and meat, as well as the sale of animals for settlement - in other enclosures or for release into the wild (Viganò et al., 2019; Pepko, 2020).

However, in today's business environment, poultry and game farms cannot operate without ensuring optimum conditions for poultry and animals to ensure their health, productivity, infectious safety and product quality (Bashchenko et al., 2020). One of the hazards to livestock and poultry is the circulation and recirculation of opportunistic microflora, as many bacteria are permanent inhabitants of the gastrointestinal tract (escherichiosis and salmonellosis are particularly dangerous and the most common bacterial diseases in hunting farms). It should be noted that pathogenic strains of Escherichia spp. and Salmonella spp. can remain viable in the environment for up to four months, while in the egg the escherichiosis pathogen persists for the entire incubation period (Pennycott & Duncan, 1999; Lutful Kabir, 2010; Barbieri et al., 2012; Díaz-Sánchez et al., 2013; Alegria-Moran et al., 2017).

Many antibacterial drugs are used to treat these diseases, which inhibit not only the pathogenic but also the beneficial intestinal microflora and lead to antibiotic-resistant strains of micro-organisms living in the organs and tissues of animals and poultry (Wasyl et al., 2018; Hunchak et al., 2020; Martyshuk et al., 2020; Varkholiak et al., 2021; Martyshuk et al., 2022; Lesyk et al., 2022). The use of chemotherapeutic drugs, which act on the pathogen, eliminate the disease and prevent livestock mortality and economic losses, has therefore become particularly relevant today (Katsaraba et al., 2022; Karpenko et al., 2022).

In Europe, colistin (in the form of sulphate) produced by *Bacillus polymyxa* var. *colistin* is most commonly used for the treatment of secondary bacterial infections of pheasants, peacocks and fallow deer. Colistin sulphate is mainly active against *Pseudomonas aeruginosa*, intestinal bacteria (*Escherichia coli, Shigella, Salmonella*) as well as capsular bacteria, *Pasteurella*. The level of resistance to colistin is low and develops slowly. High concentrations of the drug accumulate in the gut as it is poorly absorbed from the gastrointestinal tract, so colistin is prescribed for intestinal infections in animals and poultry (Bialvaei & Kafil, 2015; Cai et al., 2015; Kempf et al., 2016; Apostolakos & Piccirillo, 2018; Dalmolin et al., 2020; Chatzidimitriou et al., 2021).

As a result of the acquisition of resistance of microorganisms to antibacterial agents, their use, especially for productive animals, is strictly controlled, and only those drugs that have state registration are used for treatment. Thus, according to the List of registered veterinary drugs, feed additives, ready-made feeds and premixes, 18 drugs with the active substance colistin sulfate are allowed to be used in Ukraine (of which six are drugs with a single active substance, the rest are complex), but none of them is not intended for the treatment of bacterial infections of European fallow deer and peacocks, and only one can be used for the treatment of pheasants, which initially determined the development of the drug for the corresponding species of animals and poultry (Technical conditions of Ukraine 21.2-40781800-034:2022 «Kolidev 8M») and determination of its therapeutic effectiveness under production conditions.

The purpose of the research is to study the effectiveness of the antimicrobial veterinary drug Kolidev 8M (powder for oral use) on pheasants, peacocks and European fallow deer in the treatment of bacterial infections.

Materials and methods

Today, according to the rules of registration of veterinary drugs in Ukraine, it is mandatory to compare the therapeutic effectiveness of a newly developed drug with its already registered analogues or a drug similar in composition and form (Kotsyumbas et al., 2013). Since there are no identical analogues of Kolidev 8M (powder for oral use) currently registered, Kolin 5 (registration certificate No. AB-09383-01-20 valid until 07/06/2025, produced by Vetsintez LLC, Ukraine) was chosen as a drug to compare.

During the research, animals were manipulated following the Law of Ukraine «On the Protection of Animals from Cruelty» and the rules of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986; Council Directive 86/609/EEC, 1986).

Research on pheasants. Clinical studies of the drug Kolidev 8M on pheasants were carried out in the conditions of the aviary of the personal peasant farm Tkachuk I.B., Rivne district of the Rivne region. The total number of pheasants on the farm was 32 birds, 3 months old, weighing 1.2–1.3 kg. The death rate of pheasants at the time of examination reached 6.3%, and the percentage of clinically ill birds was 43.8%. To establish the etiological structure and epizootological features of the spread of digestive tract infections, the clinical and epizootological examination, pathoanatomical and bacteriological studies were carried out. Depression, signs of intoxication, refusal of feed, and digestive disorders were noted in pheasants, and death was noted within 2-3 days. At the autopsy of the dead bird, serous-fibrinous pericarditis, fibrinous perihepatitis, deposition of fibrin on serous covers, peritonitis, aerosacculitis, hemorrhagic diathesis, acute catarrhal enteritis, and enlargement of the spleen were noted. The diagnosis was established based on epizootological data, clinical signs and pathoanatomical changes, and isolation of the causative agent during the bacteriological studies.

