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Nanostructured Composite Drugsatescherichiosis Of Birds.

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ABSTRACT

The aim of the work was the development of experimental samples of composite preparations created on the basis of nanostructured modified montmorillonite containing clays, and their approbation in production conditions in colibacteriosis of birds. The combined use of modified montmorillonite containing clay with enrofloxacin and thymol is safe for the body of birds. During the day, the complex drug (enrofloxacin with sorbent) is almost completely eliminated from the body of birds. The use of modified montmorillonite containing clay with enrofloxacin and thymol in chickens with escherichiosis does not cause deviations in physiological parameters, as well as in the behavior of the bird. Sorbent included in the composition of the drug, provides local detoxification, has anti-adhesive activity against pathogenic microflora of the intestine and thereby reduces time of treatment of sick animals. This enterosorbent can be effectively used in the creation of complex antibacterial drugs for the treatment and prevention of infectious gastrointestinal diseases in animals.

Keywords: nanostructure, composite preparations, clay.

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INTRODUCTION

The constant growth of population and the increased need for people nutrition require a steady improvement of production of livestock products. But a sharp decrease in the number of livestock and the emergence of a deficit in the gene pool of farm animals observed in recent years exacerbated the problem of preservation of young animals [11].

Now, especially in breeding farms with the closed system of reproduction of herd, conditions where artificial ecosystems are created, in which relations between an organism of birds and conditionally pathogenic microflora become aggravated. Permanent presence in anthropourgic environment is extremely dangerous in epidemic relation to zoonoses of reemergent pathogens of colibacillosis, yersiniosis, mycoplasmosis, pasteurellosis, pulloroz and streptococcosis in birds is one of the important issues in veterinary epidemiology.

In this regard, diseases of the digestive tract of chickens are one of the most difficult problems for modern veterinary medicine. At the same time, colibacteriosis occupies one of the leading places in the nosological structure of alimentary infections. In many cases, among infectious diseases of chickens, the incidence of colibacteriosis is 37.3 %, salmonellosis – 25.4%, pasteurellosis – 19.8 % [10].

The variant multifactorial nature of this disease makes it difficult to control, as a result of which the poultry industry suffers enormous losses from the disease and death of animals in the pre - and postnatal periods of development [1, 6].

High susceptibility of birds to colibacteriosis is associated with physiological insecurity of the small intestine against colonization by Escherichia. The route of infection is aerogenic, nutritional, transovarial.

The source of the causative agent of the disease is sick and ill with colibacteriosis chickens, as well as other carriers of pathogenic strains of Escherichia [4].

Great variability of Escherichia coli strains, as well as a high degree of mutability, complicate the specific prevention and treatment of animals with colibacteriosis. Applied antimicrobial drugs (antibiotics, sulfonamides, nitrofurans) and other therapeutic agents are mostly ineffective and environmentally dangerous, due to the formation of antibiotic-resistant strains and a decrease in the overall reactivity of animals. Along with this, they are the cause of allergic conditions and often lead to the development of dysbiosis [5, 9, 12].

The use of modern vaccines is not always an effective means of combating colibacteriosis, in this regard, antibacterial and composite drugs come to the fore in the elimination of the disease. Medicinal compounds included in the composition of drugs, as a rule, have a synergistic or potentiating effect. Therefore, the resistance of microorganisms to the combined preparation develops much more slowly.

In scientific literature information about the widespread use of montmorillonite (smectite) in severe intoxication of the body, both human and animalregularly appear. They cope with pathogenic bacterianot worse than modern antibiotics. But, unlike traditional drugs, composite smectite-montmorillonite drugs remain chemically inert, and therefore completely harmless to the body.

The therapeutic effect of such drugs is much higher, as individual, even the most modern highly effective antibiotics of broad antibacterial spectrum of action is difficult to detrimental effect on resistant to chemotherapeutic compounds microflora. As a result, the main criterion for the development of combined drugs is their pharmacological effectiveness, which consists in strengthening the therapeutic effect of the created composition [3].

The therapeutic effect of natural montmorillonite-containing clays is explained by their sorption-adhesive and ion-selective properties, as well as the saturation of various chemical elements, some of which are in a biologically available form. The sorbent binds toxins, microbial cells and decay products, which are further excreted from the body. [2].

