Chapter 1

# TOXICITY STUDY OF PEGYLATED ENROFLOXACIN IN ANIMAL ORGANISM

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## INTRODUCTION

According to the World Health Organization antimicrobial resistance is one of the most dangerous health threats of the 21st century[1]. Antimicrobial drugs, which were effective a few years ago, are losing their functionality today, and their application is necessarily limited[2, 3]. Resistance of microorganisms to antibacterial drugs complicates the course of the disease due to a decrease in therapeutic properties. The cost of therapeutic measures increases. It is caused by the prolongation of thetreatment and efforts spend for searching of effective pharmacological products[4]. Bacterial infections became the biggest causes of death worldwide[5, 6].

Today, new technologies need to be developed to allow creating highly effective and safe medicines for living organisms.The development of new technologies for new antimicrobial drugs should be aimed at ensuring high antibacterial efficiency and low toxicity for the body. The search of new

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antimicrobial agent is aimed at the development of drugs with a changed molecular structure that would provide a targeted effect on the appropriate bacterial cells. These new drugsmust have a good connection with the carrier for their delivery to the affected areas and insensitivity to the action of protective enzymes of the microorganismcells[7, 8, 9]. It should be noted that among drugs, antibacterial agents have the most pronounced side effects, which limit their use[10].

Enrofloxacin belongs to the class of the most successful group of synthetic antimicrobial drugs − fluoroquinolones. It has a wide spectrum of activity against a number of gram-negative and gram-positive bacteria[11, 12]. Enrofloxacin is successfully used in veterinary medicine for the treatment of many infectiousdiseases of bacterial origin[13, 14, 15]. There is concern regarding the emergence of enrofloxacin-resistant strains of bacteria, which reduces its effectiveness.In addition, its cytotoxic effect on the living organism has been reported[16]. Therefore, the search for new compounds of enrofloxacin with improved characteristics is urgent. The last decade has

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seen active development of nanotechnology and innovative approachesfocused on combating antimicrobial resistance[17, 18, 19, 20].

One of the most promising technologies is the creation of compounds with antibacterial activity based polymers[21, 22, 23, 24]. The development of such polymers that would provide protection of antimicrobial agent from adverse environmental conditions, promote their transportation to organs and tissues, have good biocompatibility and rapid excretion from the organism is relevant[25, 26]. In particular, PEGylation is one of the most successful ways to improve drug delivery [27, 28].

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## 1. Characteristics of the antimicrobial drug enrofloxacin and its compounds

The antimicrobial drug enrofloxacin ($C_{19}H_{22}FN_3O_3$ – 1-cyclopropyl-7-(4-ethylpiperazin-1-yl)-6-fluoro-4-oxoquinoline-3-carboxylic acidEnrH) is a representative of the group of fluoroquinolones and it is also known as Enroflon, Cariflox, Baytril, Enroxil, Enroflox, Enrobioflox. Fluoroquinolones are the only class of synthetic antimicrobial drugs that have no analogues in the natural environment.This ensures their high efficiency against poly-resistant strains of microorganisms[29,, 30].

Enrofloxacin belongs to the third generation of fluoroquinolones.It is a 4-quinolone derivative and contains a piperazine ring and a fluorine atom, the presence of which significantly expands the spectrum of its antibacterial efficacy against gram-negative and gram-positive bacteria[31, 32, 33, 34, 35].

Today, enrofloxacin is used in the treatment of bacterial infections in both animals and humans. It was the first of the class of fluoroquinolones used in veterinary medicine for the treatment of patients with pathologies in the urinary and respiratory systems, skin infections in domestic and productive animals.In particular, enrofloxacin is indicated for the treatment of infectious diseases in pigs[36], horses[37, 38] and cows with mastitis[39 40].

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It is widely used for the treatment of respiratory and intestinal infections in meat poultry farming[41, 42].

Despite the fact that enrofloxacin belongs to new antimicrobial drugs and it is effective in many types of antimicrobial therapy and has a small number of side effects, recently there is concern about the emergence of resistant strains of bacteria, in particular, due to its excessive use[43]. In addition, enrofloxacin is poorly soluble in water[44]. Therefore, it creates difficulties in obtaining optimized doses of the dissolved form, which limits the bioavailability of the substance. Enrofloxacin is hygroscopic and has a bitter taste, which creates additional problems during oral administration.It has also been reported that enrofloxacin can cause a negative toxic effect on the body of animals, whichreduce its therapeutic properties[45, 46, 47].