The therapeutic effectiveness of the drug Kolidev 8M was determined in two experimental groups (n=7) of clinically ill pheasants aged 3 months, which were selected according to the principle of analogues: the first experimental group was given drinking water the drug Kolidev 8M (powder for oral use) at the rate of 0.75 g per 10 litres of drinking water daily; the second experimental group was given a drug analogue of Kolin 5 (powder for oral use) with drinking water at the rate of 1.20 g per 10 litres of water per day. The preparations were drunk for 5 days (the approximate consumption of water with the preparations was 90.0-100.0 ml/bird per day). The period of observation of pheasants was 21 days. The compositions of the complete combined feed for young pheasants and peacocks are presented in Table 1.

Studies on peacocks. Clinical studies of the drug Kolidev 8M on peacocks were carried out in the conditions of the same farm. The total number of peacocks on the farm was 23 birds, 30 days old, weighing 0.8-1.0 kg. The death rate of peacocks was 8.7%, and the percentage of clinically sick birds was 52.2%. To establish the etiological structure and epizootological features of the spread of digestive tract infections, a clinical and epizootological examination, and pathoanatomical and bacteriological studies were carried out. During the clinical examination, 30-day-old peacocks were found with lethargy, immobility, lack of appetite, thirst, secretions from the nasal sinuses, diarrhoea, difficulty breathing, eye damage in the form of conjunctivitis and blepharitis, some birds had impaired coordination of movement and paresis limbs. There were pathological-anatomical changes such as emaciated corpses, degeneration of skeletal muscles, gastroenteritis with ulcerative lesions, an increase in the size of the liver and spleen with scattered small white foci, thickening of bile, and nephropathy. The diagnosis was established comprehensively based on epizootological data, clinical signs, pathoanatomical changes, and the results of the bacteriological examination of bird droppings and blood.

Table 1 – Recipe for compound feed for pheasants and peacocks, %

Component	Bird species	
	pheasant	peacock
Corn	20.3	40.0
Wheat	11.0	27.0
Barley	6.5	-
Soybean meal	45.5	-
Sunflower meal	-	13.0
Fish meal	5.0	2.0
Meat and bone meal	5.0	8.0
Dry twigs	2.5	-
Feed yeast	-	3.0
Herbal flour	2.5	-
Tricalcium phosphate	-	0.8
Chalk	0.5	2.5
Premix	1 (P5-1)	1.5
Kitchen salt	0.2	0.2
Dry milk	-	2.0
In total	100	100

To study the antimicrobial activity of the drug Kolidev 8M, two studied groups (n = 6) of sick 30 days old peacocks were selected. According to the principle of analogue, the first group of birds was given drinking water with the drug Kolidev 8M (powder for oral use) at the rate of 1.25 g per 10 litres of drinking water daily; the second experimental group was given a drug analogue of Kolin 5 (powder for oral use) at the rate of 2.0 g per 10 litres of water per day with drinking water. Treatment with antibiotics lasted 5 days (the approximate consumption of water with drugs was 90.0-100.0 ml/bird per day). Peacocks were fed with the diet presented in Table 1. Observation of the experimental bird lasted for 21 days.

Research on European fallow deer. Before conducting experiments on fallow deer, the epizootic situation in the place of captivity of the «Bars» Hunting Farm was studied regarding the spread of associated forms of respiratory infections using epizootological, clinical and bacteriological methods. The total number of European fallow deer on the farm was 37 individuals, of which 17 were 2–3 months old and weighing 12.0–15.0 kg. In young fallow deer, the infectious disease was manifested by depression, and symptoms of respiration disorders (rapid breathing, hoarseness, desire of animals to lie, painful, frequent, and prolonged cough). No deaths were recorded, but the percentage of clinically ill animals reached 70.6%. The diagnosis was established based on the analysis of epizootological data, and clinical signs with the mandatory bacteriological examination of biomaterial from sick animals.

The study of the therapeutic effectiveness of the drug Kolidev 8M was carried out on 2 experimental groups of sick European fallow deer (2-3 months old, n = 6), which were selected according to the principle of analogues: the first studied group was given the drug Kolidev 8M (powder for oral use) with drinking water at the rate of 1 g per 150 kg of animal body weight; the second group was given a drug analogue of Kolin 5 (powder for oral use) at the rate of 1.2 g per 100 kg of the animal's body weight with drinking water. Antibiotic therapy lasted for 5 days. The animals were examined after 21 days. The diet of the European fallow deer at the Hunting Farm «Bars» consisted of the following components (Table 2).

In addition, in the diet of the animals, there were natural grass and pasture clover. Mineral feeding consisted of free access to salt-lick.

