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STUDY OF THE CHRONIC TOXICITY OF ANGIOLIN NASAL GEL

Actuality. *Intranasal drug delivery is considered a promising approach to enhancing the efficiency of neuroprotective therapy. However, long-term use of such drugs requires a comprehensive assessment of its safety.*

The aim of the study *was to evaluate the chronic toxicity of 1% Angiolin nasal gel following its prolonged administration.*

Materials and methods. *The study was conducted on white non-linear rats following intranasal administration of 1% Angiolin gel at a dose of 100 mg/kg for 180 days. The general condition of the animals, behavioral responses (Open Field test), indicators of cardiac bioelectrical activity, hematological and biochemical parameters of blood and urine, and the morphological condition of organs were assessed. Immunotoxic effects were studied based on the weight and cell count of lymphoid organs, peripheral blood, and humoral and cellular immune responses under conditions of normal immune status and cyclophosphamide-induced immunodeficiency.*

Research results. *Long-term (180-day) intranasal administration of a 1% Angiolin gel (100 mg/kg) did not cause any signs of systemic toxicity and did not affect body weight gain, body temperature, behavior, ECG results, or hematological and biochemical parameters. Morphological studies revealed no pathological changes in internal organs. The 1% Angiolin gel did not exhibit immunotoxic effects and contributed to the normalization of immune system parameters in conditions of secondary immune depression, including the normalization of peripheral blood parameters, the state of lymphoid organs, and humoral and cellular immune responses.*

Conclusion. *1% Angiolin nasal gel is characterized by a high safety profile during long-term use and possesses immunomodulatory properties, which justifies the promise of its further pharmacological study.*

Key words: *Angiolin, nasal gel, chronic toxicity, neuroprotection, nose-to-brain delivery.*

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ДОСЛІДЖЕННЯ ХРОНІЧНОЇ ТОКСИЧНОСТІ НАЗАЛЬНОГО ГЕЛЮ З АНГІОЛІНОМ

Актуальність. *Інтраназальна доставка лікарських засобів розглядається як перспективний підхід підвищення ефективності нейропротективної терапії. Однак тривале застосування таких препаратів потребує комплексної оцінки їхньої безпеки.*

Мета дослідження. *Оцінка хронічної токсичності 1%-го назального гелю Ангіолін за тривалого введення.*

Матеріали та методи. *Дослідження виконано на білих нелінійних щурах за інтраназального введення 1%-го гелю Ангіолін у дозі 100 мг/кг протягом 180 діб. Оцінювали загальний стан тварин, поведінкові реакції (тест «Відкрите поле»), показники біоелектричної активності серця, гематологічні та біохімічні параметри крові й сечі, морфологічний стан органів. Імунотоксичну дію вивчали за масою та клітинністю лімфоїдних органів, показниками крові, гуморальною та клітинною імунною відповіддю, в умовах нормального імунного статусу та циклофосфан-індукованому імуноімунодефіциту.*

Результати дослідження. *Тривале (180-денне) інтраназальне введення 1%-го гелю з Ангіоліном (100 мг/кг) не викликало ознак системної токсичності, не впливало на приріст маси тіла, температуру, поведінку, показники ЕКГ, гематологічні та біохімічні параметри. Морфологічні дослідження не виявили патологічних змін внутрішніх органів. 1%-й гель з Ангіоліном не виявляв імунотоксичної дії та сприяв нормалізації показників імунної системи в умовах вторинної імунодепресії, включно з нормалізацією показників периферичної крові, стану лімфоїдних органів, гуморальної та клітинної імунної відповіді.*

Висновки. *1%-й назальний гель з Ангіоліном характеризується високим профілем безпеки за тривалого застосування та має імуномодулюючі властивості, що обґрунтовує перспективність його подальшого фармакологічного вивчення.*

Ключові слова: *Ангіолін, назальний гель, хронічна токсичність, нейропротекція, nose-to-brain доставка.*

Relevance. The development of effective and safe drugs with neuroprotective activity is a priority direction in modern pharmacology. This is due to the high prevalence of central nervous system diseases in which the pathological process is based on universal mechanisms of nerve tissue damage: oxidative stress, mitochondrial dysfunction, neuroinflammation, excitotoxicity, and apoptosis. Consequently, the search for new compounds capable of limiting neuronal damage and maintaining the functional integrity of nervous tissue remains of high scientific and practical relevance (Pandya, 2024; Vargas, 2025; Wu, 2023; Belenichev, 2022).

