Article

Study of pharmacokinetics of gentamicin in rats under conditions of lymphotropic and intramuscular administration

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Abstract: The study of the pharmacokinetics of antibiotics on model objects makes it possible to optimize their dosage and method of administration for further clinical practice.
Aim. The aim of this study was to compare the pharmacokinetics of gentamicin sulfate in rats following intramuscular and lymphotropic pretracheal administration.
Materials and methods. The disk diffusion method was used to determine the antibiotic concentration in blood and tissue homogenate for Escherichia coli NCTC 8172. Gentamicin sulfate concentration was highest in blood samples after intramuscular administration for the first hour and lowest in pleura. In the lymphotropic method, drug concentration in tissues was higher than after muscle injection, and most antibiotics accumulated in lung tissue within the first hour. Antibiotic kinetics were either linear or logarithmic.
Results. The results indicated that the highest concentration of gentamicin sulfate was found in blood samples after intramuscular administration for the first hour, while the least amount of antibiotics accumulated in the pleura. The kinetics of gentamicin were observed to be either linear or logarithmic. The half-life of the drug for lymphotropic administration was found to be 4 hours, while for intramuscular administration, it ranged from 2 to 5 hours, depending on the object of screening. After 24 hours, regardless of the method of administration, the antibiotic was eliminated at residual amounts of no more than 10 μg/mg.
Conclusion. The study concluded that the pretracheal method of administration is more effective and can be used to optimize gentamicin treatment of bacterial infections.

Keyword: Pre-tracheal injection, residual content, lungs, lymph nodes, trachea, bronchi.

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Introduction

Gentamicin belongs to the aminoglycoside group of antibiotics. Its action is directed against gram-negative aerobic or facultative anaerobic bacteria, as it penetrates cells by oxygen-dependent active transport (Chavaes and Tadi, 2022). As evidenced by E. Hathorn, et al. (2014), mainly its action is directed against members of the Enterobacteriaceae family: Enterobacter sp., Escherichia coli, Klebsiella pneumoniae), as well as genera Haemophilus, Neisseria and Pseudomonas aeruginosa. The growth of some gram-positive microorganisms, particularly those devoid of coagulase activity and methicillin-resistant staphylococci, is partially inhibited by gentamicin, but cases of resistant strains are known. Therefore, it is usually prescribed for the treatment of meningitis, peritonitis, septicemia, and infections of the excretory system and intestinal tract. In combination with beta-lactam antibiotics, it is used to treat enterococcal infections and endocarditis. In this case, beta-lactam splits the murein wall and thus contributes to the penetration of gentamicin into the cell (Chavaes and Tadi, 2022).

According to Beganovic et al. (2018), the mechanism of action of gentamicin involves blocking the assembly of the peptide chain of microorganisms. Aminoglycosides are attached to the 16 s-RNAs of large ribosomal subunits. As a result, rRNA reading by the ribosome is disrupted and shortened or inactive proteins are synthesized. Shortened proteins adhere to the cell wall, blocking their permeability. In addition, due to a violation of translation in the cell, there is a shortage of protective proteins against oxidative stress, an excess of reactive oxygen species accumulates, and phospholipids of the cytoplasmic membrane are destroyed. This antibiotic, in combination with auxiliary drugs, is promising for inhibiting resistant strains; therefore, it is important to study its pharmacokinetics to improve its pharmacodynamics.

Chavaes, and P. Tadi (2022) reported that gentamicin is poorly absorbed in the stomach, so it is administered parenterally and is also used for local and ophthalmic purposes. After oral administration, the highest serum concentration was observed after 30-90 minutes. Antibiotics are polar compounds, so they poorly penetrate through the hydrophobic phospholipids of eukaryotic membranes and poorly bind to albumin, the main transporter of plasma. The main amount of gentamicin is excreted unchanged by the method of glomerular filtration in the kidneys: the concentration of the antibiotic in the urine is two orders of magnitude higher than in the blood. The effectiveness of this antibiotic was directly proportional to the injected concentration. Therefore, it is usually administered in large quantities to achieve the maximum post-antibiotic effect; a long time of inhibition of bacterial growth after the antibiotic content in the serum falls below the minimum inhibitory concentration. For local use in the treatment of skin infections, the content of gentamicin in the preparation is 0.1%; for ophthalmic use, 0.3%; and with intravenous administration – 5-7 mg/kg of the patient's body weight, within 30-120 minutes.