Since these farms kept a limited number of animals and poultry, as well as taking into account the principles of bioethics, the positive control group (clinically ill patients without treatment of animals or poultry) was not used. The values of blood parameters of pheasants, peacocks and European fallow deer with clinical disease manifestations before the start of treatment according to the above-described schemes were considered as control values.

Table 2 – Approximate structure of the diet of the European fallow deer, %

Component	Proportion
Oat	65
Wheat	10
Corn	25
In total	100

The effectiveness of the therapeutic activity of the experimental drug Kolidev 8M was determined by the level of preservation, the decrease in the percentage of sick animals, and the state of clinical and biochemical parameters in the blood serum of pheasants, peacocks, and fallow deer from each group at the beginning and on the 6th day after the start of therapy. Blood was collected from the birds' subwing vein and the jugular vein in European fallow deer on an empty stomach before feeding. Criteria for animal recovery were the absence of clinical signs of the disease, negative results of bacteriological tests of biological material in treated animals concerning isolated pathogens, as well as the recovery of haematological and biochemical blood parameters to physiological norms.

Evaluation of the organism functional state of the experimental animals in comparison with the control (before treatment) was carried out by determining clinical and biochemical parameters in their blood according to generally accepted methods. In the stabilized blood of animals, the following were determined: the number of erythrocytes, leukocytes and the content of total haemoglobin; in blood serum – the activity of the indicative enzymes alanine aminotransferase (ALT) (KF 2.6.1.2) and aspartate aminotransferase (AST) (KF 2.6.1.1), the level of total protein, glucose, as well as the content of the end products of protein metabolism – urea (in poultry, uric acid) and creatinine (Vlizlo, 2012).

Bacteriological studies. Biological material (heart, lungs, mesenteric lymph nodes, intestines, spleen, liver) was collected from two dead 3-month-old pheasants, two 30-day-old peacocks with disorders of the digestive tract, and six European fallow deer (2-3 months old). Clinical material (rectum smears) was collected the for isolation of infectious pathogens in the laboratory.

From the internal organs and clinical material, the primary culture of the material was carried out on meat-peptone broth (MPB). After 48 hours of incubation, uniform turbidity was noted, followed by the formation of sediment and a wall ring. From MPB, the culture was transplanted to meat-peptone agar (MPA). After 18-24 hours of incubation, the appearance of small, shiny, greyish and grey-white slightly convex wet colonies with a size of 1 to 2 mm was recorded. After that, individual colonies were transplanted onto differential media: Endo, SS agar, bismuth-sulfite agar, 5% blood agar, chocolate agar with the addition of 5% horse blood, agar and Hottinger broth.

The pathogenicity of all isolated bacterial pathogens from animals was tested on laboratory white mice by intraperitoneal injection of daily cultures. All isolates of microorganisms had pathogenic properties and caused 100% death of white mice.

The antimicrobial activity of Kolidev 8M was tested by the disco diffusion method on a dense nutrient medium of Muller-Hinton. A separate Petri dish was used for each isolated microorganism. A 24-hour bacterial suspension of *E. coli*, *Enterobacter spp., Salmonella enteritidis*, and *Pasteurella multocida*, which were isolated from pathological and clinical material from animals, was applied to the surface of the nutrient medium.

The drug was used in the form of standard disks with a content of 10 μg of active substance; the exposure was 24 hours at a temperature of 37.0 ± 0.5 ºC.

To determine the minimum inhibitory concentration (MIC) of the experimental antibiotic Kolidev 8M relative to selected field bacteria, successive serial dilutions were prepared in a liquid nutrient medium (meat-peptone broth). 0.1 ml of a 24-hour culture of *E. coli* with a concentration of microbial bodies of 106 CFU/ml was added to each test tube with the appropriate dilution. This method was used to determine the bacteriostatic activity of the drug against field isolates of *Enterobacter spp.*, *S. enteritidis*, and *P. multocida*.

The obtained data were processed by analysis of variance (ANOVA), StatPlus 7(7.6.5.0) package (AnalystSoft Inc., USA). The probability of the obtained results was assessed by the Tukey test (HSD mean difference) at a probability level of 95.0% ($p<0.05$).

Results

Enterobacteria *E. coli* and *Enterobacter spp.* were isolated from dead pheasants. *E. coli* formed colonies of medium size, round, moist, transparent, and shiny on MPA. On blood agar, the colonies of medium size are round, moist, pale, and surrounded by a transparent β-zone of hemolysis. Colonies of *Escherichia coli* on Endo medium are round, moist, and shiny with a metallic tint. The smears noted rod-shaped, gram-negative cells with slightly rounded ends.

Microorganisms *Enterobacter spp.* turbidity was caused on the MPB, slimy colonies were formed on the MPA. Yellowish colonies were recorded on Endo and SS media.

In the field of view of the microscope, mobile Gram-negative rods were observed, located singly and in short chains.

Salmonella enteritidis was identified from the pathological material from peacocks.

