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STUDY OF THE PERMEABILITY OF BLOOD-AQUEOUS BARRIER WITH TETRACYCLINE GROUP DRUGS IN NORMAL AND PATHOLOGICAL CONDITIONS

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ABSTRACT

In normal functioning, the blood-aqueous barrier provides ophthalmic homeostasis. The study of the blood-aquatic barrier is carried out in several main directions, one of which is an experimental animal study. In this work, the blood-aquatic barrier's permeability with tetracycline group drugs in pathological and normal conditions is studied using the example of three groups of laboratory rabbits. Group 1 – clinically healthy animals; group 2, group 3 – sick animals with experimentally induced pathology. Rabbits of the first and second groups were administered orally three times, with an interval of 8 hours, a tablet form of tetracycline at the rate of 25 mg/ kg of body weight, rabbits of the third group were given 3% tetracycline 3 times a day for the lower eyelid. Animals' clinical examination included palpation of the examination, affected organs, and thermometry. Biological fluids (intraocular fluid and blood) were taken from the studied animals. The article presents the data of studies of tetracycline concentration, hematological parameters of blood serum, and biochemical parameters of blood serum of the studied animals. On the 9th day after the introduction of the Staphylococcus aureus suspension, clinical recovery occurred in all animals in the second and third groups, which was expressed by normalization of the animals' general condition, the number of respiratory movements, pulse rate, stabilization of body temperature was also within the limits. In the visual analyzer, the absence of inflammatory phenomena in the iris, cornea, and conjunctiva was observed in 2 animals of the second group.

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Introduction

Blood-tissue barriers regulate the metabolic processes between blood and organ tissues and ensure the consistency of the composition of physicochemical and biological properties of tissue fluid [1]. 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 [2].

In normal functioning, the blood-aqueous barrier provides ophthalmic homeostasis [3]. Throughout its entire length, the blood-aqueous barrier is not a single structure. The concept of the blood-aqueous 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) [4]. This is a blood-tissue system of a physiological barrier regulating changes between blood and intraocular fluids [3].

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The study of the blood-aqueous barrier is carried out in several main directions:

- experimental studies on animals by introducing isolated electrodes into the tissues and media of the eye to study redox processes by polarography;
- study of the penetration of various substances into the tissues of the eye by labeled atoms;
- light and electron microscopy;
- clinical studies by fluorescence angiography and fluorometry;
- clinical and functional studies in various eye pathologies.

It has been established that the vascular-free structures of the eye are characterized by a lower intensity of redox processes, compared with the tissues of the eye provided with capillary blood supply [5]. The oxygen utilization coefficient for non-vascular tissues averages 0.4, while this coefficient for tissues with capillary circulation is twice as high - 0.8 [6].

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 [7]. The pronounced difference in redox processes reflects the peculiarities of metabolism in various tissues of the eye. In conditions of pathology, the blood-aqueous barrier can be permeable to various endogenous, exogenous, and other substances that are not correct concerning the cells and tissues of the eye. In these cases, there is a pathological permeability of the barrier with the manifestation of various clinical symptoms on the part of the eye and the development of eye diseases. The physiological, regulating, the protective blood-aqueous barrier should be considered as a set of three interrelated and interdependent blood-tissue systems: iridociliary, chorioretinal, and papillary [8].

Each of the three blood-aqueous 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 [9]. So, to ensure the trophism of the vascular-free tissues of the anterior part of the eye, the iridociliary system (both the iris and the ciliary body) passes through its barrier substances that the chorioretinal and papillary systems normally do not pass through. This is confirmed by the fact that normally a very weak staining of the anterior chamber moisture is detected during fluorescence angiography.

Tetracyclines are one of the early classes of antimicrobial drugs [10, 11]. The first tetracyclines were obtained in the late 40s [12]. Currently, due to the appearance of a large number of tetracycline-resistant microorganisms and numerous HP (Helicobacter pylori), which are characteristic of these drugs, their use is limited. The group of tetracyclines includes natural tetracycline and semi-synthetic drugs doxycycline and minocycline [13].

Tetracyclines have a bacteriostatic effect, which is associated with a violation of protein synthesis in the microbial cell [14, 15]. Tetracyclines are considered antimicrobial drugs with a wide spectrum of antimicrobial activity, but in the course of their long-term use, many bacteria have acquired resistance to them [16].

