

Article

STUDYING THE PHARMACOKINETICS OF GENTAMYCIN IN RATS WITH LYMPHOTROPIC PRETRACHEAL AND INTRAMUSCULAR INTRODUCTION

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Аннотация. The article is devoted to an experimental study of the pharmacokinetics of gentamicin in rats with lymphotropic pretracheal and intramuscular routes of administration. Data on the concentration of the antibiotic in the blood and tissues of the respiratory organs of rats in dynamics are given, it is shown that the method of lymphotropic pretracheal administration provides higher concentrations of the antibiotic in comparison with the intramuscular method. The high therapeutic efficiency of this method can be achieved due to the presence of connections between the lymphatic system, as well as organs and tissues. This circumstance allows you to deliver the drug to the affected organ directly. In addition, in the case of lymphotropic therapy in the focus, the optimal concentration of the drug is maintained for 24 hours. So there is no need for frequent administration of the drug (for example, with antibiotic therapy), you can reduce the course and daily doses of drugs. The drug, which is administered lymphotropically, is not able to have a toxic effect on the intestines, kidneys, liver, since only a tiny part of the drug enters the bloodstream.

Key words: gentamicin, method of lymphotropic pretracheal administration, intramuscular administration, concentration, focus, optimal concentration.

Introduction. The issues of prophylactic antibiotic therapy remain very relevant and far unresolved. Some authors point out the need for prophylactic antibiotic therapy when the risk of developing a purulent-septic process is high, S.M. Navashin and I.P. Fomina believe that prophylactic antibiotic therapy in surgery is indicated in the following cases: operations in obviously infected areas (on the gastrointestinal tract), general infection before surgery, weakening of the body's defenses.

The success of antibiotic therapy depends not only on the activity of the drugs and the sensitivity of microorganisms to them, but also on the duration of the preservation of the therapeutic concentration of antibiotics in the affected tissue and on the path of infection. First of all, this applies to the lymphatic system [1, 4, 9, 5]. Despite this, in the literature, there are

quite rare reports on the content of antibiotics in the lymphatic system of the organs of the chest cavity, and very few researchers pay attention to this issue [2, 6, 8]. This state of affairs has its own explanation, connected with the difficulties of obtaining lymph for research, not only in patients, but also in experimental animals.

Recommended in clinical practice schemes of intramuscular and intravenous antibiotic therapy [3,7] do not allow to create a sufficient and long-term concentration of the drug in the lymphatic system of the lungs [2, 10].

The question of the spread of antibiotics in lymph nodes regional in relation to the affected organ with traditional methods of administering antibiotics. There are only a few reports in the literature on this subject, although this issue is of fundamental importance due to the fact that it is the regional lymph nodes that are the first «biological filter» on the path of the spread of microbes and, under certain conditions, can themselves become a source of infection.

Among other reasons for the ineffectiveness of antibiotic therapy, the authors point to the erroneously chosen route of administration of drugs into the body, as well as their overdose, which leads to a general toxic and negative effect of antibiotics on individual organs and systems. Due to the decrease in the activity of antibiotics to achieve a therapeutic effect in recent years, many clinicians are forced to increase the doses of administered drugs to a critical level, which leads to an increase in undesirable side effects, such as allergic reactions, ranging from skin lesions to anaphylactic shock and occurring from 0,3 to 4,8%. The defeat of the central nervous system is noted in 1-10% of cases. Often there is toxic damage to internal organs: liver, kidneys, gastrointestinal tract - in 2.4% of cases, manifestations of «dysbacteriosis» and «superinfection» [8, 2]. The influence of large doses of antibiotics on the body's defenses by inhibiting immunogenesis has been proven [5].

Thus, summarizing the above literature data, we can assume that among the reasons for the insufficiently high efficiency of antibiotic therapy, the circumstance is important that with traditional methods of administering antibiotics, it is often not possible to achieve a therapeutic effect due to the limitation of the spread of drugs in the affected tissues and biological media of the body, in particular in the lymph. This causes the lack of sufficient contact between the antimicrobial drug and microorganisms, which leads to the emergence of antibiotic-resistant microbes and an increase in antigenic irritation from bacteria. It is also important that with the above methods of antibiotic therapy, the drug is quickly excreted from the body, which obliges frequent injections of antibiotics to maintain their therapeutic concentration in the blood, tissues and biological media. All this leads to the need to increase the doses of administered antibiotics and the frequency of injections, increasing the risk of side effects of antibiotic therapy.