According to the data obtained by C. C. Llanos-Paez et al. (2017), the average value of gentamicin excretion in adult patients without impaired renal function (with creatinine clearance higher than 60 ml/min) is 4.6 L/h/70 kg of body weight. However, the pharmacodynamic features of the drug differ significantly in patients, depending on age, body mass index, presence of critical diseases, and duration of dialysis. To optimize the therapeutic effect and avoid complications, dosing is recommended with such an interval that the residual concentration of gentamicin falls to values of 2-0.5 mg/ml and below (Hodiamont et al., 2022; Dong et al., 2021).

To improve the effectiveness of antibiotics in medical practice, their kinetics were first studied in animals. The study of the metabolism of the compound in individual organs, as well as in the blood plasma of model subjects under different conditions of administration, allows the prediction of probable side effects and specifies pharmacokinetic indices for the specified conditions and tissues. In the future, this model can be used in clinical experiments.

The aim of this study was to determine and compare the residual amounts of gentamicin sulfate in the blood and tissues in cases of pretracheal lymphotropic and intramuscular administration to model objects. The obtained data will enable better study of the peculiarities of the pharmacodynamics and pharmacokinetics of this antibiotic to further optimize its use in clinical practice.

Theoretical review. After the antibiotic enters the patient's body, the drug undergoes a cascade of processes that determine its concentration in the blood and tissues and thus determine its clinical effect: absorption, distribution, transformation, and excretion. Pharmacokinetics is determined as the change in the amount of drug in the patient's fluids and organs during the research process. The main pharmacokinetic parameters are total clearance, protein binding, bioavailability, and volume of distribution. When the drug reaches the target at a sufficient concentration, it exerts an effect on the body due to the mechanism of action. Such a process is determined by pharmacodynamics. The main criterion for the antimicrobial action of a substance is the minimum inhibitory concentration (MIC), the lowest concentration of the drug that in vitro suppresses the visible growth of microorganisms after cultivation for 16-20 hours in a medium favorable for the strain. MIC selection is carried out with a pool of concentrations that differ from each other by a factor of two (Asin-Prieto et al., 2015; Mouton et al., 2018).

Analysis of the ratio of kinetics and dynamics (PK/PD indices) allows achieving the best effect on microorganisms with minimal damage to the macroorganism and prevents the development of bacterial resistance. These indices are the time during which the concentration of the antibiotic remains above the MIC (T> MIC), the ratio of the maximum achievable concentration to the minimum

inhibitory concentration (C_{max}/MIC), and the ratio of the area under the "time-concentration" curve during the day to the MIC (AUC/MIC). Prolonged administration of an antibiotic increases the T > MIC index faster than the AUC/MIC. When focusing on indices for specific patients, one should take into account the peculiarities of the clinical picture, the state of the immune system, concomitant disorders, and the effect on the pharmacodynamics of the combination of an antibiotic with other drugs (antagonism or mutual enhancement). There are three types of drugs with antimicrobial effectiveness. Concentration-dependent with a prolonged stable result, when the long-term effect protects against the regrowth of bacteria even when the concentration drops below the MIC (aminoglycosides). Time-dependent effectiveness without a prolonged result, when it is critical to maintain the level of the drug above the MIC for as long as possible and to introduce it at several doses (beta-lactams). Concentration-independent prolonged effectiveness (macrolides, vancomycin, tetracyclines, etc.) (Wicha et al., 2021).

