Original Article

Study of blood-ocular barrier permeability by Fluoroquinolone group drugs

Arzigul Hamidovna Yahyaeva[1], Margusheva Maryana Aslanovna[2], Kyamalya Azadovna Yariyeva[3], Artem Olegovich Pogosov[4*], Nargiz Asadullaevna Ilyasova[5], Diana Rezuanovna Kokova[6]

[1]Department of Pediatrics, Medical Faculty of Stavropol State Medical University, Stavropol, Russia. [2]Department of Therapy, Medical Faculty of the North Ossetian State Medical Academy, Vladikavkaz, Republic of North Ossetia-Alania, Russia. [3]Department of Obstetrics and Gynecology, Medical Faculty of Stavropol State Medical University, Stavropol, Russia. [4]Department of Therapy, Faculty of Medicine of Stavropol State Medical University, Stavropol, Russia. [5]Department of Pediatrics, Medical Faculty of Rostov State Medical University, Rostov-on-Don, Russia. [6]Department of Obstetrics and Gynecology, Medical Faculty of Rostov State Medical University, Rostov-on-Don, Russia.

Correspondence: Artem Olegovich Pogosov, Department of Therapy, Faculty of Medicine of Stavropol State Medical University, Stavropol, Russia. ruslankalmykov777@yandex.ru

ABSTRACT

Blood-ocular barrier- specialized morphological structures that regulate the transport of fluids and substances between the vascular bed and the tissues of the eye, prohibiting the penetration of foreign cells and molecules. The permeability of various substances into the non-vascular and vascular tissues of the eye is not the same. In conditions of pathology, the blood-ocular barrier can be permeable to various endogenous, exogenous, and other substances that are not correct with respect to the cells and tissues of the eye. In this article, the permeability of the blood-ocular barrier with fluoroquinolone group drugs in the pathologies of the visual organs is considered. For this purpose, a laboratory study was conducted, during which three groups of experimental rabbits were formed (5 individuals in each group). Clinically healthy animals were included in group 1, and sick animals with experimentally induced ophthalmopathology were included in groups 2 and 3. The treatment of individuals was carried out with a solution of ciprofloxacin. A comprehensive examination of animals was carried out: clinical examination, determination of the concentration of antibacterial drugs in biological fluids, histological examination of the blood-ocular barrier, biochemical studies; hematological studies.

Keywords: Blood-ocular barrier, Blood-retinal barrier, Fluoroquinolone, Dugs, Cells

Introduction

Blood-ocular barrier- specialized morphological structures regulating the transport of fluids and substances between the vascular bed and the tissues of the eye, prohibiting the penetration of foreign cells and molecules, as well as activated immunocompetent cells and antibodies [1].

The blood-retinal barrier (external and internal) is an integral part of the blood-ocular barrier, represented by the walls of the retinal blood capillaries; the permeability of the blood-retinal barrier is lower than the average permeability of the blood-ocular barrier [2]. The inner one is formed by tight contacts between the perforated endothelium of the retinal blood vessels (for the inner layers). The outer one is formed by the retinal pigment epithelium (for the outer layers), which receives nutrients from the choriocapillaris [3].

Blood-ocular barrier performs a barrier function concerning the transparent media of the eye, regulates the composition of intraocular fluid, providing selective intake of essential nutrients into the lens and cornea [4]. Clinical studies have made it possible to clarify and expand the concept of the blood-ocular barrier, including the blood-tissue system, as well as to talk about the existence of its three components in norm and pathology: iridociliary, chorioretinal and papillary [5].

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Yahyaeva AH, Maryana Aslanovna M, Yariyeva KA, Pogosov AO, Ilyasova NA, Kokova DR. Study of blood-ocular barrier permeability by Fluoroquinolone group drugs. J Adv Pharm Educ Res. 2023;13(2):35-42. https://doi.org/10.51847/TkUIByTPhAq

The structure of blood-tissue barriers is mainly determined by the structure of the organ and differs in its specific features depending on their morphological and physiological characteristics. The main structural element of blood-tissue barriers is blood capillaries, whose endothelium in different organs and tissues has characteristic morphological features. These barriers include blood-brain, blood-ocular barriers, a barrier between blood and endolymph, as well as a barrier between blood capillaries and gonads [6].