According to a number of authors [5, 2], possible directions in the search for ways to increase the effectiveness of antibiotic therapy are to find ways to increase the concentration of antibiotics in affected tissues and environments, as well as to develop new routes of administration of drugs (endolymphatic, lymphotropic, regional, et c.), taking into account the laws spread of infection in the body.

The study of the lymphatic tracts of the lungs, liver, heart, appendix,

gallbladder in pathological conditions, carried out by the authors [3, 10], made it possible to identify compensatory changes in the lymphatic system common to all these organs, despite the fact that these organs are different, with point of view of blood circulation, systems. With inflammation of these organs, an active restructuring of the structure of the lymphatic tract occurs, the degree of which depends on the stage, form and activity of the pathological process. In the initial period of inflammation, there is a general, relatively uniform expansion of the lymphatic capillaries and vessels of all orders with a quantitative and qualitative increase in outgrowths on their walls. This leads to an increase in the capacity of the lymphatic system and the creation of conditions for the removal of an increased volume of lymph. Along with the functional reaction, a regenerative-compensatory morphological restructuring of the lymphatic system is always found, which manifests itself in the neoplasm of lymphatic vessels and capillaries, intercalary lymph nodes. New collector paths of lymph outflow appear in the form of separate, independent single, atypically located lymphatic vessels. In this case, the physiological flow of lymph from the organs to the thoracic duct may change and lymph flow occurs. The formation of lymphatic flow is important for understanding the mechanisms of endolymphatic antibiotic therapy. There are new collector ways of outflow of lymph in the form of separate, independent single, atypically located lymphatic vessels. In this case, the physiological flow of lymph from the organs to the thoracic duct may change and lymph flow occurs. The formation of lymphatic flow is important for understanding the mechanisms of endolymphatic antibiotic therapy. There are new collector ways of outflow of lymph in the form of separate, independent single, atypically located lymphatic vessels. In this case, the physiological flow of lymph from the organs to the thoracic duct may change and lymph flow occurs. The formation of lymphatic flow is important for understanding the mechanisms of endolymphatic antibiotic therapy.

Collector lymphatic vessels play an important role in limiting inflammation. And for them, as well as for lymphatic capillaries, structural and functional changes are characteristic. Already in the early stages of inflammation, swelling of the endothelium, the opening of interendothelial connections, and the expansion of the lumen of the lymphatic vessels due to their overflow with lymph are noted. These phenomena contribute to the alteration of the vascular endothelium in the form of a catarrhal process, which leads to active endothelial cells, which acquire the functions of macrophages. A number of authors indicate that infection directly into the lymphatic system contributes to the immune response through the functional activation of lymphoid tissue [1, 3, 7]. However, under conditions of increased virulence of microbes, lymphatic vessels are involved in the inflammatory process with the formation of lymphangiitis. Thus, in the lymphatic capillaries and collector lymphatic vessels during inflammation, there is a similar functional response and compensatory morphological restructuring.

The presentation of the function of the lymphatic system of the lungs in the dynamics of the inflammatory process would not be complete if we did not dwell on the role of the lymph nodes. Lymph nodes are a biological filter. They are located in several orders along the collector lymphatic vessels, which ensures the obligatory passage of lymph through them,

and only then the lymph flows into the thoracic duct and bloodstream.

The main part of the lymph from the right and left lungs flows into the paratracheal lymph nodes, which serve as a rather powerful collector that receives lymph from the lungs. That is why these lymph nodes should serve as the place of application of lymphotropic regional antibiotic therapy. In addition, the paratracheal lymph nodes are the most accessible for regional lymphatic therapy. Thus, the lymphatic system of the lungs is important in the development and course of the inflammatory response. The spread of infection along the lymphatic channel dictates the need for the introduction of antibiotics precisely in lymphatic system in order to prevent and treat bronchopulmonary bacterial complications.