These indices are related to the possible toxicity of the antibiotics. In particular, acute, concentration-dependent toxicity is most closely related to the index C_{max}, whereas toxicity developing over a long period of time is most strongly correlated with determining the cumulative effect of the drug through AUC. For potentially nephrotoxic aminoglycosides, the indicator is C_{min}, the minimum concentration. The toxicity of this group of antimicrobial compounds is determined by the degree of saturation of drug transporters. Therefore, the toxicity index is the concentration at which the transporter is saturated by 50%. Biomarker pharmacodynamics and toxicity of antibiotics are indicators of inflammation, C-reactive protein (CRP), cytokine interleukins 6, 8, 10 (IL -6, IL -8, IL -10), procalcitonin, and tumor necrosis factor-alpha (TNF-α). TNF-α is the first marker to be produced in response to pathogen reproduction. An increase in the synthesis of IL-6 may indicate the onset of action of an antimicrobial compound (Goutelle et al., 2022).

Approximate values of the indices to achieve the effect of complete or partial inhibition of bacterial growth are, as a rule, calculated on the basis of animal studies in vitro. To analyze the effectiveness of antimicrobial therapy on model objects in vivo (Sörgel et al., 2017), we studied the relationship between concentrations in plasma and tissues; PK/PD, an index that correlates with the activity of the antibiotic, time required to achieve antimicrobial activity, and a target that is key to ensuring the effectiveness of the drug.

Materials and Methods

Model objects for the experiment were white outbred rats in the amount of 50 individuals, both male and female. The body weights of the model objects were 190-210 grams. Two series of experiments were performed, with groups of 25 individuals each. The animals were injected with gentamicin sulfate via two different routes: intramuscularly and pretracheally. The dosage was determined by the concentration of 30 mg of the drug per 1 kg of body weight. Subsequently, the chest cavity was opened through chest wall thoracotomy) to remove the organs of the chest cavity and paratracheal lymph nodes. Blood samples were obtained from the femoral vein via puncture. Subsequently, the selected tissues were homogenized and the residual concentration of gentamicin sulfate was determined in both the homogenate and blood samples.

The first experimental group (25 individuals) was administered the drug pre-tracheally. Animals were previously injected with lidase at a dosage of 0.1 units/kg. The active ingredient of lidase is hyaluronidase, an enzyme that breaks down hyaluronic acid into glucosamine and glucuronic acid. Hyaluronic acid is a binding element in connective tissue. As a result of the decreased viscosity of this mucopolysaccharide, vascular and tissue permeability increases, the movement of fluids in the intercellular space accelerates, and swelling decreases. Under such conditions, lymphotropism is possible. 3-5 minutes after lidase injection, the needle was pulled to 50 mm and one dose of gentamicin sulfate (5.7-6.3 mg, depending on the body weight of the model object) was administered.

The second experimental group (25 individuals) was intramuscularly injected with the same amount of gentamicin sulfate. The injection was administered in the anterolateral area of the hind limbs. This group was considered as a control for the study of the distribution of gentamicin sulfate under classical administration conditions. To determine the amount of antibiotics administered to the organs, the trachea, bronchi, pleura, lungs, and paratracheal lymph nodes were removed.

The residual amount of gentamicin sulfate in samples of homogenized tissues and blood (volume 1-5 ml) was determined at 1, 3, 5, 8, and 24 h after administration of the drug. The concentration of the antibiotic was determined by diffusion into the agar. Escherichia coli was used as the sensitive gram-negative test culture. One hundred microliters of glycerol culture was inoculated into a 500 ml flask containing 100 ml of Luria-Bertaui nutrient medium, LB (sodium chloride, 5 g/l; yeast extract, 5 g/l; soy tryptone, 10 g/l; pH 8.0). Cells were incubated in a shaker incubator at 37 °C for 16 h with a platform rotation speed of 220 revolutions/min. Later, to grow a sample of the test culture, 100 µl of an overnight suspension of cells was sown on the surface of a Petri dish with LB agar medium (20 g of bacterial agar, Sigma, per 1 l of liquid nutrient medium), rubbed with a spatula, and incubated for 16 h at 37 °C. Paper discs with a diameter of 5 mm were placed on the surface of Petri dishes with LB agar medium, and 10 µl of the test sample containing gentamicin sulfate was added to the supernatant after sedimentation of tissue or blood homogenate. Gentamicin sulfate (Merck, 10 mg/ml) was applied to the disk as a standard for quantitative determination. The test culture grown on the cups was removed from the surface with a microbiological loop and resuspended in 4 ml of warm LB medium with agar. The suspension was evenly distributed over the surface of the cups with nutrient medium and disks with the applied samples. The cups were then incubated in a thermostat at 28 °C for 16 h. Because of the diffusion of gentamicin sulfate into the agar, sterile zones were formed around the disks with samples on the background of the lawn of the sensitive test culture. Furthermore, the diameter of the sterile zones, which was directly proportional to the concentration of the antibiotic in the sample, was measured.