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The latest scientific advances are devoted to the search for special polymers, which provide chemical link with enrofloxacin to create new effective compounds with improved antibacterial characteristics, good bioavailability for the body and high therapeutic effect[48, 49, 50].

Polymeric nanocarriers have specific physicochemical properties that ensure their biodegradability, biocompatibility, and the possibility of additional functionalization with special bioelements[51, 52, 53, 54].

It has been reported that medicinalpreparations which include an active substance conjugated with a polymer carrier had lower toxicity, improved pharmacokinetic parameters and high efficiency of therapeutic action[55, 56, 57].

The most promising carriers among polymers are synthesized from polyethylene glycol (PEG).As shown by the works of a number of scientists,

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the use of antibacterial drugs combined with PEG, or PEGylation of antibiotics, provides a high therapeutic effect[58, 59, 60, 61, 62].

PEG forms stable complexes with drugs, has a prolonged circulation in the blood, is capable of accumulation in the site of the pathological process, effectively transfers molecules into the cell and individual organelles, and has a minimal effect on the active substance.It is able to hold its chemical structure during a certain period of stay in the body, at the same time it is easily biodegradable and biocompatible, as it does not form toxic metabolites[63, 64].

A very important feature of PEG is its good solubility in water.This is due to the fact that the structure of hydrogen bonds in water does not change after the introduction of PEG based on geometric similarity[65]. At the same time, it facilitates overcoming the cellular membrane lipid bilayer[66, 67].

The created model compound of enrofloxacin with PEG-400 nanopolymer, which are covalently connected to each other, showed high antibacterial activity. According to the researchers, PEG polymer is able to

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affect the permeability of membranes, increasing the absorption of the antibacterial drug by cells[68, 69].

1. PEGylationensures an increase in the therapeutic effect of drugs, good solubility of water-insoluble compounds, and the reduction of toxicity, the creation of the desired pharmacokinetics and the accumulation of the drug in the target area[70]. PEGylation improves the efficiency of drug delivery by increasing drug concentration in the affected area while minimizing the toxic effect on the body[71, 72, 73].

Enrofloxacin molecule contains reactive carboxyl groups in its structure, which contributes to the attachment of other substances. At the same time, the high surface hydrophilicity of polyethylene glycol allows good conjugation with other compounds[74, 75].

Thus, the PEGylation of enrofloxacin occurs by joining the carboxyl ends of enrofloxacin to the polyoxyethylene hydrophilic ends of the PEG-400 nanopolymer[76]. The PEG polymer and the antimicrobial drug enrofloxacin are covalently linked together. At the same time, formed macromolecule is capable of creating self-stabilized dispersions with

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nanometer-sized particles of the dispersed phase in aqueous solutions. Stabilization of such particles in an aqueous environment is due to the formation of a structural-mechanical barrier of hydrated polyoxyethylene chains around the nucleus, in which the antimicrobial agent is located. The conducted high-performance liquid chromatography showed that the purity of the PEGylated enrofloxacin is 98–99%[77].

The formedPEGylated antibiotic enrofloxacin had good solubility in water and is stable.Good solubility of compounds due to PEGylation contributes to the efficiency of the delivery of drugs to the affected organs, and also minimizes the toxic effect on the body[78]. At the same time, high antibacterial activity of enrofloxacin compounds covalently connected with polyethylene glycol was established.It is explained by the ability of PEG polymer positively affect the permeability of membranes, thereby increasing the absorption of the antibacterial drug by cells[79]. Comparing the antibacterial effect of the antibiotic enrofloxacin in its traditional form and conjugated with PEG-400 polymer on reference strain of *Escherichia coli* ATCC 11105 microorganisms, improved efficiency of PEGylated enrofloxacin was established[80, 81].

2. In *in vivo* conditions, the circulation time for PEGylated compounds increases from several minutes to hours[82]. The branched structure of the PEG polymer molecule helps to slow down the active metabolism of the drug, which leads to an increase in the time it remains in

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the blood[83]. This is explained by the fact that the kidneys filter substances of small sizes, and PEGylated molecules, which have a larger molecular weight and a larger hydrodynamic radius than the parent molecule, are removed from the body much more slowly.This feature of PEGylated compounds increases their half-life. The hydrated chain of the PEG polymer protects the conjugated compound from access to proteases and peptidases, and reduces non-specific degradation of the drug[84, 85].