The blood-ocular barrier provides ophthalmic homeostasis in normal operation. Throughout its entire length, the blood-ocular barrier is not a single structure [7].

The concept of the blood-ocular barrier was based on experimental data and has been associated for quite a long time with the function of capillaries and epithelium in the processes of the ciliary body: to produce watery moisture and ensure the metabolism of the non-vascular tissues of the eye (vitreous, lens, cornea, trabecular apparatus) [8].

The permeability of various substances into the non-vascular and vascular tissues of the eye is not the same. Thus, in the experiment, when oxygen is inhaled, the rate of its entry into the watery moisture and the lens is on average 13-14 seconds, and into the iris is almost 3 times faster - 5 seconds [9]. The pronounced difference in redox processes reflects the peculiarities of metabolism in various tissues of the eye.

In conditions of pathology, the blood-ocular barrier can be permeable to various endogenous, exogenous, and other substances that are not correct with respect to the cells and tissues of the eye [10]. In these cases, pathological permeability of the barrier occurs with the manifestation of various clinical symptoms on the part of the eye and the development of eye diseases [11].

The physiological, regulating, protective blood-ocular barrier should be considered as a set of three interrelated and interdependent Blood-retinal systems: iridociliary, chorioretinal and papillary.

Each of the three blood-ocular barrier systems has its characteristics, they are aimed at fully ensuring the trophic tissues and cells of their eye area. Therefore, the penetration of drugs through the barriers of these structures is not the same [12].

Fluoroquinolones are a class of broad-spectrum antibiotics. They are effective against gram-positive and gram-negative bacteria [13]. Drugs of this class can resist pseudomonas infection and intracellular parasites. The latter include mycoplasmas, chlamydia, and Mycobacterium tuberculosis [14]. Fluoroquinolones are also used if the pathogen has antibiotic resistance from other groups.

The mechanism of action of fluoroquinolones is based on the blocking of two enzymes: DNA gyrase and topoisomerase [15]. As a result, both the vital activity of the microbial cell and its ability to reproduce are disrupted. This mechanism is very different from the action of antibiotics of other classes. Therefore, fluoroquinolones do not have cross-resistance with beta-lactams and aminoglycosides [16].

Fluoroquinolones are used in the treatment of infections of the genitourinary system, and sexually transmitted diseases, in gynecological practice. They are effective in the treatment of diseases of the upper and lower respiratory tract and gastrointestinal tract. They are used to fight infectious lesions of the skin and soft tissues, joints, and bones.

In addition, this class of antibiotics is used for sepsis, intraabdominal infections, liver, and biliary tract diseases, and bacterial eye damage [17, 18].

The main contraindications are pregnancy and lactation. The use of fluoroquinolones in children under 12 years of age is possible only for vital indications [19]. In addition, fluoroquinolones are contraindicated in the presence of allergic reactions in the anamnesis [20].

This article examines the effect of fluoroquinolone preparations on the permeability of the blood-ocular barrier. For this purpose, a laboratory study was conducted on rabbits.

Materials and Methods

In order to study the permeability of the blood-ocular barrier with fluoroquinolone group drugs in normal and pathological conditions, we conducted a laboratory study, during which 3 groups of five rabbits were formed. All individuals have standard indicators in size and weight, all individuals are initially healthy.

Group 1 – clinically healthy animals; groups 2 and 3 – sick animals with experimentally induced ophthalmopathology. Rabbits of the first and second groups were injected twice, with an interval of 12 hours, intravenously, into the marginal ear vein, ciprofloxacin solution at the rate of 2 mg/kg; rabbits of the third group ciprofloxacin was administered orally at a dose of 170 mg/ kg.