S. enteritidis on MPA formed delicate, translucent, slightly convex, shiny colonies, in MPB - uniform turbidity. Salmonella grew in the form of colourless colonies on Endo and SS differential diagnostic media. Black colonies were formed on bismuth-sulfite agar after 48 hours.

Small, gram-negative, mobile rods with rounded ends were recorded during microscopy.

Pasteurella multocida was isolated from clinically sick European fallow deer.

P. multocida on Hottinger's agar formed rounded, convex, translucent colonies of a smooth and moist surface with even edges and of 1-3 mm diameter. There is no zone of hemolysis on blood agar. Microscopy of smears from culture colonies showed Pasteurella in the form of polymorphic, small gram-negative rods, stained bipolarly.

The pathogenicity of all isolated bacterial pathogens from animals and poultry was tested on laboratory white mice by intraperitoneal infection. All isolates of microorganisms had pathogenic properties and caused 100% death of the mice.

When determining the sensitivity of selected isolates to the studied antibiotic Kolidev 8M, a satisfactory sensitivity was established for selected field isolates of bacteria by the disc diffusion method (Table 3).

However, according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI, 2020), the dilution testing should confirm the results of the colistin disk diffusion test. Thus, the presence or absence of bacterial growth was determined by the degree of medium transparency. The minimum inhibitory concentration (MIC) of the experimental antibiotic Kolidev 8M was determined for selected isolates of bacteria by the dilution method (Table 4).

The minimum inhibitory concentration (MIC) of the experimental antibiotic Kolidev 8M, which contributed to the lack of growth for *E. coli* and *P. multocida*, was 1.0 μg/ml, for *S. enteritidis, Enterobacter spp.* 2.0 μg/ml, respectively.

Table 3 – Sensitivity of the isolated microflora to the drug Kolidev 8M, 10 μg

Types of pathogens	Zone of growth retardation, mm
Escherichia coli	15
Enterobacter spp.	16
Salmonella enteritidis	15
Pasteurella multocida	15

Note. A zone diameter ≥15 mm demonstrates the sensitivity.

Table 4 – Minimum inhibitory concentrations of Kolidev 8M for bacterial isolates

Isolated bacteria	Kolidev 8M concentration, μg/ml	Experimental culture, ml	Bacterial growth (turbidity of the medium)
Escherichia coli	16.0	0.1	-
	8.0	0.1	-
	4.0	0.1	-
	2.0	0.1	-
	1.0	0.1	-
	0.5	0.1	+
	0.25	0.1	+
Enterobacter spp.	16.0	0.1	-
	8.0	0.1	-
	4.0	0.1	-
	2.0	0.1	-
	1.0	0.1	+
	0.5	0.1	+
	0.25	0.1	+
Salmonella enteritidis	16.0	0.1	-
	8.0	0.1	-
	4.0	0.1	-
	2.0	0.1	-
	1.0	0.1	+
	0.5	0.1	+
	0.25	0.1	+
Pasteurella multocida	16.0	0.1	-
	8.0	0.1	-
	4.0	0.1	-
	2.0	0.1	-
	1.0	0.1	-
	0.5	0.1	+
	0.25	0.1	+
Control (no antibiotics) MPA	–	–	+

Note. «+» – growth of bacteria; «-» – lack of bacterial growth. According to the criteria of the Clinical and Laboratory Standards Institute: MIC < 2 μg/ml – the microorganism strain is sensitive; MIC from 2 to 4 μg/ml – the microorganism strain is moderately sensitive; MIC ≥ 4 μg/ml – the strain of the microorganism is resistant

Therapeutic effectiveness of the drug Kolidev 8M on pheasants

Antibiotic therapy led to an improvement in the general condition of the bird on the 4th day: the pheasants became more active, appetite appeared, and the function of the digestive tract partially normalized on the 5th day, but one pheasant from the group died. Thus, the level of preservation in the first and second experimental groups of pheasants during the first week of observation decreased by 14.3% relative to the initial values. During the 2nd week, the birds' appetite was completely restored. Birds were active, but in 14.3 and 28.6%

Table 5 – Therapeutic effectiveness of the drug Kolidev 8M in comparison with Kolin 5 on pheasants (n=7)

Indicator	Observation time, weeks	Groups of pheasants	
		Experimental group I (Kolidev 8M)	Experimental group II (Kolin 5)
Presence of clinical signs, %	1	100.0	100.0
	2	14.3	28.6
	3	0	0
The survival rate, %	1	85.7	85.7
	2	85.7	85.7
	3	85.7	85.7

Note. All the pheasants had clinical signs before the treatment.

of the birds, the liquefaction of faeces was observed in the 1st and 2nd studied groups, respectively. Dead birds were not observed until the end of the experiment, so the survival of the population in both groups remained at the level of 85.7%. On the third week of the experiment, there were no clinical signs of the disease in the pheasants of both groups: the bird was active, responded adequately to external stimuli, ate and watered well, no digestive disorders were observed, the plumage was shiny and smooth (Table 5). Bacteriological analysis at the end of the experiment did not detect pathogenic microorganisms in samples from pheasants of both experimental groups.