From the point of view of rationality and economy in choosing the place of application of microcirculation correctors, antibacterial agents and in order to create a more pronounced regional tropism, S.U. Dzhumabaev et al. a method of pretracheal lymphatic therapy was developed, in which the drug is administered by puncture or catheterization of the pretracheal tissue on the anterior surface of the neck above the jugular notch. In experimental studies on the introduction of the dye by this method, the authors showed that it easily spreads down the fiber, washing the main groups of lymph nodes that are around the trachea and bronchi. They also successfully use the method in the prevention and treatment of postoperative pulmonary complications associated with circulatory disorders (edema) and inflammation.

However, there are also a number of unresolved issues, in particular, the pharmacokinetics of antibiotics with lymphotropic administration by this method has not been studied, there is no data on their distribution in blood, regional lymph nodes and tissues. The optimal place of the method of pretracheal lymphotropic administration of antibiotics among the existing methods has not been finally determined.

Methods. Experimental studies consisted of two stages. The first stage consisted in solving a particular experimental problem. It consisted of a single administration of gentamicin to outbred white rats by one of the studied methods - pretracheally and intramuscularly - followed by a thoracotomy undertaken to remove the organs of the chest cavity, paratracheal lymph nodes and puncture the femoral vein for blood sampling. The second stage consisted in determining the concentration of gentamicin in the blood and removing tissues for the preparation of a homogenate.

Gentamicin was administered once to rats at a dose of 30 mg/kg. The experiments were carried out on 50 outbred white rats of both sexes weighing 190-230 g. Two series of experiments were carried out.

In the first series of experiments, 25 rats were pretracheally injected with lidase at a dose of 0.1 U/kg to create conditions for lymphotropism. 3-5 minutes after the injection of lidase, the needle was pulled up by 0.5 cm and gentamicin was administered once at a dose of 30 mg/kg. In the second series of experiments, gentamicin was administered intramuscularly to 25 rats once at the same dose along the anterolateral surface of the hind paw. This group of animals served as a control, with the aim of studying the distribution of gentamicin in the traditional intramuscular method of administration.

To determine the concentration of gentamicin, blood sampling in a

volume of 1-5 ml and pieces of organ tissues were performed 1, 3, 5, 8, 24 hours after the administration of the antibiotic.

At the specified time, 25 animals were slaughtered in both groups, from which tissues of the paratracheal lymph nodes, trachea with bronchi, lungs, pleura and blood were taken.

The concentration of gentamicin in the blood and supernatant of the tissue homogenate was determined by agar diffusion.

Results. Analysis of the dynamics of the concentration of gentamicin with a single pretracheal lymphotropic injection at a dose of 30 mg/kg of body weight showed that the maximum concentration of the antibiotic in the blood and tissues of the respiratory organs is observed after 1 hour, as with the intramuscular route of administration, regardless of prior lymphostimulation with lidase. So, in the blood serum, the concentration of the antibiotic was $40,9 \pm 0,49$ mcg /ml after 1 hour, and after 3 hours it remained at the level of $25,9 \pm 0,49$ mkg/ml. By the end of the day, the antibiotic concentration decreased to a level equal to $0,036 \pm 0,002$ mkg / ml. The concentration area under the curve in this case was $15,2 \text{ cm}^2$ (Fig. 1.).