Results

The dynamics of residual amounts of gentamicin sulfate during 24 h under different injection methods in blood samples, paratracheal lymph nodes, pleura, lung tissue, trachea, and bronchi were studied. The amount of the injected drug, both intramuscularly and pretracheally, was 30 mg/kg body weight. In general, in the supernatant of the homogenate of tissues collected for the experiment, more gentamicin was detected during lymphotropic administration than during intramuscular administration. However, after intramuscular injection, the concentration of gentamicin sulfate in the blood exceeded the concentration of the antibiotic in the tissues by several orders of magnitude. The highest concentrations were found in the blood and tissues of the respiratory system within the first hour after administration.

In the first hour, the concentration of gentamicin sulfate in the lymph nodes (Figure 1) was 91 µg/mg of tissue with lymphotropic administration (experiment) and was 2.5 times lower (36 µg/mg) with intramuscular injection (control). At the third hour, the content of the drug in the control group remained at 75% of the upper limit and was twice as low as that in the experimental group. A day later, due to the elimination of the drug, its content decreased to the first order and amounted to 3.7 and 1.4 µg/mg, respectively. A rapid decrease in concentration (almost seven times) was observed during the first 5 h in the experimental group and more smoothly in the control group (almost five times). However, as of the 5th hour, the drug content in the experimental sample was 1.8 times higher than that in the case of internal injections, and as of the 8th hour – 1.3 times higher. One day after administration, the concentration of gentamicin after pretracheal injection was 2.5 times higher than that after intramuscular injection. Thus, lymphotropic administration ensures long-term preservation of the therapeutic value of drug concentration in the lymph nodes for 24 h.

The highest concentration of the drug in the control group was found in the blood samples (Figure 2). However, for the experimental group, the value of the maximum content for the first hour after administration was only 41 µg/ml, whereas for the control group, it was 238 µg/ml. The gentamicin sulfate content rapidly decreased to units from the first to the fifth hour after administration in the control group. In this research group, the dynamics were smoother. With lymphotropic administration, as of the 5th hour, the concentration was slightly higher than that after intramuscular injection and was 2.9 µg/ml. After a day, gentamicin was completely eliminated in both the groups.

In the first hour after lymphotropic administration, the concentration of gentamicin sulfate in the lung tissue was proportional to the amount of drug in the lymph nodes (102 µg/mg) (Figure 3). On the other hand, with intramuscular injection, in contrast to accumulation in the lymph nodes during the first hour, the concentration of the antibiotic exceeded three times and amounted to 93

μg/mg. During the first hour of the experiment, the content of gentamicin sulfate in the experimental sample exceeded the corresponding value of the control group by 9%.