The results of clinical and biochemical studies of experimental pheasants' blood before and after antibacterial therapy are shown in Table 6. The studies established (Table 6) that the disease clinical presentation of the experimental birds of the first and

Table 6 – Haematological and biochemical indices of the blood of pheasants before and after antibacterial therapy (M ± m; n = 6)

Experimental group, antibiotic	Research period	
	Before antibacterial therapy (control)	After antibacterial therapy (6th day)
Total haemoglobin (HGB), g/L		
I, Kolydev 8M	96.25 ± 1.13	125.38 ± 2.14*
II, Kolin 5	98.18 ± 1.71	125.90 ± 2.78*
Reference level	110.0–150.0	
Erythrocytes (RBC), 10^{12}/L		
I, Kolydev 8M	1.72 ± 0.16	3.78 ± 0.18*
II, Kolin 5	1.74 ± 0.12	3.65 ± 0.14*
Reference level	2.1–4.9	
Leukocytes (WBC), 10^{9}/L		
I, Kolydev 8M	34.42 ± 0.53	26.14 ± 0.54*
II, Kolin 5	35.05 ± 0.64	26.06 ± 0.33*
Reference level	19.0–29.0	
Total proteins, g/L		
I, Kolydev 8M	60.38 ± 0.84	53.90 ± 0.76*
II, Kolin 5	59.75 ± 0.73	53.45 ± 0.80*
Reference level	39.0–56.0	
Glucose, mmol/L		
I, Kolydev 8M	3.29 ± 0.11	3.96 ± 0.15*
II, Kolin 5	3.32 ± 0.13	4.02 ± 0.12*
Reference level	3.50–5.40	
ALT activity, μmol/(h×ml)		
I, Kolydev 8M	1,04 ± 0,06	0.35 ± 0.02*
II, Kolin 5	0,95 ± 0,03	0.36 ± 0.03*
Reference level	0.27–0.37	
AST activity, μmol/(h×ml)		
I, Kolydev 8M	5,16 ± 0,35	4.33 ± 0.27*
II, Kolin 5	5,10 ± 0,28	4.47 ± 0.41*
Reference level	3.71–4.81	
Uric acid, μmol/L		
I, Kolydev 8M	346,25 ± 5,89	206.36 ± 3.78*
II, Kolin 5	352,78 ± 6,31	212.67 ± 3.42*
Reference level	180.0–220.0	
Creatinine, μmol/L		
I, Kolydev 8M	27.18 ± 0.46	23.37 ± 0.35*
II, Kolin 5	27.83 ± 0.34	23.53 ± 0.41*
Reference level	20.7–25.2	

Note. * Statistically significant difference as to the control (before antibacterial therapy) at $p<0.05$.

Table 7 – Therapeutic effectiveness of the drugs Kolidev 8M and Kolin 5 on peacocks (n=6)

Indicator	Observation time, weeks	Groups of peacocks	
		Experimental group I (Kolidev 8M)	Experimental group II (Kolin 5)
Presence of clinical signs, %	1	100.0	100.0
	2	33.3	33.3
	3	0	0
The survival rate, %	1	100.0	100.0
	2	100.0	100.0
	3	100.0	100.0

Note. All the peacocks had clinical signs before the treatment.

second experimental groups was accompanied by changes in the haematological indices of their blood: a decrease in the level of total haemoglobin and the erythrocytes number and an increase in the number of leukocytes relative to the physiological values.

The use of both antibacterial drugs for the therapy of pheasants contributed to the normalization of the haematological indices. Thus, on the 6th day of the experiment in the pheasants' blood in the first and second experimental groups, the level of total haemoglobin increased by 30.3 and 28.2%, respectively. The number of erythrocytes increased by 2.1 times in both groups ($p<0.05$), and the number of leukocytes decreased by 24.1 and 25.6% ($p<0.05$) relative to the control.

In the pheasants of the first and second experimental groups with clinical signs of the disease, the content of total proteins in

Table 8 – Haematological and biochemical indices of the blood of peacocks before and after antibacterial therapy (M±m; n=6)