When taken orally, tetracyclines are well absorbed, and doxycycline is better than tetracycline. The bioavailability of doxycycline does not change, and tetracycline decreases by 2 times under the influence of food. The maximum concentrations of drugs in the blood serum are created 1-3 hours after ingestion [17]. With intravenous administration, significantly higher concentrations in the blood are quickly achieved than with oral administration. Tetracyclines are distributed in many organs and environments of the body, and doxycycline creates higher tissue concentrations than tetracycline [18].

Materials and Methods

To study the permeability of the blood-aquatic barrier with tetracycline group drugs in normal and pathological conditions, we conducted an experiment in which 3 groups of adult rabbits (n=15) were formed according to the principle of analogs.

Group 1 – clinically healthy animals; group 2, group 3 – sick animals with experimentally induced pathology. Rabbits of the first and second groups were administered orally three times, with an interval of 8 hours, a tablet form of tetracycline at the rate of 25 mg/ kg of body weight, rabbits of the third group were given 3% tetracycline 3 times a day for the lower eyelid.

Clinical examination of animals included palpation of the affected organ, examination, and thermometry. Biological fluids (blood and intraocular fluid) were taken from the studied animals.

The material was placed in 10% neutral formalin for 2-3 weeks for fixation to study the morphological structures of the visual analyzer in normal and pathological conditions. The material is an extracted eyeball obtained from clinically healthy and infected rabbits with a suspension of Staphylococcus aureus. Biochemical blood tests were performed on a Chemwell Combi V 1.03 (USA) device using Cormay test kits.

The urea concentration was determined by the reaction of urease and glutamine dehydrogenase [19]. The determination of albumin concentration consisted of the reaction of albumin with bromocresol green in an acidic medium [20]. The total protein concentration was determined by a method based on a biuretic reaction [21]. Determination of creatinine concentration is a modification of the Jaffe method without protein removal [22]. The determination of cholesterol concentration consisted of the reaction of esterase with cholesterol oxidase [23]. The determination of α-amylase activity is based on a change in the amount of 2-chloro-4-nitrophenol, the formation of which during the reaction causes an increase in the absorption coefficient at 405 nm [24]. The activity of alkaline phosphatase was determined by the kinetic method recommended by the International Clinical Federation [25].

Hematological studies were performed on the device Automated Veterinary Hematology Analyzer PCE-90 VET. Fully automatic hematological analyzer for the study of animal blood samples, including the differentiation of leukocytes by 3 subpopulations and the construction of histograms. Erythrocytes, leukocytes, and platelets are counted and measured using the Coulter method [26]. The colorimetric method determines hemoglobin [27].

Pathology of the organ of vision in animals was caused by the following method: a sterile 26 G needle was inserted into the anterior chamber of the eye and intraocular fluid was taken in a volume of 0.1 ml, after that the needle was left in the eye, the syringe was replaced and an equal volume of Staphylococcus aureus suspension was injected at a concentration of 1 billion microbial bodies in 1 ml.

Results and Discussion

After the introduction of the suspension of Staphylococcus aureus, the features of clinical signs of pathology of the visual organ were noted: day 4 – conjunctiva hyperemic, pericorneal injection, cornea edematous, iris edematous, with dilated own vessels; day 5 – lacrimation is pronounced, conjunctiva is edematous, sclera injection, corneal edema, ciliary pain.

Two hours after the morning administration of the antibiotic, biological fluids were taken from rabbits.

On the 9th day after the introduction of the Staphylococcus aureus suspension, clinical recovery occurred in all animals in the second and third groups, which was expressed by normalization of the general condition of the animals, stabilization of body temperature, pulse rate, the number of respiratory movements was also within the limits.

In the visual analyzer, the inflammatory phenomena's absence in the iris, cornea, and conjunctiva was observed in 2 animals of the second group.

The dynamics of tetracycline concentration in intraocular blood serum and fluid are presented in **Table 1**.