Following the goals and objectives of the work, a set of studies was performed: clinical examination of animals; determination of the concentration of antibacterial drugs in biological fluids of laboratory animals by the enzyme immunoassay; histological examination of blood-ocular barrier; biochemical studies; hematological studies [21-23]. Clinical examination of animals included palpation of the affected organ, examination, and thermometry.

Biological fluids (blood and intraocular fluid) were taken at the time corresponding to the structure of the experiment. Intraocular fluid was taken by corneal centesis with a 26G needle in an amount of 0.15 ml. At the same time, blood was taken from Safen's vein with a syringe with a 23G needle in a volume of 0.5 ml, after settling for 15 minutes at room temperature (22-24℃), the blood was centrifuged at a speed of 2000 rpm, the serum was separated. The resulting liquids were cryopreserved at a temperature of -20℃. Before the analysis, the samples were thawed at a temperature of 22-24℃ for 30 minutes [24].

Biochemical blood tests were performed on a Chemwell Combi V1.03 (USA) device using Cormay test kits.

The urea concentration was determined by the reaction of urease and glutamine dehydrogenase [25]. The determination of the albumin concentration consisted of the reaction of albumin with bromocresol green in an acidic medium. The total protein concentration was determined by a method based on a biuretic reaction [26]. Determination of creatinine concentration is a modification of the Jaffe method without protein removal [27]. The determination of cholesterol concentration consisted of the reaction of esterase with cholesterol oxidase [28].

Hematological studies were performed on the device Automated Veterinary Hematology Analyzer PCE-90 VET.

Leukocytes, erythrocytes, platelets are counted and measured using the Coulter method. Hemoglobin was determined by the colorimetric method.

The data obtained were processed using Microsoft Office Excel 2010 and BioStat 2007.

Results and Discussion

In the group of sick animals, depression of the general condition of laboratory animals was observed, an increase in the total body temperature to 40-41℃, the pulse rate was within 60-80 beats/min, the number of respiratory movements was also increased, and amounted to 54-56 per minute.

The following clinical signs of the pathology of the organ of vision were noted after the introduction of a suspension of Staphylococcus aureus:

1 day of the experience. A large amount of purulent discharge on the eyelids and in the conjunctival cavity, pronounced mixed injection of the eyeball, the cornea is edematous, thickened, infiltrated, blepharitis, lacrimation, photophobia, ciliary soreness, the iris is edematous, hyperemic, greenish in color, its pattern is indistinct;

2 days of experience. Copious purulent discharge, conjunctival hyperemia, pronounced swelling and hyperemia of the eyelids, ciliary soreness, lacrimation, photophobia, edematous cornea, severe swelling of the iris;

3 days of experience. Purulent discharge from the conjunctival sac, moderate edema and hyperemia of the eyelids, edematous iris, superficial injection, corneal edema:

4 days of experience. Slight edema and hyperemia of the eyelids, the iris is edematous, lacrimation is absent or slightly pronounced, the cornea is moderately edematous, the conjunctiva is bright pink, moderately edematous;

5 days of experience. Light pericorneal injection at the needle insertion site, the eyelids are calm, the cornea is transparent, the iris is calm, and the pupil reacts to light.

Pharmacotherapy of sick and healthy animals was started simultaneously, 24 hours after the introduction of the suspension, providing the clinical manifestation of the disease. Clinical signs of the disease were recorded in all animals in groups with the pathology of the organ of vision.

An hour after the morning injection, biological fluids were taken from all rabbits.

On the 7th day after the start of treatment, clinical recovery occurred in all animals, which was expressed by normalization of the general condition of the animals, stabilization of body temperature, pulse rate, and several respiratory movements.

In the visual analyzer, the absence of inflammatory phenomena in the conjunctiva, cornea, and iris was observed in three animals of group 2 and two animals of group 3.

The dynamics of the concentration of ciprofloxacin in the intraocular fluid and blood serum are shown in **Figures 1 and 2**.