It also increasesthe circulation time of polymer micelles in the blood[86, 87].

Such chemical modification of pharmacological preparations is aimed at improving their tolerability, reducing immunogenicity, and increasing the half-life after administration into the body[88, 89, 90].

In some studies, it has been proven that it is necessary to increase recommended dose of enrofloxacin by five times for effective treatment. However, the increased dose of enrofloxacin has a toxic effect on the cells of the body[91, 92].Therefore, an important stage of preclinical studies of the

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newly created antibacterial preparation of PEGylated enrofloxacin is the determination of its toxicity in laboratory animals[93], [94].

## 2. Study on toxicity of PEGylated enrofloxacin

In our research, we studied the effect of intramuscular administration of PEGylated enrofloxacin, PEG-400 nanopolymer and traditional (commercial) antibiotic enrofloxacin, on the general clinical condition of the animal organism, the main functions and structure of the liver and kidneys, the antioxidant system, hematopoiesis, blood coagulation factors, the reaction of the immune system. PEG-400 and commercial enrofloxacin were used to create PEGylated enrofloxacin. The aim of this research was to find out the biocompatibility of drugs[95] [96] [97].

All experimental rats were injected intramuscularly with the studied drugs into the thigh muscles of the lower limb once a day for four days.The control group of animals was given an intramuscular injection of a saline solution in a volume of 0.03 ml.The first experimental group was intramuscularly injected with 0.03 ml of enrofloxacin in a traditional substance (the commercial form of enrofloxacin), the second – 0.03 ml of nanopolymer PEG-400, the third – 0.03 ml of the complex of enrofloxacin with PEG-400 (a PEGylated enrofloxacin).The concentration of enrofloxacin in PEGylated and traditional forms in the solution was 1.8%.The dose of enrofloxacin in traditional and PEGylated forms was 2.7 mg per 1 kg of a rat weight, corresponding to the dose used for the treatment of animals.

The clinical investigation of laboratory animals received four-fold intramuscular injection of PEGylated enrofloxacin, traditional antibiotic enrofloxacin and nanopolymer PEG-400 during the experiment and within three weeks after the end of the administration showed no visible changes in

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the general physiological state. However, drug-induced morphological and functional organ changes are usually asymptomatic or subclinical[98]. Therefore, to identify pathological processes or minor physiological and biochemical changes in the body caused by the action of antimicrobial drugs, it is advisable to conduct laboratory studies from several directions[99]. Studies of the "red" blood of animals showed that the intramuscular injection of enrofloxacin in the traditional form, nanopolymer PEG-400 and PEGylated enrofloxacin into the body of rats does not cause pathological changes in hematopoiesis.Indicators of the number of erythrocytes and hemoglobin content, as well as hematocrit and red blood indices in the vast majority of tested animals were within the physiological range.However, 7 days after the last administration of the traditional form of enrofloxacin in rats caused a decrease in oxygen saturation of hemoglobin, which may lead to a change in the functional capacity of erythrocytes.The decrease in the number of erythrocytes and the concentration of hemoglobin was determined in individual animals. However, these datawere insignificant on the 7th day after the introduction of PEGylated enrofloxacin.These indicators increased on the 14th day, returning to the control level, and were the highest among all studied animals.It should be noted that in the animals treated with PEGylated enrofloxacin, the indicators of red blood indices were more stable and differed little from the control during the experiment[100, 101].

A positive effect on hematopoiesis due to PEGylation of enrofloxacin may be related to PEG-400 polymer ability to interact with the phospholipid bilayer of erythrocyte membranes and prevent the destruction of erythrocytes, which preserves their population[102]. In addition, thanks to its

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anti-radical properties, polyethylene glycol neutralizes free radicals, which prevents the oxidation and destruction of hemoglobin[103, 104].

Intramuscular administration of nanopolymer PEG-400, antibiotic enrofloxacin in traditional and PEGylated forms to rats caused a decrease in the number of blood leukocytes 7 days after the last injection, compared to control.However, it should be noted that the level of leukocytes was within the physiological range.In this period of the study, the number of rod-shaped neutrophils increased, but eosinophils were absent in the blood of experimental animals.Therefore, changes in the ratio of different types of leukocytes in the blood of rats after the administration of the studied substances are characterized by a reaction-response to the administration of the drug. The intensity of these changes fades after seven days. The indicators of the number of leukocytes and the leukogram did not differ much from the control animals and were physiological after the 14th and 21st days of the study[105].