Table 1. Tetracycline concentration in biological fluids, μg/mg (n = 15; M±m)

Research Day	Group of laboratory animals		
	1	2	3
Blood serum			
1	4,05 ± 0,2	3,69 ± 0,19	0,005 ± 0,0003
2	4,31 ± 0,22	4,18 ± 0,21	0,004 ± 0,0002
3	4,61 ± 0,23	4,56 ± 0,23	0,005 ± 0,0003
4	4,78 ± 0,24	4,63 ± 0,23	0,004 ± 0,0002
5	4,99 ± 0,25	4,72 ±0,24	0,005 ± 0,0003
Intraocular fluid			
1	0,71±0,04	0,81±0,14	0,048 ± 0,002
2	0,6±0,03	1,2±0,16*	0,047 ± 0,002
3	0,51±0,03	1,1±0,26*	0,062 ± 0,003
4	0,62±0,03	1,22±0,18*	0,099 ± 0,005
5	0,77±0,04	1,12±0,26*	0,105±0,006

Note: *P≤0.05, the difference is significant in relation to healthy animals

In the first group, the concentration of tetracycline in the blood serum increased by 19% during the study. In the second group, the concentration of the antibiotic in the blood serum increased by 22% during the study. In the third group, the tetracycline's concentration in the blood serum was at the same level throughout the experiment.

The blood serum's correlation coefficient in the second group is positive in relation to the data of the first group (r = 0.961), i.e., the correlation is strong (close) direct. The blood serum's correlation coefficient in the third group is positive in relation to the data of the first group (r = 0.007), i.e., the correlation is weak and direct.

In the first and second groups, the concentration of the drug in the intraocular fluid is 5.5 times lower than in the blood serum. By the fifth day of the experiment in the group of clinically healthy animals, the concentration of tetracycline increased slightly, in the second group it increased by 1.5 times, in the third group, the concentration of the antibiotic also increased by 2.2 times.

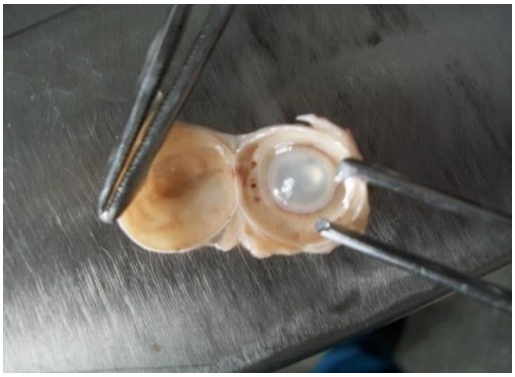
The correlation coefficient of intraocular fluid in the second group is negative in relation to the data of the first group (r = -0.361), i.e., the correlation is the average inverse. In the third group, the correlation coefficient (r = 0.388), indicates an average direct correlation, as the values of one variable increase, the value of the other increases.

Thus, in the intraocular fluid, the minimum therapeutic concentration of tetracycline in the group of clinically healthy animals was observed throughout the experiment, in the group of sick animals with oral administration of an antibiotic, tetracycline did not reach the maximum concentration by the end of the study, in the third group there was no therapeutic concentration. It should be noted that the therapeutic concentration of tetracycline in the intraocular fluid was observed in the first and second groups only for gram–positive microorganisms (0.5 - 1.5 micrograms/mg), this drug will not have a bacteriostatic effect on gram-negative microorganisms.

The concentration of the antibiotic in the intraocular fluid of sick animals was about 2 times higher than in the intraocular fluid of healthy animals, which indirectly indicates a violation of the permeability of the blood-aquatic barrier against the background of the inflammatory process.

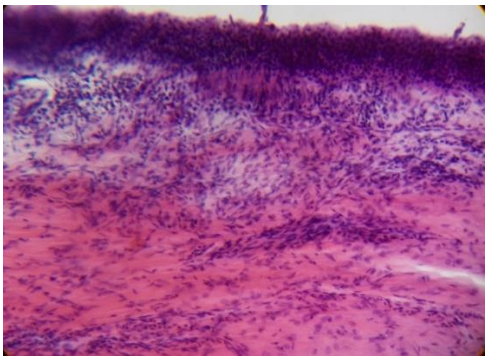
To study the structure and morphological changes of the visual organ in the caused pathology, the structures of the visual analyzer were examined **(Figures 1 and 2)**. At the same time, rabbits of all groups were euthanized by decapitation – 3 healthy animals and 3 animals with the caused pathology, 3 days after infection.

a)