The concentration of ciprofloxacin in the blood serum on the second day of the experiment in group 1 decreased by 10%, in group 2 increased by 9%, and in group 3 exceeded the previous indicator by 12%.

On the fourth day of the experiment, the concentration of the antibacterial drug in the blood serum in group 1 decreased by 2%, in group 2 by 5%, and in group 3 remained at the level of the third day.

Thus, the concentration of the antibacterial drug in the blood serum in all groups reached therapeutic (2.1 – 4.6 μg/mg) on the first day after administration and remained so throughout the study.

It should be noted that the correlation coefficient in group 2 turned out to be negative concerning the data of the first group ($r=-0.377$), this indicates an inverse average correlation (with an increase in one variable, the other decreases).

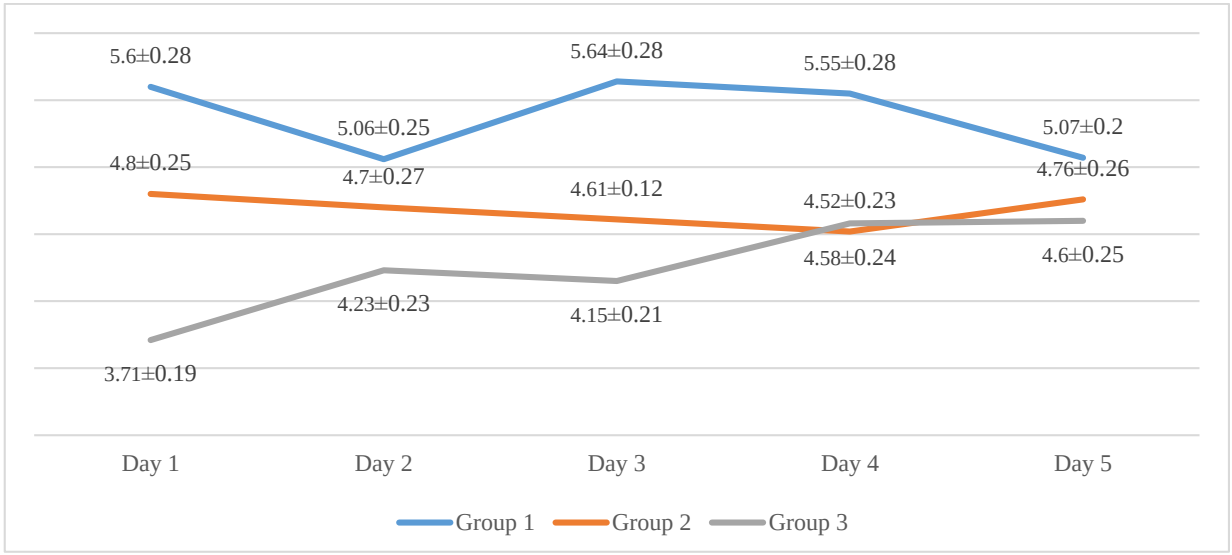


Figure 1. Dynamics of ciprofloxacin concentration in blood serum

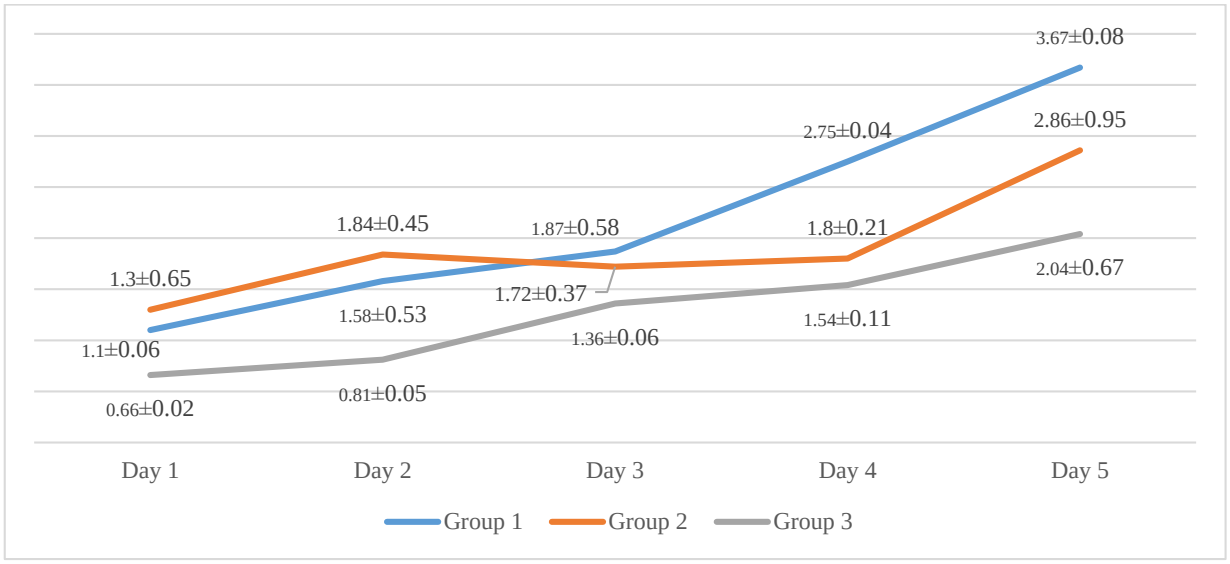


Figure 2. Dynamics of ciprofloxacin concentration in intraocular fluid

The correlation coefficient in group 3 is also negative with respect to the data of the first group (r =-0.466), i.e. the correlation is the average inverse.