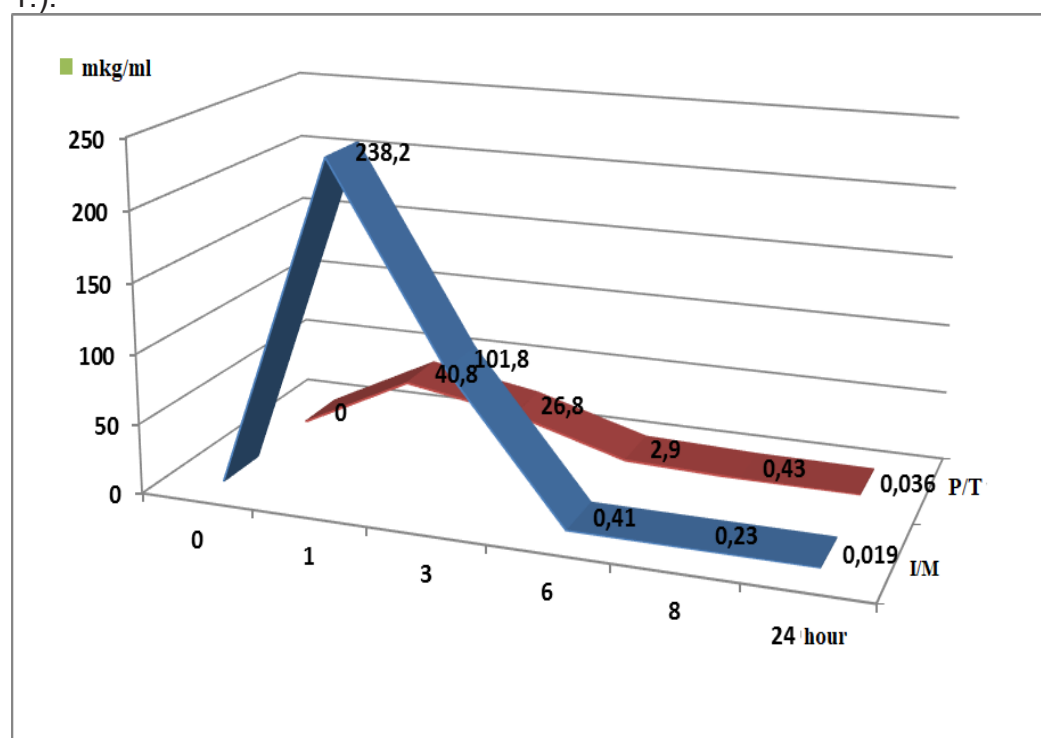


Fig.1. Dynamics of the concentration of gentamicin in the blood after a single pretracheal lymphotropic and intramuscular administration

In the tissues of the paratracheal lymph nodes, the maximum concentration of gentamicin after an hour was $90,5 \pm 12,4$ mkg/mg, after 3 hours there is a decrease in the concentration of the antibiotic, amounting to $56,3 \pm 8,4$ mkg/mg, then during the day the concentration decreases evenly, after 24 hours it was $3,6 \pm 0,19$ mkg/mg. The total area under the curve with pretracheal lymphotropic injection was 41 cm^2 (Fig. 2.).

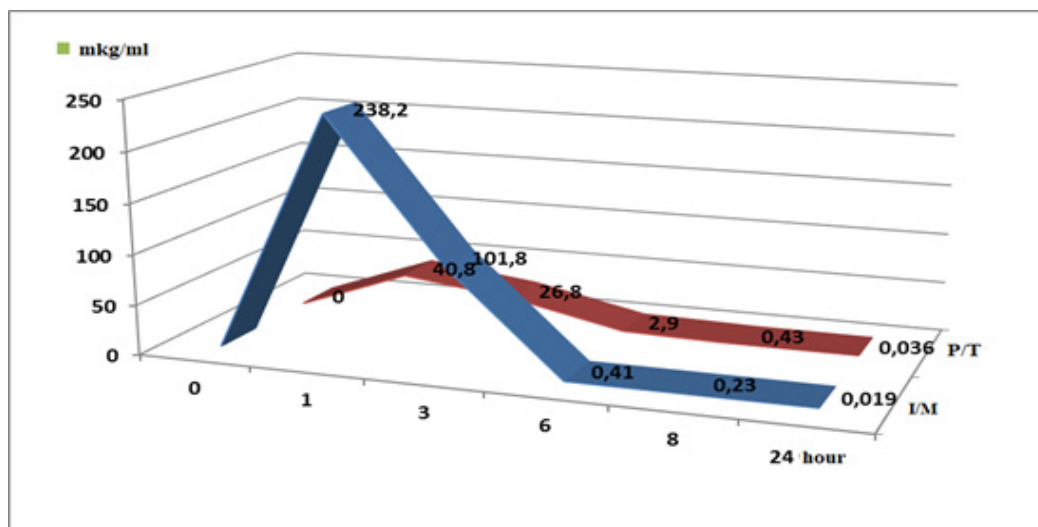


Fig.2. Dynamics of gentamicin concentration in paratracheal lymph nodes after a single pretracheal lymphotropic and intramuscular administration.