Experimental group, antibiotic	Research period	
	Before antibacterial therapy (control)	After antibacterial therapy (6th day)
Total haemoglobin (HGB), g/L		
I, Kolydev 8M	107.55 ± 1.32	146.20 ± 2.73*
II, Kolin 5	105.89 ± 1.05	149.51 ± 3.68*
Reference level	130.0–170.0	
Erythrocytes (RBC), 10^{12}/L		
I, Kolydev 8M	3.37 ± 0.11	3.71 ± 0.15*
II, Kolin 5	3.29 ± 0.13	3.62 ± 0.11*
Reference level	3.5–4.5	
Leukocytes (WBC), 10^9/L		
I, Kolydev 8M	10.28 ± 0.16	5.51 ± 0.13*
II, Kolin 5	10.19 ± 0.18	5.62 ± 0.12*
Reference level	4.0–6.5	
Total proteins, g/L		
I, Kolydev 8M	51.49 ± 0.95	42.76 ± 0.87*
II, Kolin 5	52.64 ± 0.84	44.39 ± 0.59*
Reference level	33.5–49.3	
Glucose, mmol/L		
I, Kolydev 8M	10.11 ± 0.15	12.26 ± 0.13*
II, Kolin 5	9.95 ± 0.18	12.08 ± 0.11*
Reference level	11.4–17.9	
ALT activity, μmol/(h×ml)		
I, Kolydev 8M	4.37 ± 0.09	1.04 ± 0.05*
II, Kolin 5	4.26 ± 0.05	1.01 ± 0.06*
Reference level	0.12–1.27	
AST activity, μmol/(h×ml)		
I, Kolydev 8M	15.16 ± 0.35	10.33 ± 0.27*
II, Kolin 5	15.10 ± 0.28	10.47 ± 0.31*
Reference level	1.68–12.0	
Uric acid, μmol/L		
I, Kolydev 8M	732.64 ± 6.03	476.8 ± 4.53*
II, Kolin 5	729.08 ± 5.89	480.2 ± 5.48*
Reference level	80.0–550.0	
Creatinine, μmol/L		
I, Kolydev 8M	7.23 ± 0.24	4.48 ± 0.17*
II, Kolin 5	7.47 ± 0.19	4.56 ± 0.15*
Reference level	1.72–5.22	

Note. * Statistically significant difference as to the control (before antibacterial therapy) at $p<0.05$.

the blood serum was increased relative to the reference level, as well as the values of the enzymatic activity of ALT and AST, and the concentrations of uric acid and creatinine, while glucose level decreased relative to the reference level. The use of the antibacterial drug Kolidev 8M (experimental group I) and the analogous drug Kolin 5 (experimental group II) led to the recovery of the blood serum indices of pheasants to the reference level: the decrease ($p<0.05$) in the concentration of total proteins was 10.7 and 10, 5%, uric acid – 40.4 and 39.7%, creatinine – 14.1 and 15.5%, the enzymatic activity of ALT and AST – 66.3 and 62.1% and 16.1 and 12.3%, respectively relative to their control values (before antibiotic therapy), while glucose level increased by 20.4 and 21.1%, respectively (Table 6).

Therapeutic effectiveness of the drug Kolidev 8M on peacocks

Treatment of clinically sick peacocks with antimicrobial drugs led to an improvement in their health. The bird with an appetite began to consume feed on the 5th day of treatment, and the function of the digestive tract was restored by the 8th day of the experiment, however, discharge from the nasal sinuses, conjunctivitis and blepharitis were observed by the 10th day in 33.3% of the birds of both experimental groups. On the third week of the experiment, there were no clinical signs of the disease in the peacocks of both groups: the bird was active, responded adequately to external stimuli, accepted feed and water well, no digestive tract disorders were observed, no pathological changes were observed in the areas of the eyes and nasal sinuses, plumage it was shiny and smooth (Table 7). No bird deaths were observed during the experiment, so the survival of the population was 100.0% in both experimental groups (Table 7). Bacteriological analysis at the end of the experiment did not detect pathogenic microorganisms in samples of biological material from peacocks of both experimental groups.

The results of clinical and biochemical blood tests of experimental peacocks before and after antibacterial therapy are shown in Table 8.

In the course of the research, it was established (Table 8) that the clinical picture of the disease of the experimental bird of the first and second research groups was accompanied by changes in the haematological indicators of its blood: a decrease in the level of total haemoglobin and the number of erythrocytes and an increase in the number of leukocytes relative to the physiological values of the indicators. The use of both antibacterial drugs in the therapy of peacocks contributed to the normalization of the level of haematological indicators. Thus, on the 6th day of research in the blood of peacocks of the first and second experimental groups, the level of total haemoglobin increased by 35.9 and 41.2%, the number of erythrocytes – by 10.1 and 10.0% ($p<0.05$), and the number of leukocytes decreased by 46.4 and 44.8% ($p<0.05$) relative to the control level of indicators.

During the analysis of the biochemical indicators of the blood of peacocks, it was established that in the peacocks of the first and second research groups with clinical signs of the disease, the content of total proteins in the blood serum was increased relative to the average values of its reference level, as well as the values of the enzymatic activity of ALT and AST, concentrations of uric acid and creatinine, while glucose concentration decreased relative to the reference level. The use of antibacterial drugs Kolidev 8M (the first trial) and the analogous drug Kolin 5 (the second trial) led to the restoration of the level of indicators in the blood serum of peacocks to the reference level: the decrease ($p<0.05$) in the concentration of total proteins was 17.1 and 15, 7%, uric acid – 34.9 and 34.2%, creatinine – 38.0 and 39.0%, the enzymatic activity of ALT and AST – 76.2 and 76.3% and 31.9 and 30.7%, respectively relative to their control values (before antibiotic therapy), while glucose concentration increased by 21.3 and 21.4%, respectively (Table 8).