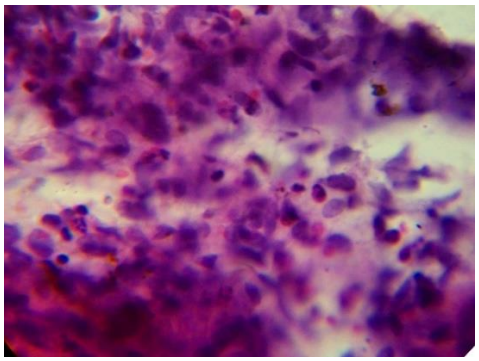


b)

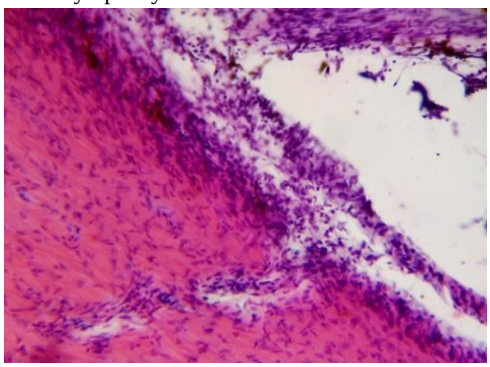
Figure 1. Hemorrhages in the scleral region



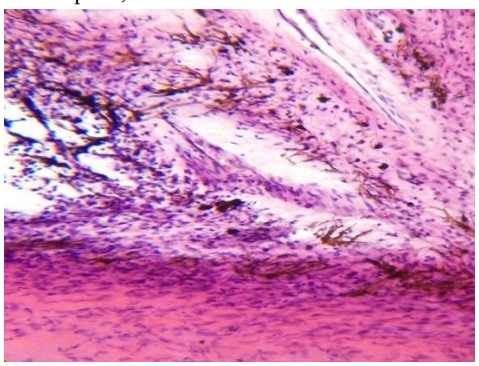
a) Pronounced swelling of the conjunctiva and lymphocytic infiltration of the sclera.



b) Accumulation of lymphocytes, macrophages, neutrophils, and hemosiderin in the sclera area.



c) Desquamation of the corneal epithelium, inflammatory infiltration by lymphocytes and macrophages.



d) Inflammatory infiltration of the cornea, desquamation of the iris epithelium.

Figure 2. Changes in the structure of the visual analyzer

The following changes in the structures of the eye were noted in animals of the second group: swelling of the conjunctival stroma and its lymphocytic infiltration, swelling and lymphocytic infiltration of the sclera, violation of the course of fibers, the cornea is edematous, phenomena of diffuse polymorphocellular inflammatory infiltration of the stroma, leukocyte infiltration of the iris with foci of purulent melting, clusters of inflammatory cells in the ciliary body, signs of uveitis in the choroid, lymphocytic infiltration of retinal layers. In animals of the third group, the changes were similar.

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

To monitor the changes occurring in the body of animals as a whole, hematological and biochemical study were carried out **(Tables 2 and 3)**.

Table 2. Hematological parameters of blood serum of laboratory animals, (n = 15; 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	8,4±0,42	8,7±0,44	13,4±0,67*	14,1±0,41*	8,32±0,42	13,9±0,7*	17,8±0,9*
Lymphocyte percentage, %	44,7±2,24	47,6±2,38	36,6±1,83*	26,7±1,34*	41,3±2,07	34,7±1,74*	22,8±1,14*
Mid-sized cell percentage, %	4,7±0,24	4,5±0, 23	3,9±0,19 *	4,9±0,25	5,61±0,19*	4,4±0,22	5,12±0,26
Granulocyte percentage, %	50,6±2,53	48,0±2,4	59,5±2,98*	68,4±3,42*	53,1±2,66	60,9±3,1*	72,1±3,61*
Red Blood Cell, $*10^{12}$/L	5,8±0,3	6,2±0,31	5,6±0,28	5,2±0,26	5,94±0,3	4,9±0,25*	4,3±0,22*
Hemoglobin Concentration, g/L	120,1±6,0	125,7±6,8	116,9±5,9	107,4±5,4*	120,3±5,23	100,9±5,1*	98,7±4,94*
Hematocrit, %	35,2±1,8	38,7±1,94	34,1±1,71	31,8±1,6	36,0±1,5	29,6±1,5*	27,2±1,4*
Platelet, $*10^9$/L	220,5±11,0	154±7,0*	252± 13,0	217±10,0	148±6,0*	297±15*	244±12,0

Note: *P≤0.05, the difference is significant in relation to the background indicators

After the last administration of tetracycline in the group of clinically healthy animals, the leukocyte count decreased by 4%, in the group of sick animals with oral administration of tetracycline increased by 4%, in the group of sick animals with tetracycline ointment, this indicator increased by 21%. Thus, the content of leukocytes in the second and third groups throughout the experiment exceeded the limits of the norm, due to the body's response to the introduced pathogenic agent.