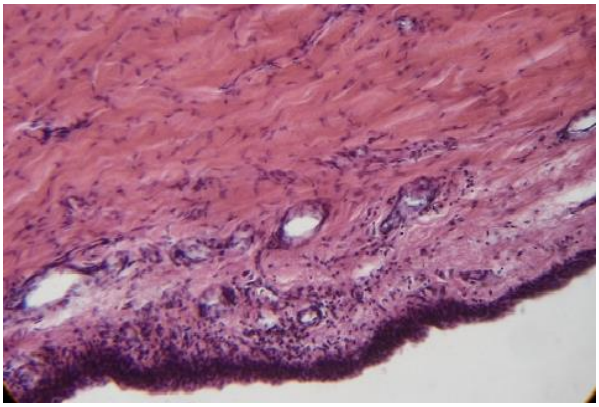
In the group of clinically healthy animals on the second day of the experiment, the concentration of ciprofloxacin increased by 30%, in the group of sick animals with intravenous administration of an antibacterial drug, its concentration increased unreliably by 29%, in the group of sick animals with oral administration of an antibacterial drug increased unreliably by 18%.

By the fourth day, the studied indicator in the group of clinically healthy animals increased by 32%, in the group of sick animals with intravenous administration of ciprofloxacin increased by 4%, in the group of sick animals with oral administration of ciprofloxacin by 12%, and the increase in the concentration of the drug in the groups of sick animals was also unreliable.

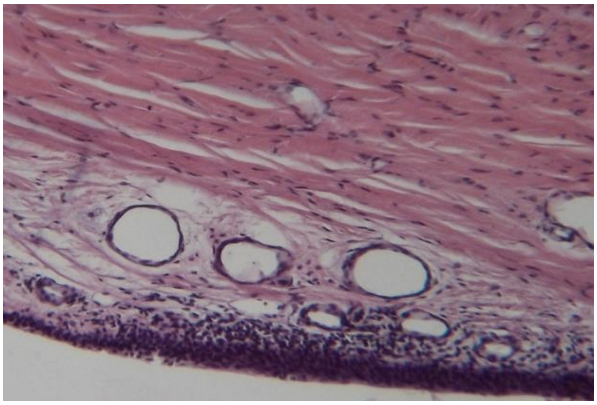
The correlation coefficient of intraocular fluid in group 2 is positive in relation to the data of group 1 (r=0.898), i.e. the correlation is strong (close) direct. In the third group, the correlation coefficient is close to 1 (r=0.965), which indicates a strong direct correlation, as the values of one variable increase, the value of the other increases.