Despite significant progress in the development of neuroprotective agents, its practical application is often limited due to low bioavailability, insufficient penetration across the blood-brain barrier, and the risk of systemic adverse effects with long-term use. For this reason, it is particularly important to develop alternative routes for drug delivery to the central nervous system that ensure more targeted transport of the active agent to brain tissue (Wu, 2023; Won, 2023; Crowe, 2018; Crowe, 2022; Zhang, 2025; Bhunia, 2023).

Currently, the intranasal route of administration is considered one of the most promising approaches for delivering drugs to the brain. According to current understanding, the transport of compounds following intranasal administration can occur via the olfactory and trigeminal pathways, which allows for partial bypassing of the blood-brain barrier. Recent studies show that this strategy can ensure rapid delivery of pharmacologically active substances to the central nervous system and is of particular interest for the treatment of neurodegenerative, vascular and traumatic brain injuries. However, the efficacy of nose-to-brain delivery varies significantly depending on the properties of the molecule, the composition of the dosage form, and the experimental conditions (Crowe, 2018; Qiu, 2025).

Gel and mucoadhesive dosage forms occupy a special place in the development of intranasal medications. According to some authors, nasal gels can increase the residence time of the drug on the nasal mucosa, reduce mucociliary clearance, and thereby increase the possibility of absorption of the active ingredient (Zhang, 2025; Crowe, 2018; Bhunia, 2023; Qiu, 2025; Alwali, 2026). Recent studies also demonstrate that mucoadhesive and mucus-penetrating systems can improve drug retention in the nasal cavity and facilitate more reproducible delivery to the CNS; however, their advantages must be evaluated in conjunction with indicators of local tolerability and the safety of excipients (Singh, 2013).

With regard to neuroprotective agents, interest in intranasal delivery is further driven by the potential to enhance therapeutic efficacy while reducing the systemic burden on the organism. Recent studies describe the successful use of intranasal administration for the delivery of neurotrophic factors, antioxidant and mitochondria-targeted compounds, insulin, and other candidates for the treatment of CNS diseases and injuries (Manni, 2021; Li, 2022). At the same time, the authors emphasize that the promise of this route of administration does not eliminate the need for a comprehensive toxicological evaluation, especially with regard to the anticipated long-term use of the drug.

From a toxicological perspective, the study of chronic toxicity is of great importance, because it is precisely such studies that allow for the characterization of a drug's safety profile under prolonged repeated administration, the identification of target organs sensitive to toxic effects, the assessment of dose- and exposure-dependent effects, and the establishment of the reversibility or irreversibility of the observed changes (Trakhtenberg, 2020). The EMA guidance on repeated-dose toxicity explicitly states that the primary objective of such studies is to characterize the toxicological profile of a compound following repeated administration, including the identification of target organs, the exposure-response relationship, and the potential reversibility of toxic effects (EMA, 2010; Sewell, 2022).

Our previous studies have shown that Angiolin exhibits significant neuroprotective properties in cases of brain

injury of various origins, combining high efficiency with a favorable safety profile (Belenichev, 2023; Aliyeva, 2024; Aliyeva, 2025). To ensure rapid and effective delivery of the active ingredient to brain tissue, an intranasal gel dosage form was developed, which is of particular interest for use in newborns who have undergone prenatal hypoxia (Belenichev, 2024; Belenichev, 2025). Intranasal delivery of neuroprotective compounds has a compelling pharmacological rationale, and gel mucoadhesive formulations are considered a promising method for enhancing the efficiency of nose-to-brain transport (Patharapankal, 2023; Huang, 2024). At the same time, existing literature and regulatory data indicate the need for a mandatory complex assessment of the chronic toxicity of such drugs, including an analysis of both systemic and local effects (Katare, 2024; Clementino, 2025; Shrewsbury, 2023). In this regard, the study of the chronic toxicity of a 1% nasal gel containing Angiolin is a necessary step in its preclinical assessment and justification of the prospects for further pharmacological investigation.

The aim of the study is to evaluate the chronic toxicity of a 1% Angiolin nasal gel following prolonged administration in the experiment.

Materials and methods. Chronic toxicity studies of a 1% nasal gel containing Angiolin were conducted in accordance with the requirements of Order No. 1803 of the Ministry of Health of Ukraine dated October 25, 2024 "On the Approval of the Procedure for Conducting Preclinical Studies of Medicinal Products" and applicable bioethical standards (European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, 1986; as amended in 1998) and the "General Ethical Principles for Animal Experiments" (Kyiv, 2001). The study protocols and their results were approved by the Bioethics Committee of ZDMFU (No. 7 dated April 20, 2025).