The aim of this work was to develop experimental samples of composite preparations created on the basis of nanostructured modified montmorillonite containing clays, and their approbation in production conditions with colibacteriosis of birds.

To achieve this goal, the following tasks were carried out:

- to determine the sensitivity of E. coli to fluoroquinolone preparations and developed on their basis composite preparations and other compositions using montmorillonite containing clays;
- to find out the pharmacokinetics of the composite drug (enrofloxacin with sorbent) in the body of chickens at individual giving with drinking water;
- to study the therapeutic effectiveness of the developed composite preparations in production conditions on the unfavorable colibacteriosis herd of birds.

Experimental technique

When preparing the necessary compositions, we used a specially developed sorbent (an environmentally friendly multi - purpose sorbent based on domestic raw materials with increased sorption efficiency of both Exo-and endotoxins of enteropathogenic microorganisms and ions of iron, copper and chromium), which was obtained by modifying montmorillonite containing clay [7]. In total, two composite preparations were developed: a combination of enriched montmorillonite containing clay with enrofloxacin and a combination of enriched montmorillonite containing clay with thymol.

The sensitivity of pathogenic strains of Escherichia coli to fluoroquinolones isolated from diseased birds was determined by the method of two-time serial dilutions in a liquid nutrient medium (MPB), and composite preparations (combinations: enrofloxacin with montmorillonite containing clay and thymol with montmorillonite containing clay) – on a dense nutrient medium (MPA).

On the basis of hydrodynamic calculations the principle of the technological process of obtaining a stable microsuspension of montmorillonite clay with enrofloxacin was planned and worked out, used for the treatment and prevention of escherichiosis of birds. The duration of sedimentation of the complex preparation in drinking water is more than 30 hours [8].

The distribution and elimination of enrofloxacin was studied in 2-month-old chickens of cross “Rhodonite”. Quantitative determination of enrofloxacin in the samples was carried out by diffusion in agar (test microbe E. coli MB 3804) with determination of concentration by standard curves.

The composite preparation (enrofloxacin with sorbent) was once injected into the goiter with drinking water (in the volume of 5 ml) with the help of a probe to the experimental chickens. The dose of enrofloxacin was 2.5, 5.0 and 10.0 mg/kg of body weight, and the amount of fine montmorillonite containing clay was constant – 60 mg/kg of body weight. The control groups of chickens were injected identical doses of enrofloxacin without sorbent by the same method.

The pharmacokinetics of each dose of the studied drugs was determined in three groups of chickens (5 heads in each). For sampling of blood, litter and internal organs in control and experimental chickens after a single oral injection of the drugs, the birds were slaughtered in 3, 12 and 24 hours.

In preliminary experiments, the ability of the developed sorbent to bind toxins of pathogenic strains of Escherichia coli at a concentration of 100 mg/ml was revealed. The ability of adsorption of the sorbent on the surface of the fimbriae and the cell wall of Escherichia was also established, which in turn prevents the adhesion of the E. coli on the epithelial cells of the gastrointestinal tract and ultimately prevents their further reproduction.

Therapeutic effect of complex preparations (composition of enrofloxacin and thymol with montmorillonite containing clay) was tested on day-old chickens infected with colibacteriosis.

Within 5 days the drug was drunk to chickns of three experimental groups with drinking water containing 2 g/l of sorbent and enrofloxacin in concentrations of 50, 100 and 200 mg/l. The control chickens

received: the first group drinking water with sorbent (2 g/l suspension), 2-4 groups received drinking water containing enrofloxacin in appropriate concentrations: 50, 100 and 200 mg/l, and the fifth group received drinking water. In each group there were 50 heads of chickens.

The therapeutic effect of the complex drug (sorbent in combination with thymol), in which the thymol content was 10.5 %, was tested on five groups of chickens with a colibacteriosis clinic. The first, second, third and fourth groups of chickens received within 5 days a complex preparation with forage in the corresponding concentrations: 3, 2, 1 and 0.5 g/kg of compound feed. The control group was fed with enriched sorbent at a concentration of 3 g/kg of feed.