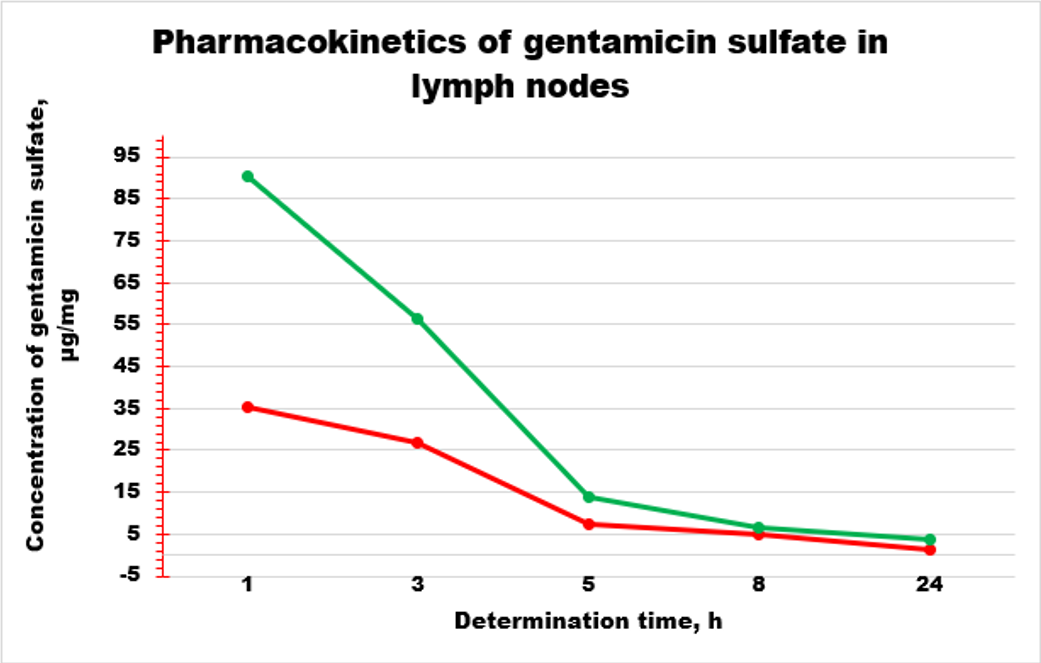

Figure 1. Pharmacokinetics of gentamicin in lymph nodes after intralesional (red colour) and pretracheal (green colour) administration.

Source: Compiled by the author.

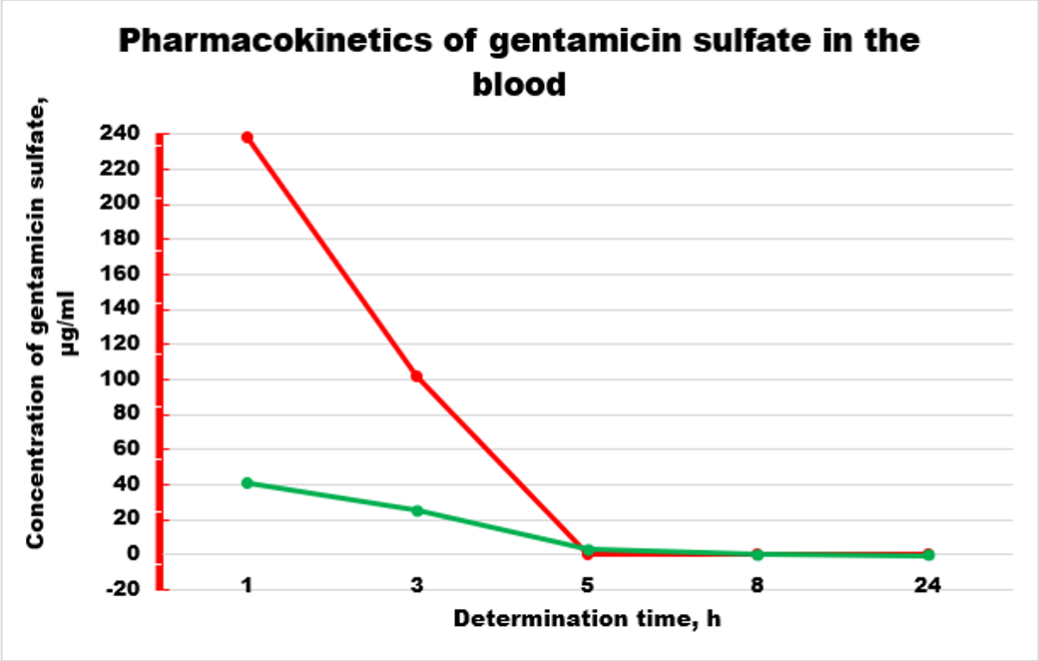

Figure 2. Pharmacokinetics of gentamicin in blood after intramuscular (red colour) and pretracheal (green colour) administration

Source: Compiled by the author.