The relative content of lymphocytes, monocytes, and granulocytes was within the physiological norm in the first group, in the second and third groups the number of lymphocytes was below the normal limit, and the number of granulocytes exceeded the normal limits. These changes in the number of leukocytes in groups of sick animals correspond to the response to the introduced pathogenic agent.

The number of red blood cells after the last blood collection in the first group did not significantly change, in the second group, it decreased by 12% and by 17% in the third group. A decrease in the number of red blood cells in groups with experimentally induced ophthalmopathology is associated with 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, in the group of sick animals with oral administration of tetracycline decreased by 14%, in the group of sick animals with tetracycline ointment, the concentration of hemoglobin was 8% lower than normal. Hematocrit in the second and third groups was also below normal. A decrease in the hematocrit number and hemoglobin concentration in the blood of sick animals is associated with a decrease in the number of red blood cells.

By the fifth day of the experiment, the number of platelets decreased by 4% in the first group, increased by 18% in the second group, and by 11% in the third group. The platelet count was within the groups of sick animals and the physiological norm in the group of clinically healthy animals throughout the study.

Thus, hematological indicators confirm the presence of an acute inflammatory process in the body of animals.

The activity of alanine aminotransferase in the clinically healthy group increased by 7% by the end of the experiment, in the group of sick animals with oral administration of tetracycline increased by 7%, in the group of sick animals with tetracycline ointment there were no significant changes in this indicator.

After the last administration of tetracycline, the activity of aspartate aminotransferase in the group of clinically healthy animals increased by 3%, in the group of sick animals with oral administration of tetracycline, the activity of alanine aminotransferase increased by 9%.

In the group of clinically healthy animals, there were no significant changes in the activity of γ-glutamyltransferase after the last blood collection. On the last day of the study, the activity of γ-glutamyltransferase was within the normal limits, while it increased by 15% in the second group, and remained at the same level in the third group.

Amylase activity after the last administration of the antibiotic in the group of clinically healthy animals did not significantly change, in the group of sick animals with tetracycline ointment by 11%, in the group of sick animals with oral administration of tetracycline by 9%.

On the fifth day of the experiment, the activity of alkaline phosphatase in the first group increased by 2%, and in the second and third groups by 4%. The alkaline phosphatase's activity is higher than normal in groups of sick animals, which is explained by the body's response to the introduced pathogenic agent.

Table 3. Biochemical parameters of blood serum of laboratory animals, (n = 15; M±m)

Indicators	Background indicators	Day 1			Day 5		
		Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
ALAT, Units/l	57,8±2,9	62,1±3,73	69,6±3,43*	55,7±2,79	67,3±3,1*	75,2±3,7*	64,9±3,5
ASAT, Units/l	80,9±4,1	89,3±4,5	95,7±4,79*	73,9±3,7	92,4±5,0*	105,3±5,3 *	88,4±4,42
GGT, Units/l	6,5±0,33	6,0±0,3	8,9±0,45*	6,23±0,26	6,6±0,37	10,5±0,53*	6,2±0,46
Amylase, Units/l	175,5±8,8	171,6±8,9	223,1±11,2*	199,2±9,9 *	185,3±9,3	244,0±12,2 *	224,2±11,2*
Alkaline phosphatase, Units/l	7,5±0,38	7,62±0,4	18,1±0,9*	18,8±0,94 *	7,8±0,42	18,9±0,94*	19,6±0,98*

