Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

PHARMACOKINETICS OF AMIKACIN IN EYE MEDIA USING VARIOUS DRUGS

Markha Khozh-Akhmedovna Bersanova[1], Lina Magomedovna Batkhieva[1], Tamar Elbrusovna Baramiya[2], Daniela Georgievna Birkaya[2*], Elena Vladimirovna Belokobylskaya[2], Zulmira Temirsoltanovna Saidova[2]

1. ***Department of Therapy, Medical Faculty of the Moscow State Medical and Dental University named after A. I. Evdokimov, Moscow, Russia.***
2. ***Department of Therapy, Pediatric Faculty of Rostov State Medical University, Rostov-on-Don, Russia.***

ARTICLE INFO

Received:
06 Apr 2023
Received in revised form:
12 Jun 2023
Accepted:
15 Jun 2023
Available online:
28 Jun 2023

Keywords: Blood-ocular barrier, Amikacin, Cerebrolysin, Nicotinic acid, Selenpropionics

ABSTRACT

In the treatment of eye diseases caused by various bacteria, it is extremely important to achieve a therapeutic dose of the drug in the affected organ on time. Otherwise, antibiotic resistance may develop. However, the situation is complicated by the fact that the permeability of the blood-ocular barrier of the inflamed eye drops significantly, and the therapeutic dose of most antibiotics is reached only within 3-4 days of treatment. This article uses the example of laboratory animals (rabbits) to study ways to increase the permeability of the blood-ocular barrier. To do this, individuals who have been injected with a strain of microorganisms Staphylococcus aureus are treated with the antibiotic amikacin. The effect of drugs Cerebrolysin, nicotinic acid, and Selenpropionics on the rate of penetration of the antibiotic into the affected organ is being studied. The course of the disease and the general well-being of rabbits are monitored, and the biochemical and hematological parameters of blood are analyzed. In addition, on the first and fifth day of the course of the disease, the concentration of amikacin in biological fluids was determined: in the blood serum and the intraocular fluid.

To Cite This Article: Bersanova MKA, Batkhieva LM, Baramiya TE, Birkaya DG, Belokobylskaya EV, Saidova ZT. Pharmacokinetics of Amikacin in Eye Media Using Various Drugs. Pharmacophore. 2023;14(3):107-13. https://doi.org/10.51847/qZS08gqJvC

Introduction

Studies of the permeability of the blood-ocular barrier with antibacterial drugs have shown that they reach a therapeutic concentration in the affected organ only on the 3rd day after administration [1]. This can lead to the appearance of resistant strains of microorganisms. It is known that the blood-tissue barrier of the body prevents the passage of medicinal substances [2]. Thus, the purpose of this scientific work is to develop a scheme for the administration of pharmacological drugs that facilitates the penetration of chemotherapeutic agents through the blood-ocular barrier to achieve therapeutic concentrations of antibiotics in the eyeball.

The choice of medicines was carried out based on literature data, practical experience, and cost. To solve this goal, the following were selected: cerebrolysin, nicotinic acid, and selenpropionix.

Cerebrolysin

Cerebrolysin is a drug that is widely used in medicine for the treatment of various neurological diseases [3]. It contains a complex of neuropeptides derived from the pig brain. Cerebrolysin has unique properties that determine its effectiveness in the treatment of many neurological disorders [4].

Cerebrolysin is used to treat various cerebrovascular diseases, such as strokes and transient ischemic attacks [5]. It improves blood circulation in the brain, increases metabolic processes, and protects nerve cells from damage [6]. Cerebrolysin is

Corresponding Author: Daniela Georgievna Birkaya; Department of Therapy, Pediatric Faculty of Rostov State Medical University, Rostov-on-Don, Russia. E-mail: bucky99@yandex.ru.