3. It is reported that PEG polymer provides "invisibility" for the system of mononuclear phagocytes and opsonizing proteins (immunoglobulins and complement factors)[106, 107, 108, 109].

PEGylation increases the stability of an active substance during transportation and prevents its capture by the organs of the reticulo-endothelial system[110].

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In addition, PEG is a hydrophilic polymer that promotes resistance to plasma protein binding and prevents aggregation caused by salts and serum proteins.Therefore, PEGylated peptides are more protected from opsonization and active phago- and endocytosis by cellular structures of the macroorganism[111, 112].

Thus, PEGylation prevents opsonization and phagocyte recognition of injected antimicrobial drugs, avoiding immune reactions[113]. During the entire experiment, the rate of erythrocyte sedimentation was within physiological values, which indicates the absence of an inflammatory reaction in the body. A rare but serious side effect of antibiotics is their inhibitory effect on hemostasis and blood coagulation factors[114].

We found that the intramuscular administration of a traditional form of enrofloxacin to rats on the 7th day after the last injection of the drug caused a decrease in the total number of platelets in the animals.At the same time, injections of PEGylated enrofloxacin into the body of rats do not cause changes in indicators related to blood coagulation factors[115].

The introduction of drugs into the body leads to a violation of the body's antioxidant system[116].

In particular, antimicrobial drugs stimulate cellular respiration with subsequent acceleration of the endogenous formation of reactive oxygen species and stimulate peroxide oxidation of lipids[117]. An increase in active

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forms of oxygen in the body leads to the development of oxidative stress[118, 119, 120].

Laboratory studies of the blood of rats on the 7th, 14th and 21st days after the last injection of the traditional form of enrofloxacin, PEG-400 polymer and PEGylated enrofloxacin showed that the content of TBC-active products depended on the injected substance and the time of the study.It was established that the amount of TBC-active products in the blood of animals injected with the traditional antibiotic enrofloxacin was significantly higher than in rats injected with PEGylated enrofloxacin[121, 122]. This may indicate an intensification of the processes of lipid peroxidation after the introduction of the "pure" enrofloxacin.

It is reported[123], that fluoroquinolones contain Carboxyl and Oxygen-containing groups in the molecule, which causes the formation of bonds with phospholipids and glycoproteins and leads to the disruption of the cytoplasmic membrane structures, changes in their electrophysiological characteristics, inactivation of membrane-bound enzymes, disruption of ion homeostasis and damage and death of cells. We suggest that it is the reason why the activity of antioxidant defense enzymes (superoxide dismutase, catalase, glutathione peroxidase) was the lowest in the blood of animals that received traditional antibiotic enrofloxacin during 21 days after the last injection. This is an unfavorable sign, which indicates an increase in the processes of POL and an inadequate reaction of AOS[124].

Therefore, the four-time intramuscular administration of enrofloxacin in the traditional form to experimental rats contributes to the accumulation of

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TBC-active products in the blood and a decrease in the activity of antioxidant defense enzymes.At the same time, the indicators of TBC-active products in the blood were the lowest in animals that were injectedwithPEGylated form of enrofloxacin, which may indicate the absence of a toxic effect on body cells.At the same time, the activities of SOD, catalase, and GPX in the blood during the experiment in animals that intramuscularly received PEGylated enrofloxacin were stable and corresponded to the formation of LPO products.Thus, the administration of PEGylated enrofloxacin to animals does not cause excessive formation of products of lipid peroxidation and does not have a negative effect on the body's antioxidant status.The obtained results indicate the inhibition of LPO processes and the physiological course of the body's antioxidant protection.According to the researchers, PEG has some effect on biological membranes, increasing free radical oxidation and lipid peroxidation[125]. This, in turn, leads to the activation of the genes encoding antioxidant enzymes (SOD, CAT, and GPX).Rapid mobilization of antioxidant protection systems occurs. For many years, fluoroquinolones have remained one of the most promising drugs in terms of their antibacterial capabilities. They are of real interest for clinical practice. However, their use can cause side effects on the liver and kidneys[126, 127, 128, 129, 130].

In particular, functional disorders and structural changes occur in the liver with the development of hepatitis, parenchymal necrosis, and cholestatic jaundice[131, 132].

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Hepatotoxicity is one of the most common drug-related side effects[133, 134].

The level of toxic effects of drugs on the liver can be diagnosed by blood biomarkers, which characterize the functional state and structure of hepatic cells[135].