Thus, the minimum therapeutic concentration of ciprofloxacin in the intraocular fluid was achieved in a group of clinically healthy animals and a group of sick animals with intravenous administration of ciprofloxacin on day 3, in a group of sick animals with oral administration of ciprofloxacin, the therapeutic concentration of the applied antibacterial drug was obtained only on day 5 of the studies. It should be noted that there was no significant difference in the groups of sick animals. In this regard, only three animals from group 2 and two animals from group 3 had a complete clinical recovery of the visual organ after pharmacotherapy.

To study the structure and morphological changes of the visual organ in the caused pathology, the structures of the visual analyzer were studied **(Figures 3a and 3b)**. At the same time, rabbits of all groups were euthanized by decapitation – 3 healthy animals and 3 animals with the caused pathology, 3 days after infection.



a)



b)

Figure 3. Lymphocytic infiltration of the sclera along the sclerotomy openings: a) moderate, b) weak

During light microscopy, the following changes in the structures of the eye were observed in group 2 animals: weak lymphocytic infiltration of the episclera, vasodilation of the sclera, moderate lymphocytic infiltration along the sclerotomy openings, weak inflammatory edema in the cornea, vasodilation and inflammatory cell infiltration in the iris, weak inflammatory infiltration was observed in the vascular membrane, the retina was infiltrated by single lymphocytes. In group 3 animals, the changes were similar.

Thus, a change in the micromorphology of eye structures in the vascular membrane forming the Blood-retinal barrier has been established. A weak inflammatory infiltration was registered.

In order to monitor the changes occurring in the body of animals as a whole, hematological and biochemical study were carried out **(Tables 1 and 2)**.

In the group of clinically healthy animals, there were no significant changes in the content of leukocytes on day 5 of the experiment, in the group of sick animals with intravenous administration of ciprofloxacin, the number of leukocytes increased by 16%, in the group of sick animals with oral administration of ciprofloxacin, this indicator increased by 35%.

Thus, the content of leukocytes in the first group was within the physiological norm. In the second and third groups, this indicator exceeded the limits of the norm. This fact is explained by the presence of a pathogenic agent in the body of animals and the development of the inflammatory process.

The relative content of lymphocytes, monocytes, and granulocytes in the group of clinically healthy animals was within the physiological norm.

Table 1. Hematological parameters of blood serum of laboratory animals (M±m)

Indicators	Background indicators	Day 1			Day 5		
		Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
White Blood Cell, $*10^9$/L	8.5±0.4	8.7±0.45	12.5±0.7	11±0.5	8.7±0.6	14.5±0.8	18±0.8
Lymphocyte percentage, %	48.5±2.4	52.3±3.2	40±2.8	45±2.5	68±3.5	32±1.6	28±0.9
Mid-sized cell percentage, %	4.9±0.24	3.8±0.25	5.2±0.25	4.7±0.23	5.2±0.3	4.4±0.23	3.9±0.2
Granulocyte percentage, %	46.5±2.3	44±0.33	56±2.9	52±2.7	28±1.4	67±3.1	69±3.4
Red Blood Cell, $*10^{12}$/L	5.9±0.25	5.8±0.28	5.5±0.25	6.2±3.2	5.8±0.28	4.8±0.21	3.8±1.8
Hemoglobin Concentration, g/L	146±7.5	140±7.1	134±6.6	104±6	134±5.3	98±3.8	96±4.2
Hematocrit, %	37±1.8	36±1.8	34±2	29±1.4	36.2±1.5	27±1.8	22±1.2
Platelet, $*10^9$/L	250±12.5	260±13	320±14	300±11	248±12	372±12	320±13

In the group of sick animals with intravenous administration of ciprofloxacin, the relative content of lymphocytes on the last day of the study was below the norm, while the relative content of granulocytes exceeded the upper limit of the norm, which confirms the presence of inflammation in the body of sick animals.