Creatinine, mmol/l	80,9±4,1	72,7±3,64	112,7±5,64*	93,7±3,19 *	85,3±4,3	113,5±5,7*	95,7±4,79*
Urea, mmol/l	6,7±0,34	6,91±0,35	9,5±0,48*	9,09±0,46	7,2±0,36	10,2±0,51*	10,4±0,53*
Cholesterol, mmol/l	0,9±0,1	0,87±0,04	1,5±0,08*	1,1±0,06	1,0±0,1	1,4±0,06*	1,2±0,05*
Glucose, mmol/l	6,5±0,33	7,2±0,36	5,5±0,28*	5,1±0,2*	6,22±0,31	5,49±0,27*	4,9 ± 0,25*
Total protein, g/l	60,5±3,0	57,1±2,86	59,4±3,0	60,3±3,02	59,7±2,99	63,1±3,16	62,2 ± 3,11
Albumin, g/l	30,9±1,55	32,8±1,64	48,2±2,41*	50,9±2,6*	29,4±1,47	53,4±2,67*	55,1 ± 2,76

Note: *P≤0.05, the difference is significant in relation to the background indicators

The serum creatinine content in the group of clinically healthy animals did not significantly change by the end of the experiment, in the group of sick animals with oral administration of tetracycline remained at the level of the first day of the experiment, in the group of sick animals with tetracycline ointment, the creatinine content increased by 2%.

After the last administration of tetracycline, the amount of urea increased by 4% in the first group, by 7% in the second group, and by 13% in the third. The increase in this indicator is explained by the pathology caused by the organ of vision.

The cholesterol content in the group of clinically healthy animals was within the normal range, by the fifth day of the experiment in the group of sick animals with oral administration of tetracycline, this indicator decreased by 7%, in the group of sick animals with tetracycline ointment increased by 8%.

In the first group, there was no reliability of changes in glucose content in the blood serum on the last day of the study, in the second group this indicator was at the same level during the experiment, in the third it decreased by 4%.

The total protein content after the last tetracycline administration in the group of clinically healthy animals increased by 4%, in the group of sick animals with oral administration of an antibiotic by 6%, and in the group of sick animals with tetracycline ointment by 3%.

After the last blood collection in the first group, there were no significant changes in the albumin content, in the second group it increased by 10%, in the third group the amount of albumin increased by 8%. Thus, throughout the study, this indicator in the groups of sick animals was higher than normal, which is explained by the body's inflammatory reaction to the pathogenic agent that is introduced.

Conclusion

After the introduction of the suspension of Staphylococcus aureus, the features of clinical signs of pathology of the visual organ were noted: day 4 – conjunctiva hyperemic, pericorneal injection, cornea edematous, iris edematous, with dilated own vessels; day 5 – lacrimation is pronounced, conjunctiva is edematous, sclera injection, corneal edema, ciliary pain.

On the 9th day after the introduction of the Staphylococcus aureus suspension, clinical recovery occurred in all animals in the second and third groups, which was expressed by normalization of the animals' general condition, the number of respiratory movements, pulse rate, stabilization of body temperature was also within the limits. In the visual analyzer, the absence of inflammatory phenomena in the cornea, iris, and conjunctiva was observed in 2 animals of the second group.

In the first group, the concentration of tetracycline in the blood serum increased by 19% during the study. In the second group, the concentration of the antibiotic in the blood serum increased by 22% during the study. In the third group, the concentration of tetracycline in the blood serum was at the same level throughout the experiment.

In the first and second groups, the concentration of the drug in the intraocular fluid is 5.5 times lower than in the blood serum. By the fifth day of the experiment in the group of clinically healthy animals, the concentration of tetracycline increased slightly, in the second group it increased by 1.5 times, in the third group, the concentration of the antibiotic also increased by 2.2 times. Thus, in the intraocular fluid, the minimum therapeutic concentration of tetracycline in the group of clinically healthy animals was observed throughout the experiment, in the group of sick animals with oral administration of an antibiotic, tetracycline did not reach the maximum concentration by the end of the study, in the third group there was no therapeutic concentration. It should be noted that the therapeutic concentration of tetracycline in the intraocular fluid was observed in the first and second groups only for gram–positive microorganisms (0.5 - 1.5 micrograms/mg), this drug will not have a bacteriostatic effect on gram-negative microorganisms.

The concentration of the antibiotic in the intraocular fluid of sick animals was about 2 times higher than in the intraocular fluid of healthy animals, which indirectly indicates a violation of the permeability of the blood-aquatic barrier against the background of the inflammatory process.

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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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