indicated in the treatment of the consequences of traumatic brain injuries, such as post-traumatic disorders, memory and concentration disorders, headache, and vestibular disorders [7]. It promotes the restoration of nervous functions and accelerates the rehabilitation process. Cerebrolysin is used in the complex therapy of degenerative diseases of the nervous system, such as Alzheimer's disease and Parkinson's disease [8]. It helps slow down the progression of these diseases and improves the quality of life of patients. Cerebrolysin has a pronounced neuroprotective effect. It helps to protect nerve cells from damage and improves their survival and functional state [9]. Cerebrolysin stimulates microcirculation and improves blood supply to the brain. This contributes to the delivery of oxygen and nutrients to nerve cells, which contributes to their recovery and efficiency [10]. Cerebrolysin has antioxidant properties, due to which helps to reduce the level of oxidative stress in the nervous system [11]. This is especially important in neurodegenerative diseases, where oxidative stress is one of the causes of damage to nerve cells. Cerebrolysin stimulates metabolic processes in the nervous system, increasing energy metabolism and protein synthesis. This helps to restore nerve cells and improve their functions. Cerebrolysin has a vasodilating effect, in particular on smooth muscles. The mechanism of its effect on the vessels of the brain consists in inhibiting the entry of extracellular calcium through electrogenic and chemosensitive channels and in inhibiting its mobilization from the intracellular depot during depolarization of the membranes of vascular smooth muscle cells [12].

Nicotinic Acid

Nicotinic acid, also known as niacin or vitamin B3, is an important nutrient for the human body [13]. It has a wide range of applications in medicine and plays an important role in maintaining the health of various body systems. Nicotinic acid participates in metabolism and plays an important role in regulating the metabolism of carbohydrates, fats, and proteins. It promotes the conversion of food into energy, maintains a normal level of glucose in the blood, and participates in the synthesis of lipids [14]. Nicotinic acid has antioxidant properties, which means that it protects the body's cells from damage caused by free radicals. This is especially important for protecting the cells of the nervous system and heart [15]. Nicotinic acid plays a role in the normal functioning of the nervous system. It participates in the synthesis of neurotransmitters such as serotonin, norepinephrine, and dopamine, which are responsible for the transmission of nerve impulses and mood [16].

Nicotinic acid easily overcomes biological membranes, both due to passive diffusion and with the participation of several specific transport mechanisms, and also improves microcirculation, which has a pronounced short-term vasodilating effect. A 1% solution of nicotinic acid is a specific anti-gallagric agent. When using erythemic doses for healthy individuals, nicotinic acid causes a short-term expansion of peripheral vessels and presumably contributes to an increase in the permeability of antibacterial drugs through the blood-ocular barrier [17].

In additional studies, it was determined that the erythemic dose of nicotinic acid, which ensures the penetration of the antibiotic through the blood-ocular barrier in sufficient therapeutic concentration, is 0.15 mg/kg [18].

Selenpropionics

Currently, many complex preparations and biologically active additives containing selenium for systemic use are used in ophthalmology. The next drug we studied is selenpropionix.

Selenpropionix is an organic selenium compound that is widely used in medicine and the food industry [19]. It has unique properties and has many applications in the field of healthcare. Selenpropionix is a strong antioxidant that helps protect the body's cells from damage caused by free radicals [20]. This is especially important for maintaining the health of the cardiovascular system and preventing the occurrence of chronic diseases. Selenpropionix plays an important role in maintaining the normal function of the immune system. It helps strengthen the immune system, increase the activity of natural killers, stimulate the production of antibodies, and improve the body's response to infections and inflammation. Selenpropionix exhibits anticancer activity [21]. It can reduce the risk of developing certain types of cancer, such as prostate, breast, lung, and bowel cancer. It can also help in the fight against cancer cells and limit their growth. Selenpropionix plays an important role in maintaining the health of the heart and blood vessels [22]. It helps to reduce cholesterol levels in the blood, regulates blood pressure, prevents the formation of blood clots, and improves blood flow.

Thus, the drug has immunomodulatory, anabolic, antioxidant, and anti-inflammatory properties due to the complex of biologically active substances included in its composition.

Amikacin

Amikacin is an antibiotic belonging to the group of aminoglycosides [23]. It has a wide spectrum of antibacterial action and is active against various gram-negative and gram-positive bacteria. Amikacin has a strong antibacterial effect and is effective against many bacteria, including those that cause eye infections [24]. It can be used to fight gram-negative and gram-positive bacteria such as Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, and others [25].