In the tissues of the trachea and bronchi, the maximum concentration of gentamicin after 1 hour is $80,3 \pm 10,5$ mkg/mg, after 3 hours the content of gentamicin decreases to $72,4 \pm 9,3$ mkg/mg. During the day, there is a uniform decrease in the level of the antibiotic and after 24 hours its content remains at the subtherapeutic level and is equal to $4,9 \pm 0,3$ mkg/mg. In graphical analysis, the concentration area under the curve was $47,0$ cm² (Fig. 3.).

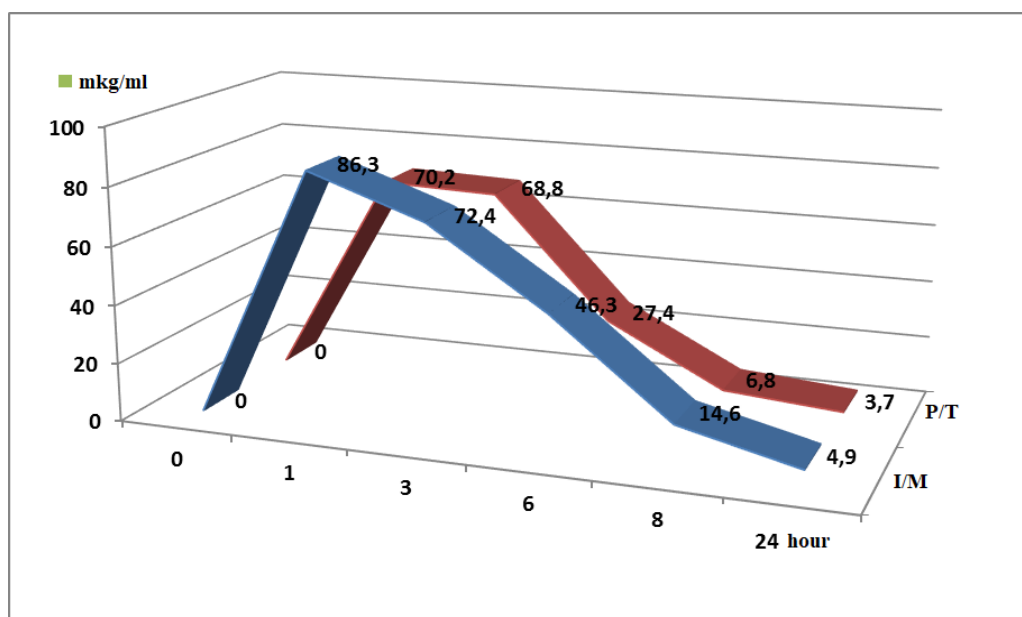


Fig.3. Dynamics of gentamicin concentration in the trachea and bronchi after a single pretracheal lymphotropic and intramuscular administration.

In the lungs with pretracheal lymphotropic administration, the content

of gentamicin after 1 hour was $102,4 \pm 13,3$ mkg / mg, decreasing after 3 hours to a level of $53,3 \pm 3,3$ mkg /mg. During the day, its concentration decreases smoothly, after 24 hours it was equal to $9,8 \pm 0,44$ mkg /mg. With a graphical representation, the area under the curve was $50,9 \text{ cm}^2$ (Fig. 4.).