The formation of groups of birds for experiments in production conditions was carried out on the principle of analogues, which took into account age, breed, live weight, physiological state, productivity, health. 5 days of experience and 14 days after completion of experiments clinical observations were conducted, the incidence and mortality of chickens were taken into account. Before and after the course of treatment feces of experimental animals and parenchymal organs and tissues of fallen chickens were exposed to microbiological examination.

The state of health of chickens was judged by weight gain, safety, and data of periodic clinical examination.

RESEARCH RESULTS AND DISCUSSION

The minimum suppressive concentration (MSC) of norfloxacin, ciprofloxacin and enrofloxacin was in the range of 0.1-0.5, 0.01-0.25 and 0.05-0.12 µg/ml, respectively (table1).

Table 1: Antimicrobial activity of quinolone-class drugs

Microorganism	MSC (µg/ml) of fluoroquinolones		
	norfloxacin	ciprofloxacin	enrofloxacin
Escherichiacoli	0,1-0,5	0,01-0,25	0,05-0,12

Enrofloxacin was the most effective drug, which was the basis for its use in the development of a complex drug.

The MSC of enrofloxacin composition with montmorillonite containing clay (ratio 1:1) was 0.01-0.10 µg/ml (in this case recalculation on AIof enrofloxacin was made). Apparently, montmorillonite containing clay, having the ability of adhesion on the surface of the cell wall of bacteria and fimbriae, contributed to the manifestation of the synergistic action of the composition.

A complex compound obtained by treating the modified montmorillonitecontaining clay with a solution of thymol, containing 10.5% of thymol at a concentration of 3.125 mg/ml MPA acted bacteriostatic, at concentrations of 12 and 25 mg/ml – cydno.

Pharmacokinetic properties of enrofloxacin in the body of chickens were characterized by a large volume of distribution and a long period of elimination, low binding of serum proteins and good bioavailability.

Due to the presence of the sorbent, the concentration of enrofloxacin in the serum of experimental chickens, after a single individual forced injection of the solution into the goiter using a probe, was lower than that of control chickens after receiving only enrofloxacin. At the same time, the duration of its detection in the blood serum of experimental chickens in concentrations exceeding the Escherichia IPC was 12 hours less (table 2).

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Table 2: The concentration of enrofloxacin in blood serum of chickens

The dose of enrofloxacin, mg/kg	The concentration of enrofloxacin in the feeding with drinking water, µg/ml			The concentration of enrofloxacin in the feeding with the sorbent, mg/ml		
	Time of sampling (receiving), hour					
	3	12	24	3	12	24
2,5	0,06±0,005	-	-	0,03±0,001	-	-
5,0	0,13±0,005	-	-	0,08±0,008	-	-
10,0	0,13±0,003	0,65±0,015	0,06±0,002	0,1±0,004	0,50±0,005	-

In the control group in the dung of birds a slight trend of increase of the content of the drug was traced (especially in the first three hours), the experimental group with the dose of 5.0 mg/kg of body weight in 12-24 hours, the amount of the drug is increased compared to the control, while the dose of 10.0 mg/kg of body weight concentration of the drug significantly increased only after 24 hours (table 3). This level of enrofloxacin content in the litter can be explained by the fact that the sorbent, being an active ion exchanger, partially binds the drug and prevents its absorption from the intestinal lumen.

Table 3: Concentration of enrofloxacin in chicken dung

The dose of enrofloxacin, mg/kg	The concentration of enrofloxacin in the feeding with drinking water, µg/ml			The concentration of enrofloxacin in the feeding with the sorbent, mg/ml		
	Time of sampling (receiving), hour					
	3	12	24	3	12	24
2,5	2,60±0,051	1,90±0,023	0,66±0,008	2,60±0,040	2,00±0,016	0,50±0,017
5,0	4,60±0,121	3,2±0,063	0,60±0,016	4,50±0,279	4,7±0,158	0,86±0,018
10,0	6,70±0,174	9,44±0,342	0,50±0,012	5,52±0,125	7,00±0,114	1,12±0,013

In the small intestine, compared with the thick one (table4, 5), the drug was detected within 3-12 hours, in concentrations significantly lower, both in the control and experimental groups. At the same time, 24 hours later, the content of enrofloxacin in the studied parts of the intestine was almost identical. It should also be emphasized that the level of fluoroquinolone drug in the large intestine of experimental chickens in 12-24 hours after its injection was significantly higher than in the control group.