The use of amikacin in ophthalmology:

1. Treatment of bacterial conjunctivitis. Amikacin can be used in ophthalmology to treat bacterial conjunctivitis, which is characterized by inflammation of the mucous membrane of the eye caused by bacterial infection. Amikacin helps to eliminate bacterial pathology and alleviate the symptoms of conjunctivitis.
2. Treatment of purulent eye infections. Amikacin can be used to treat various purulent infections of the eye, such as purulent keratitis and purulent endophthalmitis. It can suppress the growth and reproduction of bacteria that have entered the eye, and prevent the development of serious complications.

3. Preoperative prevention. In some cases, amikacin can be used in ophthalmology as a preoperative prophylaxis to prevent the occurrence of infections after surgical interventions on the eyes.

Materials and Methods

Correction of pharmacokinetics in the eye media using various drugs was performed for amikacin. This antibacterial drug was chosen due to its high therapeutic efficacy and low level of toxicity [26].

For the experiment, 80 adult rabbits were taken without any diseases. All rabbits were artificially injected with a suspension of Staphylococcus aureus in the eyeball area. For further research, the rabbits were divided into 4 similar groups of 20 individuals each.

Rabbits of the first (control) group of amikacin were injected twice intramuscularly, into the posterior femoral muscle group with a syringe with a 26G needle at a dose of 0.1 mg/kg; rabbits of the second experimental group amikacin were administered simultaneously with cerebrolysin at a dose of 0.25 mg/ kg, the third experimental group was administered amikacin according to a similar scheme, and nicotinic acid was administered intramuscularly at a dose of 0.15 mg/kg per head 40 minutes after the introduction of amikacin, the fourth group was injected with selenpropionix at a dose of 0.15 mg/ kg an hour before the introduction of the antibiotic.

Pharmacotherapy of animals was started simultaneously, 24 hours after the introduction of the culture, providing the clinical manifestation of the disease. Clinical signs of the disease were recorded in all animals.

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

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

Results and Discussion

On the 6th day after the introduction of the Staphylococcus aureus suspension, clinical recovery occurred – in 6 animals in the first group, in 9 animals in the second group, in 14 animals in the third group, in 6 animals in the fourth group, which was expressed by the absence of inflammatory phenomena in the eyeball.

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

Table 1. The concentration of amikacin in biological fluids, µg/mg

Research Day	Group 1 (control)	Group 2 (experimental) Cerebrolysin (0.25 mg/kg)	Group 3 (experimental) Nicotinic acid (0.15 mg/kg)	Group 4 (experimental) Selenpropionics (0.15 mg/kg)
Blood serum				
1	4.23±0.19	3.59±0.18	3.20±0.16	3.89±0.19
2	4.12±0.21	3.72±0.22	3.27±0.2	4.0±0.18
3	3.65±0.18	3.95±0.2	3.36±0.16	4.15±0.2
4	4.76±0.29	4.13±0.25	3.48±0.21	4.21±0.22
5	4.51±0.27	4.27±0.21	3.57±0.18	4.33±0.23
Intraocular fluid				
1	1.72±0.17	1.93±0.1	3.58±0.17	1.8±0.1
2	2.5±0.39	2.19±0.13	3.22±0.16	2.0±0.11
3	2.85±0.693	2.6±0.13	4.36±0.22	2.2±0.12
4	3.41±0.67	3.09±0.15	3.71±0.19	2.85±0.09
5	2.92±0.74	3.7±0.19	4.71±0.24	3.11±0.17

In the blood serum, the concentration of amikacin in the control group decreased by 3% after 24 hours. On the 4th day of the experiment, the concentration of the antibiotic increased by 23%.

In group 1, the concentration of the antibiotic increased by 3% on the second day of the study and increased by 4% on day 4.

In the blood serum, the concentration of amikacin in group 2 increased by 2% after 24 hours. On the 4th day of the study, the concentration of the antibiotic increased by 3%.

The concentration of the antibiotic in group 3 increased by 3% on the second day. On the 4th day of the study, the concentration of the antibiotic decreased by 1%.

Thus, the concentration of amikacin in the blood serum in all groups was therapeutic (3-5 mcg/ml) throughout the experiment.