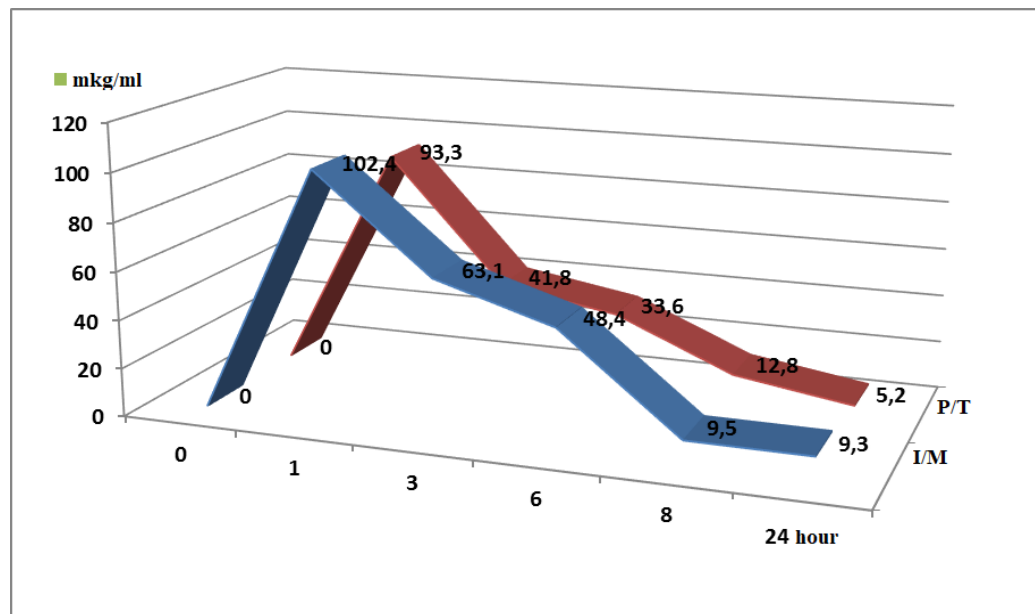
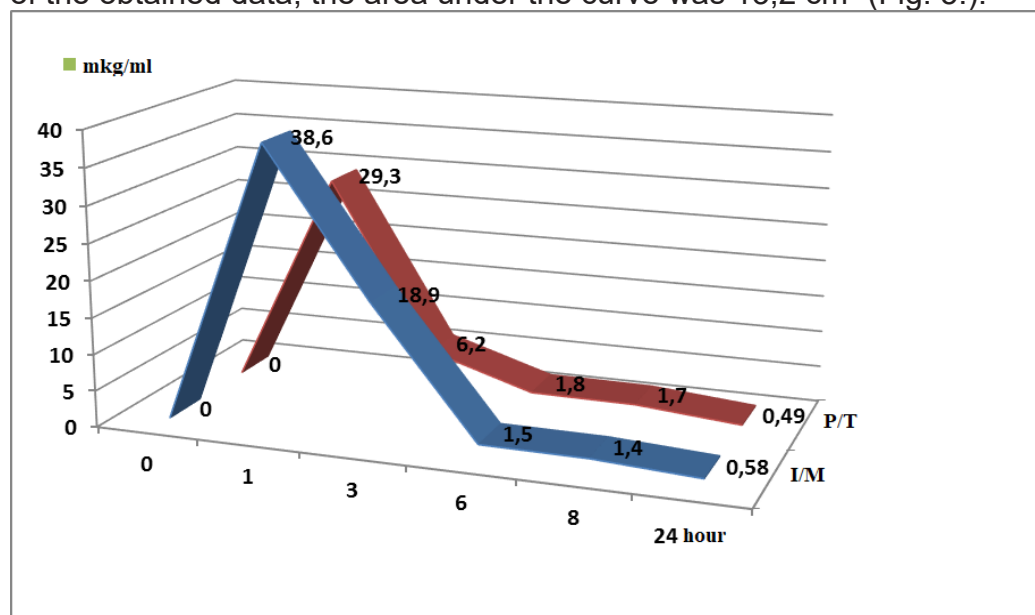


Fig.4. Changes in the concentration of gentamicin in the lung tissue after a single pretracheal lymphotropic and intramuscular administration.

In the pleural tissue, the antibiotic content after 1 hour was $38,6 \pm 3,2$ mkg / mg, after 3 hours its concentration decreased to $18,9 \pm 0,9$ mkg / mg, and during the day the concentration of gentamicin with both methods of administration was approximately the same values, equaling $0,58$ mkg / mg after 24 hours with pretracheal administration. In the graphical analysis of the obtained data, the area under the curve was $13,2 \text{ cm}^2$ (Fig. 5.).



From the above data of experimental studies, it follows that higher concentrations of the drug in the above biological substrates are provided

with the lymphotropic pretracheal route of administration of gentamicin compared with the intramuscular route of administration. To illustrate this, we present a table of comparative dynamics of the concentration of gentamicin in the studied substrates after a single intramuscular and pretracheal administration in the same dose.