Table 4: Concentration of enrofloxacin in the small intestine (intestines with contents) of chickens

The dose of enrofloxacin, mg/kg	The concentration of enrofloxacin in the feeding with drinking water, µg/ml			The concentration of enrofloxacin in the feeding with the sorbent, mg/ml		
	Time of sampling (receiving), hour					
	3	12	24	3	12	24
2,5	0,10±0,007	0,50±0,012	0,09±0,001	0,85±0,021	0,60±0,016	0,09±0,002
5,0	0,30±0,010	0,09±0,004	0,09±0,002	0,10±0,004	0,20±0,006	0,14±0,005
10,0	0,35±0,024	0,75±0,022	0,35±0,010	0,45±0,014	0,85±0,033	0,50±0,005

Table 5: Concentration of enrofloxacin in the large intestine (intestines with contents) of chickens

The dose of enrofloxacin, mg/kg	The concentration of enrofloxacin in the feeding with drinking water, µg/ml			The concentration of enrofloxacin in the feeding with the sorbent, mg/ml		
	Time of sampling (receiving), hour					
	3	12	24	3	12	24
2,5	2,20±0,147	1,12±0,016	0,09±0,015	1,00±0,070	1,30±0,023	0,18±0,003
5,0	5,60±0,255	3,90±0,110	0,09±0,002	4,60±0,126	5,20±0,093	0,20±0,004
10,0	7,70±0,116	14,80±0,276	0,95±0,030	10,40±0,383	22,00±0,679	2,15±0,105

On the basis of the conducted studies it was found that after 12-24 hours the dose of enrofloxacin (5 and 10 mg/kg of body weight) in the composite preparation creates higher concentrations in the intestinal

lumen than when it is given without sorbent. In addition, the concentration of the drug in the small intestine exceeded its MSC for Escherichia (0.05-0.12 µg/ml) in 1.2-7.1, in the thick – 1.7-183.3 times.

During the entire period of observation in the liver of birds of the experimental group the content of enrofloxacin was higher than in the lungs (table 6, 7), but at the same time, in the liver and lungs of the experimental group, the level of enrofloxacin was almost the same as in the control group.

Table 6: Concentration of enrofloxacin in chicken liver

The dose of enrofloxacin, mg/kg	The concentration of enrofloxacin in the feeding with drinking water, µg/ml			The concentration of enrofloxacin in the feeding with the sorbent, mg/ml		
	Time of sampling (receiving), hour					
	3	12	24	3	12	24
2,5	0,21±0,004	0,34±0,005	0,20±0,006	0,35±0,007	0,30±0,010	2,00±0,016
5,0	0,34±0,005	0,40±0,010	0,35±0,009	0,37±0,010	0,40±0,011	0,40±0,011
10,0	0,50±0,018	1,00±0,026	0,95±0,064	0,85±0,029	1,00±0,023	0,75±0,042

Table 7: Concentration of enrofloxacin in the lungs of experimental birds

The dose of enrofloxacin, mg/kg	The concentration of enrofloxacin in the feeding with drinking water, µg/ml			The concentration of enrofloxacin in the feeding with the sorbent, mg/ml		
	Time of sampling (receiving), hour					
	3	12	24	3	12	24
2,5	0,18±0,005	0,20±0,004	0,25±0,009	0,17±0,007	0,18±0,005	0,19±0,004
5,0	0,40±0,009	0,21±0,004	0,19±0,004	0,20±0,004	0,20±0,004	0,18±0,004
10,0	0,35±0,010	0,19±0,007	0,40±0,028	0,60±0,010	0,20±0,002	0,40±0,014

As a result of the experiment, it was found that giving enrofloxacin to the chickens of the experimental groups in concentrations of 50, 100 and 200 mg/l of drinking water containing 2 g/l of sorbent contributed to 70, 95 and 95 % (respectively) of their recovery.