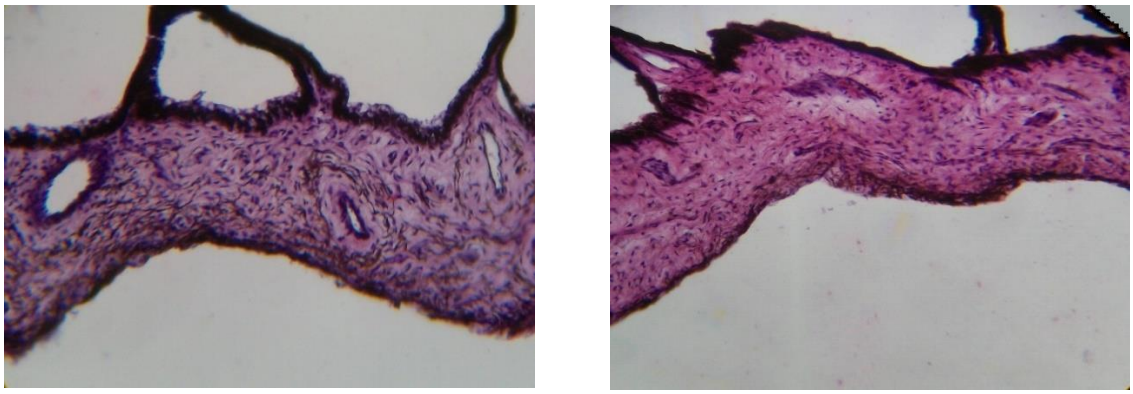
In the intraocular fluid in the first group, the concentration of amikacin increased by 31% on the second day of the study. On the fourth day, the concentration of the antibiotic increased by 16% and reached therapeutically.

In the second group, the concentration of amikacin increased by 12% after 24 hours. By the fourth day of the experiment, the concentration of the antibiotic reached therapeutically. On the fifth day, this indicator increased by 16%.

In the intraocular fluid in the third group, the concentration of amikacin decreased by 10% on the second day of the study. On the fourth day, this indicator decreased by 15%. Thus, the therapeutic concentration of amikacin in the intraocular fluid was observed throughout the experiment.

In the fourth group, the concentration of amikacin increased by 10% after 24 hours. By the fourth day of the experiment, the concentration of the antibiotic increased by 23%. On the fifth day, the concentration of amikacin reached therapeutically.

Thus, as a result of the conducted research, we found out how the concentration of amikacin changes against the background of the use of drugs by various groups. If we need to achieve a high therapeutic concentration after the first administration, then the use of nicotinic acid in an erythemic dose with an antibiotic will be optimal, if a gradual increase in the therapeutic concentration of amikacin is required, then cerebrolysin is suitable for this treatment regimen [27].



a) The iris against the background of the use of nicotinic acid. b) The iris. The control group.

Figure 1. Changes in the iris of the eye

During light microscopy, the following changes were observed in the structures of the eye **(Figure 1)**: slight cellular infiltration in the sclera, mild inflammatory edema of the cornea, moderate inflammatory lymphocytic infiltration in the iris, vasodilation, which led to increased permeability of the vascular wall (increased pinocytosis vesicles in the cytoplasm, the presence of cytoplasmic outgrowths, loosening of the basement membrane), a week after the introduction of the pathogenic agent in the iris, the vessels were narrowed, the vascular membrane and ciliary body are weakly infiltrated by lymphocytes, there is weak infiltration in the retina [28]. 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 observe the changes occurring in the body of animals as a whole, hematological and biochemical studies were carried out **(Tables 2 and 3)**.