Laboratory animals. The study involved 104 white non-linear rats, comprising 52 males and 52 females, aged 1 month and weighing 100–110 g. For individual experiments, 42 white non-linear rats were used, and for the assessment of immunotoxicity, 32 mature female rats were used. The animals were obtained from Biomodelservice (Kyiv, Ukraine). The animals underwent a 7-day acclimatization period. After a veterinary examination, the animals were housed under standard conditions in polycarbonate cages (5 animals per cage) at a temperature of 20–24 °C, humidity of 30–70%, and a 12/12-hour light-dark cycle. The animals received a standard diet and water ad libitum. Autoclaved alder sawdust was used as bedding.

Chronic toxicity study design. A 1% Angiolin nasal gel was administered intranasally, which corresponded to the intended clinical route of administration and ensured high neuroavailability. The gel was administered twice daily at a dose of 100 mg/kg – twice the conventional therapeutic dose (50 mg/kg) – at 0.25 mL per nostril with a 1-hour interval. The control group received equivalent volumes of gel without the active ingredient. The duration of administration was 180 days, which was in accordance with methodological recommendations for drugs intended for 30-day clinical use. Every day throughout the experiment, the animals were examined, and their general condition, feed and water intake, and the condition of their coat and mucous membranes were recorded. To conduct these studies, animals in each group (n = 21) were randomized into 3 subgroups of 7 animals each. In the first subgroup, parameters were measured 60 days after drug administration; in the second, 90 days; and in the third, 180 days. Body weight, behavioral responses, cardiovascular parameters, and biochemical, hematological, and urinary parameters were assessed. In animals of the last subgroup, organ samples were also taken for histological examination at the end of the experiment on day 180.

Behavioral and functional methods. Motor and emotional activity were assessed using the "Open Field" test, recording horizontal and vertical motor activity, grooming, the number of boluses, and exploratory activity during 3 minutes. Cardiac function was assessed by electrocardiography on day 180 in II standard lead, with evaluation of PQ, QRS, QT, and RR intervals using the CardioLab system.

Biochemical and hematological studies. Biochemical blood serum studies were performed on a BioChem SA analyzer. Total protein, creatinine, ALT, AST, and alkaline phosphatase activity, as well as glucose levels, were determined using standard methods on days 60, 90, and 180. Hematological tests included the assessment of erythrocytes and leucocytes counts, hemoglobin, erythrocyte sedimentation rate (ESR), and hematocrit using standard methods on days 60, 90, and 180.

Histological studies. Organs were fixed in 10% neutral formalin, subjected to standard processing, embedded in paraffin, stained (hematoxylin-eosin), and analyzed microscopically.

Assessment of immunotoxicity. The immunotoxic effects of the drug were evaluated based on the weight and cellularity of lymphoid organs, hematological parameters, and indicators of humoral and cellular immune responses in rats with normal immune status and in rats with cyclophosphamide-induced secondary immunodeficiency. The drug was administered intranasally at a dose of 100 mg/kg for 14 days; control animals received a gel base without the active ingredient.

After 90 days of drug administration, changes in a number of behavioral parameters were observed. In particular, animals receiving 1% Angiolin gel showed a statistically significant increase in horizontal motor activity, as evidenced by a higher number of crossed squares compared to the control group. At the same time, an increase in the number of standing postures was recorded, indicating activation of vertical motor activity. A tendency toward increased exploratory activity, assessed by the "burrow reflex" indicator, was also noted. The emotional component of behavioral responses was characterized by an increase in the number of grooming acts compared to the control group, which may indicate a decrease in anxiety levels in the animals.

According to the presented results, by the end of the observation period, no significant negative changes in behavioral indicators were detected following the administration of 1% Angiolin nasal gel. The horizontal and vertical motor activity of the animals remained comparable to control values. At the same time, exploratory activity as measured by the "burrow reflex" was higher compared to the control group, and the number of grooming acts also increased, indicating a continued trend toward enhancement of the exploratory component of behavior and a reduction in anxiety.

Thus, prolonged (180-day) intranasal administration of 1% Angiolin gel at a dose of 100 mg/kg does not have a negative effect on the animals' motor activity. On the contrary, the results obtained indicate a beneficial effect of the drug on the emotional and behavioral responses of the animals, as evidenced by increased exploratory activity and reduced anxiety.