In the control groups treated with enrofloxacin in the same doses, but without sorbent, the therapeutic efficacy of the drug was 75, 80 and 96% of chicken recovery, respectively. At the same time, it should be noted that the chickens recovered in the experimental groups for 4-5 days of treatment, and in the control – after 5-day treatment. In groups 1 and 5 there was 100% mortality of birds.

In a production environment on the chickens suffering from colibacillosis the performance of a suspension of the complex preparation was tested, containing in drinking water 100 mg/l of enrofloxacin and 2 g/l of the modified sorbent. The effectiveness of treatment was 95 %. In parallel, the bird with colibacteriosis was treated with enrofloxacin in a concentration of 200 mg/l of drinking water, which contributed to the recovery of 96% of the sick chickens.

3-day drinking composite drug by chickens (2 g/l sorbent and enrofloxacin in concentrations of 100 mg/l) for preventive purposes prevented the manifestation of colibacteriosis. At the same time, only technological waste of chickens in the amount of 3% was noted. The same results were obtained when chickens were fed with enrofloxacin at a concentration of 200 mg/l.

After the course of treatment, the therapeutic efficacy of the composite drug (sorbent in combination with thymol) was 44% in the first group, 80% in the second, 68% in the third, and 56% in the fourth. In the control group, the mortality of birds did not stop, so veterinary workers of the poultry farm were forced to use drugs traditionally used in this economy. The reason for the low therapeutic effectiveness of the composite drug in the first group was the poor palatability of the feed, because it had a sharp smell of thymol. Low concentrations of the drug in the feed of chickens of the third and fourth groups also did not contribute to a high therapeutic effect.

The preventive effect of 3-day giving of complex compound sorbent with thymol in a concentration of 2 g/kg of feed was 96 %.

CONCLUSIONS

On the basis of our data, it can be argued that the combined use of modified montmorillonite containing clay with enrofloxacin and thymol does not have a toxic effect on the body of chickens. During the day, the complex drug (enrofloxacin with sorbent) is almost completely eliminated from the body of birds.

As a result of the conducted researches it is established that:

- MSC of composition of enrofloxacin with montmorillonite containing clay (ratio 1:1) is the most effective and is in the range of 0.01-0.10 µg / ml;

-the effectiveness of the suspension of the complex drug containing 100 mg/l of enrofloxacin and 2 g/l of modified sorbent in drinking water in the treatment of chickenswith colibacteriosis was 95 %;

- 3-day drinking of composite preparation by chickens (2 g/l of sorbent and enrofloxacin in concentrations of 100 mg/l) with the preventive purpose interfered manifestation of colibacteriosis, technological waste of chickens was 3 %;

- after a course of treatment with a complex drug (sorbent in combination with thymol), in which the thymol content was 10.5 %, the therapeutic effectiveness of the composite drug was: in the first group 44 %, in the second – 80 %, in the third-68 %, and in the fourth-56 %;

- preventive effect of 3-day giving of complex compound of sorbent with thymol in concentration of 2 g/kg of feed was 96 %.

Studies found that the combined use of modified montmorillonite containing clay with enrofloxacin and thymol does not cause deviations in physiological parameters, as well as in the behavior of birds. Body temperature in animals of all groups during the experiment varied within normal limits (from $40.8^0$to 41.8^0C).

Therapeutic and prophylactic doses of these drugs did not have a toxic effect.

The developed drugs can be used in the prevention of digestive disorders and the treatment of young birds suffering from gastroenteritis of infectious etiology, this will reduce the absorption of bacterial toxins, as well as the products of putrefaction of intestinal contents, which will greatly accelerate the process of recovery of sick animals, as well as reduce their morbidity and consumption of expensive antibacterial drugs. In addition, the use of these drugs will contribute to the production of environmentally friendly eggs and poultry meat.

The use of natural montmorillonite-containing enterosorbents in combination with chemotherapeutic compounds is safe for the body of birds. The sorbent, which is part of the composite preparation, carries out local detoxification, has an anti-adhesive effect in relation to the pathogenic intestinal microflora and, thereby, reduces the treatment time of sick animals. This enterosorbent can be effectively used in the creation of complex antibacterial drugs for the treatment and prevention of infectious gastrointestinal diseases in animals.

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