Table 1

biological substrate		The concentration of gentamicin in blood serum (mcg/ml) and tissues (mcg/mg) with a single intramuscular and lymphotropic pretracheal injection at a dose of 30 mg/kg				
		1	3	5	8	24
		time after administration (h)				
Blood	in	238,2±18,2	101,8±7,8	0,41±0,06	0,23±0,02	0,019±0,004
	l	40,9±0,49	25,6±0,49	2,9±0,1*	0,43±0,1	0,036±0,002
paratracheal nodes	in	35,5±1,2	26,8±0,2	7,4±0,2	5,1±0,49	1,4±0,12
	l	90,5±12,4*	56,3±8,4*	13,9±1,2*	6,7±1,02*	3,6±0,19*
trachea bronchi	in	70,2±7,3	68,8±10,1	27,4±0,5	6,5±0,1	3,7±0,2
	l	80,3±10,5*	72,4±9,3*	45,3±2,4*	14,6±0,7*	4,9±0,3
Lungs	in	93,3±3,2	41,8±2,3	33,5±0,6	12,8±1,2	5,2±0,46
	l	102,4±13,3*	53,3±3,3*	48,9±0,5*	20,1±1,2*	9,8±0,44*
Pleura	in	23,9±0,49	6,2±0,49	1,8±0,19	1,7±0,22	0,48±0,05
	l	38,6±3,2*	18,9±0,9*	1,5±0,12	1,4±0,1	0,58±0,05

Note: v-intramuscular, l-lymphotropic method: *-significantly different values for the compared routes of administration (P<0.05).

For a more complete and visual representation of the kinetics of the antibiotic in the blood and tissues, it is advisable to conduct a comparative analysis of the concentrations obtained with the lymphotropic pretracheal and intramuscular routes of administration. An analysis of the distribution of gentamicin in the blood of white rats with various routes of administration shows that the intramuscular route of administration (traditional) creates the maximum peak concentration, among other indicators, during the first hour, but by 3 hours there is a decrease in the concentration of the antibiotic by more than 2 times from the initial value. And after 5 hours, the intramuscular method does not provide a therapeutic concentration of the drug in the blood. If the peak concentration of gentamicin in the studied media after 1 hour is conditionally taken as 100%, then its concentration in the blood by the 3rd hour decreased by 57,3%, and by the 5th hour, amounting to 0,17%, decreased by more than 99%. With the lymphotropic method of administration, the highest concentration also falls on the period of the first hour, which indicates a relatively rapid absorption of the drug in a sufficiently high concentration into the blood, despite the swelling of the pretracheal tissue created by the use of lidase as a lymphatic drainage stimulator. The dynamics of the concentration of gentamicin in the blood after lymphotropic administration after 3 hours decreased by 37,4%, by 5 hours - by 93%, by 8 hours - by 99%. Data on the content of gentamicin in the blood for both methods of administration after 24 hours are almost identical. This dynamics indicates that after 5 hours the content of the antibiotic with the lymphotropic method of administration remains at a

subtherapeutic level of 2,9-0,1 mkg /ml, which is 7 times higher than the corresponding indicator obtained with intramuscular injection. In a graphical representation, the concentration curve for lymphotropic administration is smoother than for intramuscular administration. After 24 hours, with both methods of administration, only "traces" of the antibiotic remain in the blood, and with lymphotropic administration, it is approximately 2 times higher than that with intramuscular administration.

And (&) Discussion. Analyzing the data of experimental studies on the content of gentamicin in the blood, it can be said that the pretracheal lymphotropic method of antibiotic therapy using a single dose of 30 mg/kg in rats provides, compared with intramuscular administration, although not high, but more stable and long-term maintenance of blood saturation.