4. Conducted biochemical blood tests and histological analysis of liver tissues of experimental animals indicate that PEGylated enrofloxacin has lower hepatotoxicity then traditional enrofloxacin[136]. In particular, the study of the functional state of the liver of rats showed that the indicators that characterize liver health or pathology (the content of total bilirubin, cholesterol and albumin in the blood serum) after the intramuscular administration of PEGylated enrofloxacin were at a physiological level throughout the study period[137]. The administration of PEGylated enrofloxacin caused the highest cholesterol levels in the blood serum of animals. It should be noted that these cholesterol increase was in physiologically range. Therefore, it can be regarded as the stability of its synthesis in liver cells[138]. At the same time, PEGylation of enrofloxacin did not affect protein synthesis function of the liver, which was indicated by a higher, compared to other groups, albumin content in the blood serum of rats[139, 140].

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Indicators of the content of globulin fractions in blood serum were also stable, which is a sign of the absence of irritation of the cells of the reticuloendothelial system by the administered drugs[141].

5. Markers of cytolysis of hepatocytes are an increase in the activity of liver indicator enzymes[142]. Our studies of the activity of alanine aminotransferase (ALT) in blood serum showed that in rats that received intramuscular injections of PEGylated enrofloxacin, the activity of the enzyme was lower than in the control and two other experimental groups. At the same time, the activity of ALT in the blood of animals that received the "pure" substance of enrofloxacin remained high for three weeks after the end of the injections, which may indicate thedamage to liver cells.At the same time, the activity of aspartate aminotransferase (AST) in the blood serum of rats in the first days of the experiment was higher in the experimental groups that received PEG-400 nanopolymer and PEGylated enrofloxacin[143]. It is obvious that the increase in the AST activity in the blood serum of rats injected with studied substances may be associated with their active penetration into the cells and mitochondria, where this enzyme has high activity[144]. Consequently, this is manifested by increased release of AST through cell membranes and entry into the bloodstream.Additionally, PEG polymer has a branched molecular structure, which slows down the active metabolism of the drug and leads to an increase in the time of active circulation of PEGylated enrofloxacin in the blood[145]. On the 14th and 21st days after the last injection, the activity of AST in the blood of animals that received PEGylated enrofloxacin decreased compared to those that were injected with the traditional antibiotic enrofloxacin.If we compare the

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activity of the enzyme in the experimental groups, it can be assumed that enrofloxacin in its traditional form penetrates much more slowly from the muscle tissue (injection site) into the bloodstream and is metabolized in the liver tissue, compared to PEG-400 nanopolymer and PEGylated enrofloxacin.The established fact can be characterized as an improvement in the rate of penetration and accumulation in the cells of enrofloxacin connected to PEG-400 nanopolymer for its transport purposes.PEGylation ensures the efficiency of the delivery of drugs due to an increase in their concentration at the injection site. Simultaneously, PEGylation minimize the toxic effect of the drug on the body[146, 147, 148].

Therefore, based on the dynamics of ALT and AST activity in the blood of animals, it can be concluded that in rats injected with PEGylated enrofloxacin, damage to liver cells is possible only in the first days after intramuscular injections, and their recovery is faster than after intramuscular injections of the traditional antibiotic enrofloxacin.

6. Similar changes were found investigating the activity of gamma-glutamyl transpeptidase (γGT) and alkaline phosphatase (ALP) in the blood serum of rats.Thus, 7 days after the last administration of the drugs the activity of these enzymes was higher in the blood of animals that received the traditional antibiotic enrofloxacin than in those that received PEGylated enrofloxacin.High activity of γGT in the blood may indicate intrahepatic cholestasis and damage to liver cells that form intrahepatic bile ducts[149]. High ALP activity indicates extrahepatic cholestasis and damage to the cells that form the extrahepatic bile ducts[150, 151].

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At the same time, in the blood serum of rats injected with PEGylated enrofloxacin, the activities of γGT and ALP were low throughout the study, which may indicate the absence of a toxic effect on liver cells.