Study of cardiac bioelectrical activity parameters in rats following administration of 1% Angiolin gel. Analysis of electrocardiographic parameters demonstrated that during a course of intranasal administration of 1% Angiolin gel during 180 days, no significant changes in myocardial bioelectrical activity were observed in the experimental animals (Table 3).

It was found that the drug had no effect on the main parameters of the cardiac conduction system. In particular, no changes were observed in the PQ interval, which reflects the speed of electrical conduction through the atrioventricular junction, or in the QRS interval, which characterizes ventricular depolarization. QT interval parameters, reflecting ventricular depolarization and repolarization processes, also remained stable compared to the control group.

Analysis of the RR interval and heart rate indicated that the study drug had no effect on cardiac rhythm. The amplitude characteristics of the P and R waveforms did not differ from control values, indicating the preservation of normal electrical activity in the atria and ventricles.

The data obtained indicate the absence of disturbances in myocardial bioelectrical activity during prolonged intranasal administration of 1% Angiolin gel. The maintenance of stable ECG parameters indicates the absence of a negative effect of the drug on the functional state of the cardiovascular system.

Peripheral blood parameters dynamics during 180-day administration of 1% Angiolin gel. Prolonged intranasal administration of 1% Angiolin gel for 180 days was not accompanied by statistically significant changes in hematological parameters compared with the control group (Table 4). The levels of erythrocytes, leukocytes, hemoglobin, erythrocyte sedimentation rate, hematocrit, and maximal erythrocyte resistance were within the physiological range. The small fluctuations observed in individual parameters were not statistically significant and were likely due to the natural variability of hematopoietic processes.

Analysis of the leukocyte differential count (Table 4) also revealed no significant differences between the experimental and control groups. The ratio of major leukocyte populations, including lymphocytes, monocytes, eosinophils, segmented and band neutrophils, remained within physiological ranges. The minor deviations observed in the quantitative ratio of individual leukocyte morphological forms were not statistically significant and did not indicate the development of inflammatory, allergic, or toxically induced changes in the hematopoietic system.

Thus, 180-day intranasal administration of 1% Angiolin gel at a dose of 100 mg/kg does not affect the morphological composition of peripheral blood and does not cause disturbances in the hematopoietic system in experimental animals.

Morphological assessment of the condition of organs and tissues. Macroscopic examination revealed no pathological changes in the animals following

Table 3

Changes in cardiac bioelectrical parameters following intranasal administration of 1% Angiolin gel on day 180

	ECG intervals, ms				Waveform amplitude, mV		Heart rate
	PQ	QRS	Q-T	RR	P	R	
Control	45,0 ± 1,36	16,0 ± 0,73	81,0 ± 0,68	142,0 ± 5,30	0,08 ± 0,018	0,51 ± 0,027	427,2 ± 19,35
Angiolin Gel 100 mg/kg	43,0 ± 1,53	16,3 ± 0,91	80,0 ± 0,52	139,0 ± 3,96	0,05 ± 0,005	0,52 ± 0,063	433,3 ± 12,66

Table 4

Dynamics of changes in peripheral blood parameters in experimental rats after nasal administration of 1% Angiolin gel during 180 days

Indicator	Groups (N=7)	
	Control	Angiolin Gel 100 mg/kg
Erythrocytes, g/L	5,48 ± 0,24	4,95 ± 0,13
Leukocytes, g/L	6,45 ± 0,81	5,65 ± 0,52
Hb, g/L	129,0 ± 1,32	130,7 ± 2,46
ESR, mm/h	4,17 ± 0,54	3,83 ± 0,70
Hematocrit, %	37,0 ± 0,82	38,5 ± 1,09
Max. resistance, %	0,35 ± 0,01	0,36 ± 0,01
Lymphocytes, %	42,7 ± 3,95	50,7 ± 2,67*
Monocytes, %	4,50 ± 0,56	2,83 ± 0,60
Eosinophils, %	2,83 ± 0,54	2,33 ± 0,55
Segmented neutrophils, %	49,0 ± 4,07	45,2 ± 3,23
Band neutrophils, %	1,17 ± 0,31	0,33 ± 0,21*

Note: * – differences are significant $p < 0.05$ in relation to the control group.

Normal physiological values for white rats: erythrocytes 4.31–11 g/L, leukocytes 5–25.6 g/L, hemoglobin: 120–192 g/L, Westergren ESR at 1 hour: 2.5–6 mm, hematocrit: 35–55%, maximum erythrocyte resistance: 0.34–0.36% NaCl.