Therapeutic effectiveness of the drug Kolidev 8M in European fallow deer

The use of the experimental drug Kolidev 8M led to positive changes in the fallow deer on the 5th day of treatment. Respiratory pathologies were not registered, and the animals moved actively, but the cough persisted in 33.3% of the animals of both experimental groups until the 14th day of the experiment. During the entire experimental period, the death of fallow deer was not noted, therefore, the survival of the deer population was 100% in both experimental groups (Table 9). Bacteriological analysis at the end of the experiment did not detect pathogenic microorganisms in the samples from the European fallow deer of both experimental groups.

The results of clinical and biochemical blood tests of fallow deer before and after antibacterial therapy are shown in Table 10.

Haematological studies established that the content of total haemoglobin in the blood of sick European fallow deer was at the lower limit, and the number of erythrocytes was within the reference level, while the number of leukocytes increased for both experimental groups. The use of both antibacterial drugs for the therapy of European fallow deer contributed to the normalization of the haematological indices. Thus, on the 6th day of the experiment in the blood of European fallow deer of both experimental groups, the level of total haemoglobin increased by 8.7 and 7.1% ($p<0.05$), and the number of erythrocytes only tended to increase, while the leukocytes number decreased by 45.4 and 42.5% ($p<0.05$) relative to the control.

Blood biochemical analysis established that the total protein and creatinine content in the sick fallow deer blood serum was not significantly different relative to the reference value in both experimental groups. As this takes place, the enzymatic activities of ALT and AST, the number of leucocytes and uric acid content increased in ill deer, while glucose concentration was within the reference level. Administration of the antibacterial drug Kolidev 8M and the similar drug Kolin 5 led to the restoration of blood parameters of fallow deer to reference levels: urea concentrations decreased by 32.7 and 34.0%, and creatinine by 19.4 and 20.1%, respectively, relative to the control levels. The enzymatic activity of ALT decreased by 74.1 and 69.7%, and AST – by 73.6 and 70.9%, respectively ($p<0.05$) relative to their control values before antibiotic therapy. (Table 10).

Table 9 – Therapeutic effectiveness of the drugs Kolidev 8M and Kolin 5 in European fallow deer (n=6)

Indicator	Observation time, weeks	Groups of European fallow deer	
		Experimental group I (Kolidev 8M)	Experimental group II (Kolin 5)
Presence of clinical signs, %	1	100.0	100.0
	2	33.3	33.3
	3	0	0
The survival rate, %	1	100.0	100.0
	2	100.0	100.0
	3	100.0	100.0

Note. All the peacocks had clinical signs before the treatment.

Table 10 – Haematological and biochemical indices of the blood of European fallow deer before and after antibacterial therapy (M ± m; n = 6)

Experimental group, antibiotic	Research period	
	Before antibacterial therapy (control)	After antibacterial therapy (6th day)
Total haemoglobin (HGB), g/L		
I, Kolydev 8M	82.60 ± 1.75	89.80 ± 1.05*
II, Kolin 5	81.78 ± 1.16	87.60 ± 1.46*
Reference level	80.0 – 130.0	
Erythrocytes (RBC), 10^{12}/L		
I, Kolydev 8M	8.50 ± 0.15	8.82 ± 0.13
II, Kolin 5	8.43 ± 0.17	8.81 ± 0.18
Reference level	6.0 – 11.0	
Leukocytes (WBC), 10^{9}/L		
I, Kolydev 8M	15.02 ± 0.21	8.20 ± 0.15*
II, Kolin 5	14.95 ± 0.19	8.60 ± 0.14*
Reference level	6.0 – 10.0	
Total proteins, g/L		
I, Kolydev 8M	89.50 ± 1.60	87.20 ± 1.05
II, Kolin 5	89.93 ± 1.34	86.90 ± 0.74
Reference level	53.1 – 88.2	
Glucose, mmol/L		
I, Kolydev 8M	4.60 ± 0.33	4.63 ± 0.32
II, Kolin 5	4.51 ± 0.23	4.58 ± 0.27
Reference level	3.0 – 5.0	
ALT activity, μmol/(h×ml)		
I, Kolydev 8M	2.86 ± 0.18	0.74 ± 0.06*
II, Kolin 5	2.90 ± 0.15	0.88 ± 0.08*
Reference level	0.56 – 2.31	
AST activity, μmol/(h×ml)		
I, Kolydev 8M	3.60 ± 0.07	0.95 ± 0.02*
II, Kolin 5	3.58 ± 0.11	1.04 ± 0.05*
Reference level	0.70 – 2.52	
Uric acid, μmol/L		
I, Kolydev 8M	8.32±0.26	5.60±0.38*
II, Kolin 5	8.41±0.42	5.55±0.47*
Reference level	3.5 – 6.0	
Creatinine, μmol/L		
I, Kolydev 8M	179.34 ± 3.35	144.59 ± 2.86*
II, Kolin 5	178.58 ± 3.08	142.70 ± 3.23*
Reference level	88.0–177.0	

Note. * Statistically significant difference as to the control (before antibacterial therapy) at $p<0.05$.