The number of lymphocytes and granulocytes also in the third group, as well as in the second after the last blood collection, is beyond the norm due to the body's response to the introduction of a suspension of Staphylococcus aureus.

The number of red blood cells after the last blood collection in the first group remained at the same level, by 13% in the second group, and by 39% in the third group. The content of erythrocytes on the 5th day of the experiment in the second and third groups was below normal, which is explained by the presence of an acute inflammatory process in the body.

The concentration of hemoglobin by the fifth day in the group of clinically healthy animals did not significantly change, by 16% in the group of sick animals with intravenous administration of ciprofloxacin and by 9% in the group of sick animals with oral administration of ciprofloxacin. Thus, the concentration of

hemoglobin in the groups with experimentally induced ophthalmopathology after the last blood collection was below normal, this is due to the resulting hemolysis of erythrocytes.

The obtained hematocrit data indicate a lack of erythrocytes in the blood of groups 2 and 3.

By the fifth day of the experiment, the number of platelets decreased by 5% in the first group, increased by 11% in the second group, and by 4% in the third group. The platelet count was within the physiological norm in the group of clinically healthy animals and groups of sick animals throughout the study.

On the 5th day of the experiment, the activity of alanine aminotransferase in the group of clinically healthy animals decreased by 3%, in the group of sick animals with intravenous administration of ciprofloxacin decreased by 5%, in the group of sick animals with oral administration of ciprofloxacin, the activity of the enzyme decreased by 7%.

The activity of aspartate aminotransferase in the first group decreased by 5% during the experiment, and in the second group by 7%. In group 3, there is an increased activity of AST after the first administration of an antibacterial drug, by the last administration this indicator decreases by 6%.

In the group of clinically healthy animals, the activity of γ-glutamyltransferase remained within normal limits throughout the study. In the group of sick animals with intravenous administration of ciprofloxacin on the last day of the study, the activity of gamma-glutamyltransferase decreased by 10%, in the group of sick animals with oral administration of ciprofloxacin, this indicator also did not exceed the norm, after the last blood draw it decreased by 2%.

On the fifth day of the experiment in the group of clinically healthy animals, amylase activity remained at the level of the first day of the experiment, in the second group it increased by 9%, and in the third group by 4%. Thus, amylase activity in all groups throughout the experiment was within normal limits.

The activity of alkaline phosphatase in the group of clinically healthy animals did not significantly change by the end of the study, in the group of sick animals with intravenous administration of ciprofloxacin by 9%, in the group of sick animals with oral administration of ciprofloxacin by 7%.

The activity of alkaline phosphatase is higher than normal in groups of sick animals, which indicates the body's reaction to the infection caused.

The serum glucose level after the last administration of ciprofloxacin increased by 9% in the first group, decreased by 24% in the second group, and increased by 4% in the third group.

Table 2. Biochemical parameters of blood serum of laboratory animals (M±m)

Indicators	Background indicators	Day 1			Day 5		
		Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
ALAT, Units/l	56±2.8	72±3.5	78±3.8	92±4.5	68±3.4	74±3.2	84±4.2
ASAT, Units/l	86±5.2	98±4.8	104±5.2	130±5.1	94±4.5	96.8±6	122±6.1
GGT, Units/l	5.7±0.3	5.4±0.3	10.9±0.3	12.1±0.4	5.6±0.4	9.8±0.5	12±0.6
Amylase, Units/l	173±8.6	190±5	172±6	184±9	190±6	189±9.2	192±8.6
Alkaline phosphatase, Units/l	9.5±0.5	8.8±0.3	22±1.2	27±1.4	9.2±0.3	24±1.1	29±1.6
Glucose, mmol/l	6.4±0.3	5±0.22	5.8±0.3	4.6±0.23	5.4±0.3	4.2±0.2	4.7±0.2
Creatinine, μmol/l	108±5.2	112±5	114±5.7	118±5.4	124±6.2	120±3.6	124±6
Urea, mmol/l	7.6±0.4	5.5±0.3	10±0.6	10.4±0.6	4.9±0.2	9.8±0.4	10±0.6
Total protein, g/l	61±3	60±2	66±3.5	69.3±3.2	61±1.5	71±3.6	72±3.8
Cholesterol, mmol/l	1.1±0.05	1.3±0.06	1.7±0.03	2±0.02	1.2±0.05	1.5±0.06	1.8±0.09
Albumin, g/l	29±1.5	31±1.5	47±2.4	49.6±1.8	32±1.8	48.6±1.6	54±2.6