During the histological examination of the liver tissues of animals that received the substance of the traditional antibiotic enrofloxacin, within three weeks after the last administration of the drug, signs of granular dystrophy, lysis, paranecrosis, and necrosis of the liver parenchyma and pyknosis of hepatocyte nuclei were established.In the animals that received PEG-400 polymer, the morphological indicators of the liver on the 7th, 14th and 21st days of the experiment did not show pathological changes. The cytoplasm of individual cells acquired a foamy or granular appearance only in the first days after the introduction. It was established that individual liver cells with signs of atrophy, granular dystrophy, paranecrosis, and necrosis were found during histological examination of liver in the group of rats that received PEGylated enrofloxacin on the 7th day of the experiment.However, on the 14th and 21st days after the last injection, in these animals the morphological state of the liver was unchanged and identical to the structure of the control group.

Thus, histological studies of liver tissues showed that changes in its structure are registered 7 days after the end of drug administration, both for injections with traditional form of antibiotic enrofloxacin and PEGylated enrofloxacin.In subsequent studies, no changes in the liver structure were found after the use of PEGylated enrofloxacin.Enrofloxacin in its traditional form caused liver parenchyma disruption for three weeks.The results of biochemical studies of animal blood and histological analysis of liver tissuesproved that PEGylated enrofloxacin has lower hepatotoxicity, compared to the traditional substance of enrofloxacin[152]. Nephrotoxic reactions of fluoroquinolone antimicrobials range from 0.2 to 0.8%[153, 154]. According to the instructions for use, enrofloxacin does not cause a nephrotoxic effect[155].

7. According to our research, during the entire experiment, creatinine concentration in the blood serum of animals of all groups did not exceed the

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upper limit of physiological values[156]. It should be noted that serum creatinine is one of the main biomarkers of nephrotoxicity, as it is freely filtered by the renal glomeruli and, without being reabsorbed by the tubules, is completely excreted by the kidneys[157]. These properties of creatinine made it an important marker for assessing the functional state of the kidneys[158]. However, an increase in creatinine content in the blood occurs with significant damage to the kidneys, and its normal value does not always indicate the absence of a violation of the kidneys structure[159]. Therefore, our histological studies of the kidneys of experimental rats showed a structural disorder.Morphological changes in the structure of the kidneys were established in experimental rats after intramuscular injections of the traditional form of enrofloxacin during the 21st day after the last administration of the drug.Signs of granular dystrophy, foci of paranecrosis and necrosis of nephrocytes of convoluted tubules were registered in rats of this group[160]. Other researchers also point to this[161]. They administered enrofloxacin to animals at a dose of 75 ml/kg for 10 days and observed clear histological changes in the kidneys.In particular, experimental animals showed signs of progressive nephrotoxic necrosis and membrane rupture in the proximal and distal convoluted tubules.

8. Fourfold administration of PEGylated enrofloxacin to experimental animals caused only minor histological changes in the kidneys and only during the first seven days after the injections.

9. Studies conducted by other scientists also indicate that PEG with a molecular weight of 400 Daltons is optimal for conjugation with antimicrobial drugs and does not have adverse effects on renal

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function.PEGylation does not cause morphological changes in the structure of kidneys in experimental rats and leads to a decrease in the nephrotoxicity of antibacterial drugs[162].

## CONCLUSIONS

PEGylation of enrofloxacin increases the size and molecular weight of conjugated biomolecules, increases their pharmacokinetics, pharmacodynamics, solubility in water, protection against enzymatic degradation, reduces hepatotoxicity and nephrotoxicity, inhibits the negative impact on hematopoiesis and hemostasis, limits immunogenic and antigenic reactions, inhibits lipid peroxidation, maintaining the physiological course of antioxidant protection.

## SUMMARY

Enrofloxacin belongs to new antimicrobial drugs of the class of fluoroquinolones.Its use is effective for many types of antibiotic therapy and has few side effects.However, there is a concern about the emergence of strains of bacteria resistant to the enrofloxacin.PEGylation of enrofloxacin with nanopolymer PEG-400 showed an improvement in the antibacterial activity of a newly created drug.This is due to the fact that PEG-400 polymer present in a newly created drug is able to influence the permeability of membranes, increasing its absorption by cells. PEGylation of enrofloxacin increases the size and molecular weight of conjugated biomolecules, improves their pharmacokinetics, pharmacodynamics, solubility in water, and protection against enzymatic degradation.Four-time intramuscular administration of enrofloxacin in PEGylated form to experimental rats has a less pronounced toxic effect on the animal body, compared to the traditional enrofloxacin. PEGylated erofloxacin has lower hepatotoxicity and nephrotoxicity, does not induce a negative impact on hematopoiesis, hemostasis, immunogenic and antigenic reactions, and does not disrupt the activity of the body's antioxidant defense enzymes.

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