Table 2. Hematological parameters of blood serum of laboratory animals

Indicators	Background indicators	Research Day	Group 1	Group 2	Group 3	Group 4
White Blood Cell, $*10^9$/L	9.1±0.5	Day 1	9.9±0.6	9.2±0.46	9.0±0.45	10.6±0.53
		Day 5	16.7±0.84	16.3±0.8	15.6±0.7	16.9±0.85
Lymphocyte percentage, %	43.9±2.2	Day 1	41.4±1.0	44.6±2.2	37.0±1.9	44.8±2.2
		Day 5	35.0±1.7	35.7±1.7	36.6±1.8	34.6±1.73
Mid-sized cell percentage, %	3.3±0.17	Day 1	3.0±0.5	3.1±0.16	3.7±0.19	2.8±0.14
		Day 5	2.8±0.14	2.6±0.13	3.0±0.1	2.5±0.13
Granulocyte percentage, %	53.4±2.7	Day 1	56.4±2.82	52.3±2.62	59.3±2.97	52.4±2.6
		Day 5	62.3±3.1	61.7±3.1	60.4±3.0	62.9±3.15
Red Blood Cell, $*10^{12}$/L	5.4±0.27	Day 1	5.72±0.2	5.3±0.27	5.83±0.3	5.21±0.2
		Day 5	4.8±0.24	5.0±0.25	5.1±0.26	4.9±0.25
Hemoglobin Concentration, g/L	130.3±6.5	Day 1	131.0±6.6	127.2±6.4	140.0±7.0	119.2±6.0
		Day 5	101.1±5.1	104.2±5.2	107.3±5.4	103.6±5.2
Hematocrit, %	35.7±2.0	Day 1	37.0±1.85	36.7±1.84	38.3±1.9	33.9±1.7
		Day 5	29.1±1.5	31.7±1.6	32.4±1.62	30.9±1.5
Platelet, $*10^9$/L	293.1±15.0	Day 1	333±16.0	375±18.0	291±13.0	247±12.0
		Day 5	362±15.0*	390±13.0*	307±11.0	268±12.0

In the control group, the number of leukocytes after the last administration of amikacin increased by 40%, in group 2 by 44%, in group 3 this indicator increased by 42%, and in group 4 by 37%.

The relative content of granulocytes in all groups was above the normal limit, which is associated with a response to the injected infectious agent.

The number of red blood cells on the 5th day of the experiment in the control group decreased by 16%, in the second group by 6%, in the third group by 12%, and in the fourth group, this indicator decreased by 6%. The content of red blood cells on the last day of the experiment in all groups was below normal, which is explained by the use of the drug.

The concentration of hemoglobin on the last day of the study in the first group increased by 23%, in the second group by 18%, in the third group by 23%, and in the fourth group, this indicator increased by 13%. Thus, the concentration of hemoglobin in all groups after the last blood collection was below normal, this is due to the effect of the antibacterial drug on erythropoiesis. By the end of the experiment, the hematocrit was below normal in all groups, which is explained by the lack of red blood cells in the blood.

The number of platelets in the control group decreased by 16% on the fifth day of the study. In group 2, the content of platelets in peripheral blood increased by 4% after the last administration of amikacin. In group 3, this indicator increased by 5%. In group 4, the number of platelets increased by 8% during the study.

The activity of alanine aminotransferase after the last administration of amikacin in the control group increased by 3%. In group 2, it increased by 2%. In group 3, this indicator increased by 8%. In group 4, the activity of alanine aminotransferase increased by 7% on day 5 of the experiment.

In the first group, the activity of aspartate aminotransferase on the last day of the experiment increased by 4%, in the second group by the last administration of amikacin increased by 9%; in the third group, this indicator decreased by 5% on the 5th day of the experiment, in the fourth group, the activity of aspartate aminotransferase after the last administration of the antibiotic increased by 6%.

Table 3. Biochemical parameters of blood serum of laboratory animals

Indicators	Background indicators	Research Day	Group 1	Group 2	Group 3	Group 4
ALAT, U/l	54.1±2.7	Day 1	53.7±1.69	51.9±2.6	50.4±1.52	53.1±2.66
		Day 5	55.6±2.78	52.8±2.7	54.7±2.74	57.2±2.86
ASAT, U/l	82.5±4.13	Day 1	85.9±4.3	80.3±4.0	81.2±4.1	84.5±4.23
		Day 5	89.8±4.5	88.6±4.43	85.3±4.27	90.1±4.5
GGT, U/l	7.1±0.36	Day 1	8.21±0.41	5.9±0.3	6.47±0.32	12.03±0.6
		Day 5	10.37±0.52	6.44±0.3	8.11±0.4	13.5±0.7
Amylase, U/l	222.5±11.1	Day 1	259.1±13.0	189.8±9.5	292.7±14.6	231.0±11.6
		Day 5	286.4±14.0	193.7±9.0	254.2±13.0	241.4±12.0
Alkaline phosphatase, U/l	7.2±0.3	Day 1	18.8±0.94	17.9±0.9	16.7±0.84	18.2±0.91
		Day 5	23.5±1.18	21.6±1.1	20.2±1.0	23.1±1.16
Creatinine, μmol/l	75.3±4.0	Day 1	85.24±4.26	109.6±5.48	62.21±3.11	102.3±5.1
		Day 5	77.67±3.88	92.3±4.6	66.4±3.3	111.7±5.5
Urea, mmol/l	7.8±0.39	Day 1	8.8±0.44	9.5±0.48	9.3±0.46	8.5±0.43
		Day 5	10.4±0.52	10.1±0.51	10.2±0.51	10.0±0.5
Cholesterol, mmol/l	0.7±0.04	Day 1	0.9±0.05	1.3±0.1	2.0±0.04	1.8±0.09
		Day 5	0.4±0.02	1.1±0.1	2.5±0.13	1.5±0.08
Glucose, mmol/l	5.6±0.3	Day 1	4.32±0.21	6.3±0.34	4.28±0.22	5.31±0.27
		Day 5	4.58±0.23	6.1±0.31	5.72±0.29	5.91±0.2
Total protein, g/l	57.5±3.0	Day 1	56.8±2.84	56.5±2.8	57.3±2.87	56.0±2.8
		Day 5	57.1±2.81	58.9±2.95	59.3±3.0	57.1±3.0
Albumin, g/l	29.6±1.5	Day 1	28.5±1.43	26.4±1.22	30.1±2.01	28.5±1.23
		Day 5	29.3±1.47	26.3±1.24	32.9±2.3	34.2±1.71