180 days of intranasal administration of 1% Angiolin gel. The meninges and brain tissue, as well as the organs of the thoracic and abdominal cavities and the pelvis, exhibited normal anatomical characteristics, with no signs of inflammation, edema, or destructive changes. The gastric mucosa remained intact, without erosive or ulcerative lesions. The relative weights of the liver, spleen, lungs, heart, and kidneys in animals receiving 1% Angiolin gel did not differ significantly from control values (Table 5).

Table 5

Relative weight of internal organs in rats after 180 days of intranasal administration of Angiolin gel (M + m)

Organs (g/100 g body weight)	Groups (N = 7)	
	Control	Angiolin Gel 100 mg/kg
Liver	3,5 ± 0,08	3,6 ± 0,10
Spleen	0,48 ± 0,019	0,46 ± 0,014
Lungs	0,49 ± 0,014	0,46± 0,020
Heart	0,37 ± 0,020	0,44 ± 0,020
Kidneys	0,43 ± 0,016	0,38 ± 0,013

Microscopic examination confirmed that the morphological structure of the internal organs was unchanged. In the kidneys, the normal architecture of the cortex and medulla was preserved; the glomeruli and tubules had a typical structure. In the liver, the overall trabecular structure was preserved, and there were no signs of inflammatory infiltration. No dystrophic changes in cardiomyocytes were detected in the myocardium. The gastric mucosa showed no signs of inflammation, atrophy, or destruction. No pathological changes were detected in the brain tissue; only mild perivascular edema was noted. In the lung tissue, moderate changes were observed in the form of thickening of the interalveolar septa and hyperemia of the vessels, without pronounced inflammatory or destructive processes. The structure of the spleen was normal, with the ratio of red to white pulp preserved.

Thus, the results of the morphological study indicate the absence of toxic effects of 1% Angiolin gel following 180 days of intranasal administration at a dose of 100 mg/kg.

Study of the immunotoxic properties of 1% Angiolin gel. An assessment of the immunotropic activity of 1% Angiolin gel showed that the drug exerts a modulatory effect on parameters of specific immunity both in the presence of normal immune status and under conditions of cyclophosphamide-induced immunosuppression.

It was established that cyclophosphamide administration was accompanied by a statistically significant decrease in the weight of the thymus and spleen, their mass coefficients, as well as the number of lymphoid cells in these organs compared to the control (Table 6). When 1% Angiolin gel was administered to intact animals, a tendency toward an increase in the mass and cellularity of lymphoid organs was observed without signs of immune system inhibition. The use of Angiolin gel in the presence of cyclophosphamide contributed to a partial restoration of these parameters, indicating its immunomodulatory effect.

Analysis of peripheral blood parameters showed that cyclophosphamide caused leukopenia, a decrease in the relative lymphocyte count, and an increase in the neutrophil percentage. The use of Angiolin gel in combination with cyclophosphamide was accompanied by normalization of these parameters and their convergence toward the values of the control group. The obtained results indicate the drug's regulatory effect on the cellular composition of peripheral blood under conditions of immunodeficiency.

When evaluating the humoral immune response, it was found that 1% Angiolin gel at a dose of 100 mg/kg, in animals with initially normal immune status, did not significantly alter antibody production. At the same time, under conditions of cyclophosphamide-induced imunodeficiency, the drug significantly increased the number of lymphoid cells in the spleen, the concentration of antibody-producing cells, and the total number of antibody-producing cells compared

to the group receiving only cyclophosphamide. This indicates a reduction in the imunodepressive effect of the cytostatic agent and stimulation of the functional activity of B-lymphocytes (Table 7).

A study of the cell-mediated immune response in a delayed-type hypersensitivity reaction showed that cyclophosphamide significantly reduced the severity of the local inflammatory response. Administration of Angiolin gel to animals with normal immune status, as well as after cyclophosphamide administration, was accompanied by an increase in the paw weight difference and the DTH index. This indicates a stimulating effect of the drug on the cellular component of immunity (Table 8).

Thus, 1% Angiolin gel possesses significant immunomodulatory properties, manifested in the normalization of parameters of lymphoid organs, restoration of the cellular composition of peripheral blood, and stimulation of humoral and cell-mediated immune responses in conditions of cyclophosphamide-induced immunological deficiency.