Comparison of the content of gentamicin in the paratracheal lymph nodes with different methods of administration showed that the highest concentration is created after 1 hour with lymphotropic pretracheal administration, amounting to $90,5 \pm 12,4$ mkg/mg versus $35,5 \pm 1,2$ mkg /mg intramuscularly. After 3 hours, the content of the drug with intramuscular injection, amounting to 75% of the peak concentration, respectively, was lower than the corresponding indicator for lymphotropic administration by more than 2 times. In the future, during the day, this trend continues, there is a sharp decrease in the content of the antibiotic when administered intramuscularly. After 5 hours, it decreases by 3,5 times, and during this period, with lymphotropic administration, the concentration of the drug is 1,8 times higher than that with intramuscular administration. The content of the drug in the lymph nodes obtained with lymphotropic administration after 8 hours is 1,3 times higher than that with intramuscular injection. After 24 hours, the lymphotropic concentration is 2,5 times higher than that with intramuscular administration of gentamicin.

Thus, lymphotropic pretracheal administration of an antibiotic showed that this method makes it possible to create in the paratracheal lymph nodes relatively more and long-term concentrations of the drug, which remain at the therapeutic and subtherapeutic levels during the day.

As for the pharmacokinetics of gentamicin in the respiratory organs, in the tissues of the trachea and bronchi in the first hour after lymphotropic administration, the concentration obtained is higher than with intramuscular administration by 16,1 mkg/mg (18,7%). After 5 hours, the intramuscular content of the drug decreases by more than 2,5 times, while it is also more than 2 times lower than the corresponding content of gentamicin in the trachea obtained with lymphotropic administration. In the future, the concentrations obtained with intramuscular injection after 8 and 24 hours are several orders of magnitude lower than those obtained with lymphotropic administration. The graphical analysis also shows that the concentration curve for the lymphotropic route of administration is smoother and more uniform. The total area of concentration under the curve with lymphotropic administration is 33,2% higher than that with intramuscular administration of the antibiotic.

In lung tissues, the maximum concentration after 1 hour with lymphotropic administration is higher than that with intramuscular administration by 8,9%, the content of the antibiotic after 3, 5 and 8 hours with lymphotropic administration is also higher than with intramuscular administration, respectively, by 21,6, 31,5 and 42,7%. Further, after 24

hours, the difference in the content of the antibiotic in the tissues of the lungs with the compared methods of administration is significant. It is almost 2 times higher with lymphotropic administration of the corresponding concentration with intramuscular administration. It should also be noted that after 24 hours, the content of the antibiotic with intramuscular administration decreases by 18 times from the initial maximum concentration, and with lymphotropic - by 14,4 times. The decrease in lymphotropic concentration in the tissues of the lungs, as in other substrates, occurs more evenly and smoothly than with intramuscular administration.

Analysis of the content of the antibiotic in the pleural tissue showed that the values of the maximum concentrations are the lowest among identical ones in other tissues, with the highest value equal to $38,8 \pm 3,3$ mkg /mg, obtained with lymphotropic administration and 1,6 times higher than identical with intramuscular administration. After 3 hours, the gap between the corresponding indicators increases by 3 times. In subsequent time periods, the indicators are approximately the same. After 24 hours, only «traces» of the antibiotic in the pleura were determined with both methods of administration. The total area under the curve with lymphotropic administration is almost 45,9% more than that with the intramuscular method.

When comparing the average daily content of gentamicin in tissues in relation to the content in the blood, it turned out that the indicators obtained with lymphotropic administration are also higher than those with intramuscular administration.

Thus, the obtained experimental data proved that relatively high and long-lasting concentrations in the paratracheal lymph nodes and respiratory organs are achieved with the lymphotropic pretracheal route of administration than with the intramuscular route, which undoubtedly indicates the advantage of this method over the traditional one.

It should also be noted that with intramuscular administration, there are sharp fluctuations in the content of the drug in the blood, which is not the case with lymphotropic administration. The relatively low peak content of gentamicin in the blood with lymphotropic administration, which exceeds the average therapeutic concentrations, a slow decrease in the concentration of the antibiotic in the blood can provide a general therapeutic effect. As for the content of gentamicin in the paratracheal lymph nodes and tissues of the respiratory organs in rats, high therapeutic concentrations are noted here with a slow decrease during the day. It is also valuable that with a single lymphotropic administration of the indicated dose of an antibiotic, its long-term concentrations are retained in all tissues, which is an important point in the prevention and treatment of bronchopulmonary complications.

The obtained dynamics of gentamicin concentrations in the studied substrates allows us to resolve the issue of the multiplicity of lymphotropic and intramuscular administration of the drug.

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