Discussion

During the last decade, due to the introduction and spread of carbapenem-resistant strains, interest in colistin has been renewed. However, in November 2015 in China, bacteria containing the MCR-1 gene, which codes for resistance to colistin, was isolated from pets fed antibiotics for the first time. In July 2016, Belgian scientists isolated a new MCR-2 gene, and in June 2017, MCR-3 was described in the USA (Pylypenko et al., 2019). To date, 10 MCR genes (from MCR-1 to MCR-10) have been described, they were found in isolates from humans, animals, animal products and the environment. In particular, these genes are carried by *Escherichia coli, Klebsiella, Salmonella, Citrobacter, Enterobacter, Pseudomonas, Aeromonas, Alcaligenes* and *Acinetobacter baumannii.* Unfortunately, this gene was found in plasmids that can be transferred from one bacterium to another, and the term «MCR» just means plasmid-mediated colistin resistance (Anyanwu et al., 2021; Gonzalez-Avila et al., 2021; Hernández-Mendoza et al., 2022).

A study of the effectiveness of the colistin-containing antibiotic Kolidev 8M (powder for oral use, DAVIE LLC, Ukraine) on pheasants, peacocks and deer that did not previously treat with this active substance showed a lack of resistance against isolates of *E. coli, Enterobacter spp., P. multocida* and *S. enteritidis*, which is probably a guarantee of its successful use in breeding ornamental birds and hunting ungulates.

However, the occurrence of colistin resistance gene MCR-1 in *Escherichia coli* in wild ungulates has already been recorded. These studies describe the detection of plasmid-mediated resistance to colistin in *E. coli* of wild ungulates in Portugal: 151 resistant isolates of the Enterobacteriaceae family from 181 samples collected from different species of wild ungulates throughout Portugal were tested for MCR genes (four MCR-1-positive *E. coli* were detected in four

individuals of fallow deer that were selected in the same hunting ground) (Torres et al., 2021; Torres et al., 2022).

The effectiveness of the drugs is confirmed by a fairly quick levelling of the main symptoms of animal diseases, which took from 10 to 14 days, including a 5-day treatment. In particular, the recovery of appetite and the function of the digestive tract in the birds on the 5-8th day is worthy of attention. It is a good prognostic criterion for recovery. This was confirmed by the 100.0% survival of European peacocks and fallow deer. However, pheasant survival was somewhat lower (85.7%) which can be explained by the late start of treatment. As is known, the normal functioning of the digestive tract is ensured by the predominance of normal microflora over pathogenic ones and promotes the absorption of nutrients (Vicentini et al., 2021).

Another positive effect of the use of the antibiotic Kolidev 8M, as well as the analogous drug (Kolin 5), is their effect on the haematological and biochemical parameters of the blood of treated animals. Thus, in patients at the beginning of treatment, the blood pattern indicated the presence of inflammatory reactions in their body, strengthening natural detoxification processes in the liver and kidneys. After applying antibiotic therapy, haematological and biochemical indices reached the physiological norm on the 6th day, which, in addition to the metabolism restoration, indicates the absence of toxic effects of the drugs in the recommended doses and form. That is important because of described nephrotoxic (Heybeli et al., 2019; Rosas Espinoza et al., 2021; Eronmosele et al., 2021; Mirjalili et al., 2022) and neurotoxic (Wadia & Tran 2014; Ajiboye, 2018; Öz Gergin et al., 2022) actions of colistin.

Conclusions

Data obtained allow us to establish that the veterinary drug Kolidev 8M (powder for oral use) has a bactericidal effect on gram-negative microorganisms *Escherichia coli, Enterobacter spp., Pasteurella multocida* and *Salmonella enteritidis*, which cause damage to the digestive and respiratory systems of pheasants, peacocks and European fallow deer.

Based on the results of clinical and biochemical studies, we noted that the use of the veterinary drug Kolidev 8M in the antibacterial therapy of pheasants, peacocks and European fallow deer did not cause haemo-, nephro- and hepatotoxic effects.

The veterinary drug Kolidev 8M (powder for oral use) has high therapeutic efficiency in the prescribed dose, method and frequency of use. It contributed to the increase in the survival rate of pheasants, peacocks and European fallow deer and was not inferior to the bactericidal effect of the analogous drug.

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