Conclusions. Based on the combined behavioral, physiological, hematological, biochemical, and

Table 6

Morphological parameters of lymphoid organs and peripheral blood in rats after administration of Angiolin gel (n = 8)

Indicator		Control	Cyclophos-phamide	Angiolin gel	Angiolin gel + Cyclo-phosphamide
		0,2 ml/ 0,9% NaCl	150 mg/kg	100 mg/kg	100 + 150 mg/kg
Thymus	Mass, mg	36,8 ± 2,22	30,01 ± 2,62*	38,5 ± 2,11#	33,5 ± 1,82
	Mass coeff.	1,78 ± 0,09	1,42 ± 0,10*	1,89 ± 0,06#	1,59 ± 0,11
	Lymphoid cells (10^6)	151,3 ± 4,96	120,1 ± 5,33*	172,1 ± 5,36#	149,4 ± 5,82#
Spleen	Mass, mg	195,5 ± 6,21	144,0 ± 5,34*	226,3 ± 8,11#	172,5 ± 5,33#
	Mass coeff.	8,02 ± 0,35	6,1 ± 0,31*	8,36 ± 0,58	6,89 ± 0,30
	Lymphoid cells (10^6)	206,4 ± 10,53	158,5 ± 6,12*	228,1 ± 7,67#	178,4 ± 10,1
Peripheral blood	Leukocytes, $\times10^9$/L	7,0 ± 0,4	5,7 ± 0,2*	6,9 ± 0,4#	6,1 ± 0,3
	Neutrophils, %	21,7 ± 4,8	42,5 ± 0,8*	27,4 ± 5,8	33,7 ± 4,9#
	Lymphocytes, %	76,5 ± 4,7	57,2 ± 4,1*	67,8 ± 3,2*	63,3 ± 2,0#
	Monocytes, %	1,1 ± 0,4	0,6 ± 0,2*	2,1 ± 0,5	1,6 ± 0,7#
	Eosinophils, %	0,8 ± 0,3	1,1 ± 0,1*	1,9 ± 0,5*	1,5 ± 0,3

Note: * – statistically significant compared to control animals, $p < 0.05$;

– statistically significant compared to animals that received a cyclophosphamide injection.

Table 7

Number of antibody-producing cells (APC) in the spleen of rats administered Angiolin gel after cyclophosphamide injection

Groups	Dose	Number of lymphoid cells in the spleen, $\times10^6$	APC concentration in the spleen, $\times10^6$	Number of APCs in the spleen, $\times10^3$
Control	0,2 ml/ 0,9% NaCl	224,9 ± 9,3	229,4 ± 8,2	195,1 ± 8,5
Cyclophos-phamide	150 mg/kg	143,3 ± 6,2*	305,1 ± 7,5	75,2 ± 5,2*
Angiolin gel	100 mg/kg	212,2 ± 8,5	207,3 ± 7,1	187,3 ± 6,2
Angiolin gel + Cyclo-phosphamide	100 mg/kg + 150 mg/kg	178,1 ± 5,5#	274,5 ± 6,3#	121,2 ± 5,8#

Note: * – statistically significant compared to control animals, $p < 0.05$;

– statistically significant compared to animals that received a cyclophosphamide injection.

Table 8

Delayed-type hypersensitivity reaction index in rats after cyclophosphamide administration and use of Angiolin gel

Groups	Dose	Paw mass difference, mg	DTH index, %
Control	0,2 ml/ 0,9% NaCl	9,38 ± 0,46	9,91 ± 0,34
Cyclophos-phamide	150 mg/kg	5,52 ± 0,32*	5,67 ± 0,41*
Angiolin gel	100 mg/kg	11,61 ± 0,21*	10,15 ± 0,45
Angiolin gel + Cyclo-phosphamide	100 mg/kg + 150 mg/kg	7,92 ± 0,47#	7,54 ± 0,21#

Note: * – statistically significant compared to control animals, $p < 0.05$;

– statistically significant compared to animals that received a cyclophosphamide injection.

morphological results, it was established that 180 days of intranasal administration of 1% Angiolin gel at a dose of 100 mg/kg, which is two times higher than the therapeutic dose, does not cause structural or functional disorders. The drug did not exhibit hepatotoxic, nephrotoxic, cardiotoxic, or immunotoxic effects, and under conditions of cyclophosphamide-induced imunodeficiency, it demonstrated immunomodulatory properties. The obtained results indicate a high safety profile of 1% Angiolin gel in long-term use.

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