The activity of γ-glutamyltransferase in the control group increased by 12% by the end of the study, remaining within the normal range. In group 2, the activity of γ-glutamyltransferase increased by 8%. In group 3, this indicator increased by 20% on the fifth day. In group 4, the activity of γ-glutamyltransferase increased by 11% on the last day of the experiment. Amylase activity by the 5th day of the experiment in the control group, the second and fourth increased by 9%, 2%, and 4%, respectively, in the third group this indicator decreased by 13%. Thus, amylase activity in all groups was within the physiological norm. The activity of alkaline phosphatase in the control group increased by 20% after the last blood collection, remaining within the normal range. In group 2, this indicator increased by 17% after the final administration of the antibiotic. In group 3, the activity of alkaline phosphatase increased by 14% on the fifth day of the experiment. In group 4, the indicator increased by

21%. The activity of alkaline phosphatase is higher than normal in all groups, which indicates the body's reaction to the infection caused.
The serum creatinine content in the control group by the end of the experiment decreased by 9%, in the second group by 16%, increased in the third group by 6%, and in the fourth group by 8%. Thus, the amount of creatinine in the blood serum in all groups was within the normal range.
In the control group, the urea content increased by 15% after the last blood collection. In group 2, this indicator increased by 6%. In group 3, this indicator increased by 9%. In group 4, the urea content decreased by 15%. The increased content of urea in all groups is explained by the pathology of the visual organ.
By the fifth day of the experiment, the cholesterol content decreased by 23% in the first group, 15% in the second group, 17% in the fourth group, and increased by 20% in the third group. Thus, the amount of cholesterol in the blood serum in the first, second, and fourth groups was within the normal range, in the third group this indicator increased by the end of the study, which is explained by the effect of nicotinic acid on lipid metabolism.
In the control group, the serum glucose level remained at the same level throughout the study. In group 2, this indicator decreased by 3% after the final administration of the antibiotic, in group 3 it increased by 25%. In group 4, the glucose content on the 5th day of the experiment increased by 10%. The total protein content after the last administration of the antibiotic in the first group remained at the same level, increased in the second group by 4%, in the third group this indicator increased by 3%, and in the fourth by 2%.
In the control group, the serum albumin content increased by 3% on the 5th day of the experiment. In group 2, this indicator remained at the same level throughout the study. In group 3, the albumin content increased by 9% after the last blood collection. In group 4, the amount of albumin on the 5th day of the experiment increased by 17%.

Conclusion

The conducted studies of hematological and biochemical parameters of blood showed the standard course of the disease [29, 30]. However, the study of the concentration of amikacin in the blood serum and the intraocular fluid showed how the concentration of amikacin changes against the background of the use of drugs of various groups. If we need to achieve a high therapeutic concentration after the first administration, then the use of nicotinic acid in an erythemic dose with an antibiotic will be optimal, if a gradual increase in the therapeutic concentration of amikacin is required, then cerebrolysin is suitable for this treatment regimen.

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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