The serum creatinine content in the group of clinically healthy animals increased by 10% by the end of the experiment. In the group of sick animals with intravenous and oral administration of ciprofloxacin, this indicator increased by 5% and 4%, respectively.

In group 1, the serum urea content decreased by 9% during the study, in group 2 by 2%, in group 3, this indicator also decreased by 2% after the last administration of the antibacterial drug. The amount of urea in groups of sick animals is in the upper limit of the norm, which is explained by the pathology of the organ of vision caused.

The total protein content after the last administration of ciprofloxacin increased in the group of clinically healthy animals by 2%, in the group of sick animals with intravenous administration of an antibacterial drug by 9%, and with oral administration of an antibacterial drug by 3%.

The cholesterol content in the group of clinically healthy animals was within the normal range. After the last blood draw, the amount of cholesterol decreased by 12% in the second group and by 10% in the third group. This indicator in the groups of sick animals was within the limits of the norm.

In the group of clinically healthy animals, the albumin content was within normal limits, after the last blood collection, the amount of albumin in the first group increased by 7%, in the second group by 3%, in the third group by 6%. This indicator in groups of sick animals was above the normal limits throughout the study, which is explained by the inflammatory reaction of the body to the introduced pathogenic agent. Thus,

hematological and biochemical indicators confirm the presence of an acute inflammatory process in the body of animals.

Conclusion

Fluoroquinolones occupy a very important place in modern therapy of infectious diseases. They are indicated for severe generalized infections, proven resistance of the pathogen to other classes of antibiotics, and are suitable for empirical therapy. Fluoroquinolones are prescribed for Pseudomonas aeruginosa infection, Mycobacteria, chlamydia, and mycoplasmas. Their high efficiency has been confirmed by more than 30 years of application in clinical practice. However, with frequent use of these drugs, the risk of developing resistance of microorganisms to fluoroquinolones increases. This is especially true of outpatient practice. In this regard, it is recommended to use fluoroquinolones strictly according to indications, reserving them, if possible, for the treatment of severe infections.

According to the results of the laboratory study, the concentration of the antibacterial drug in the blood serum in all groups reached therapeutic (2.1-4.6 μg/mg) on the first day after administration and remained so throughout the study. The minimum therapeutic concentration of ciprofloxacin in the intraocular fluid was achieved in a group of clinically healthy animals and a group of sick animals with intravenous administration of ciprofloxacin on day 3, in a group of sick animals with oral administration of ciprofloxacin, the therapeutic concentration of the applied antibacterial drug was obtained only on day 5 of the studies. Only three animals from group 2 and two animals from group 3 had complete clinical recovery of the visual organ after pharmacotherapy. During light microscopy, the following changes in the structures of the eye were observed in animals of groups 2 and 3: weak lymphocytic infiltration of the episclera, vasodilation of the sclera, moderate lymphocytic infiltration along the sclerotomy openings, weak inflammatory edema in the cornea, vasodilation and inflammatory cell infiltration in the iris, weak inflammatory infiltration was observed in the vascular membrane, the retina was infiltrated by single lymphocytes. The leukocyte count in group 1 was within the physiological norm. In groups 2 and 3, this indicator exceeded the limits of the norm. This fact is explained by the presence of a pathogenic agent in the body of animals and the development of the inflammatory process. The relative content of lymphocytes, monocytes, and granulocytes in the group of clinically healthy animals was within the physiological norm.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: The protocol for experiments with laboratory animals complied with the requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes.

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