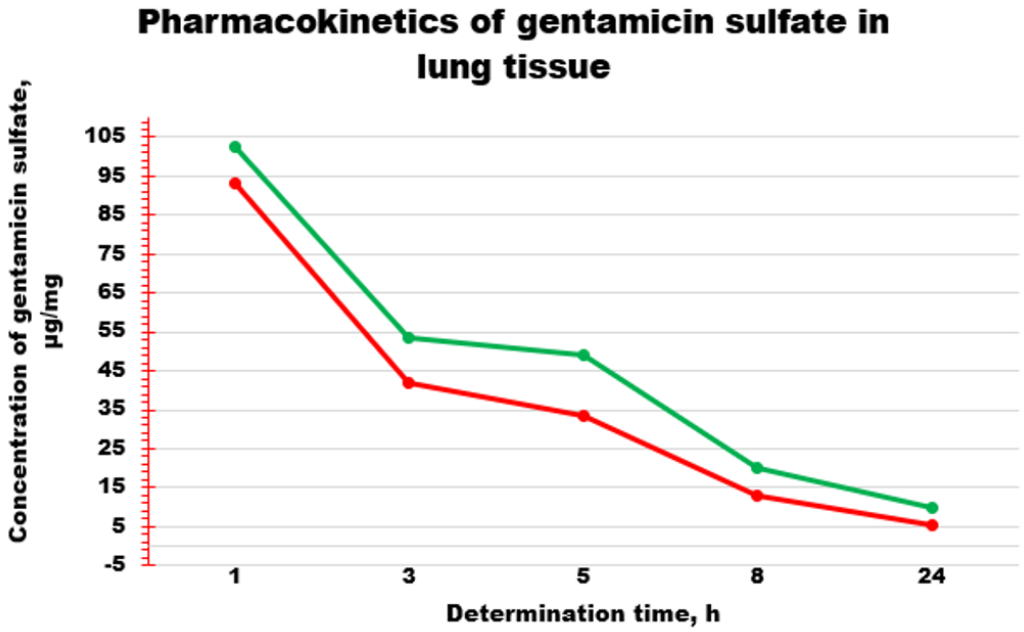

Figure 3. Pharmacokinetics of gentamicin in lung tissue after intralesional (red colour) and pretracheal (green colour) administration

Source: Compiled by the author.

After 3, 5, and 8 h, the concentration of the drug in the lungs of the experimental group remained higher than that of the intramuscular injection group (by 22%, 32%, and 43%, respectively). The residual content gradually decreases in both experimental groups within 24 hours and after a day amounts to 5.2 µg/mg for the control group and about 10 µg/mg for the experimental group. It should be noted that a day after administration, the concentration of gentamicin sulfate drops 18 times under the classical injection condition and decreases 14 times under the pretracheal administration condition. The dynamics of change in the experimental version were smoother and more even than those of the control. Thus, the administration of the drug affects its pharmacokinetics in the lungs. The dynamics in the bronchi and trachea were similar to those in the lung tissue. In particular, in the first hour, the antibiotic concentration was 80 µg/mg in the experimental group and 70 µg/mg in the control group (Figure 4).

Rapid elimination from the tissue was observed from 3 to 8 h of observation, both with pretracheal and intramuscular injections, up to levels of 14.6 µg/mg in the experimental sample and 6.5 in the control sample. In particular, 5 h after intramuscular injection, the content of the drug was reduced by 2.5 times, but it was still twice as low as the residue characteristic for this point after lymphotropic manipulations. A day after the introduction of gentamicin sulfate in both groups, the residual amount in the bronchi and trachea equalized and decreased on average to 4 µg/mg. When comparing the two graphs, with lymphotropic administration, the kinetics changed more smoothly than in the control group, and the area of the conditional triangle under the curve of antibiotic concentration after pretracheal administration was 13% greater than that after intramuscular injection.

The lowest amount of antibiotics accumulated in the pleural tissue (Figure 5). In the first hour after lymphotropic administration, it was 39 µg/mg, and after intramuscular administration, it was 24 µg/mg (in the experimental group, it was 1.6 times higher than that with the classical method). After 3 h, the difference between the methods was tripled. In general, for a lymphotropic injection, the content of gentamicin sulfate decreased rapidly for up to 5 h. From 5 h to 24 h, the decline was slow. At the last control point in both groups, the gentamicin sulfate content reached an average of 0.5 µg/mg.

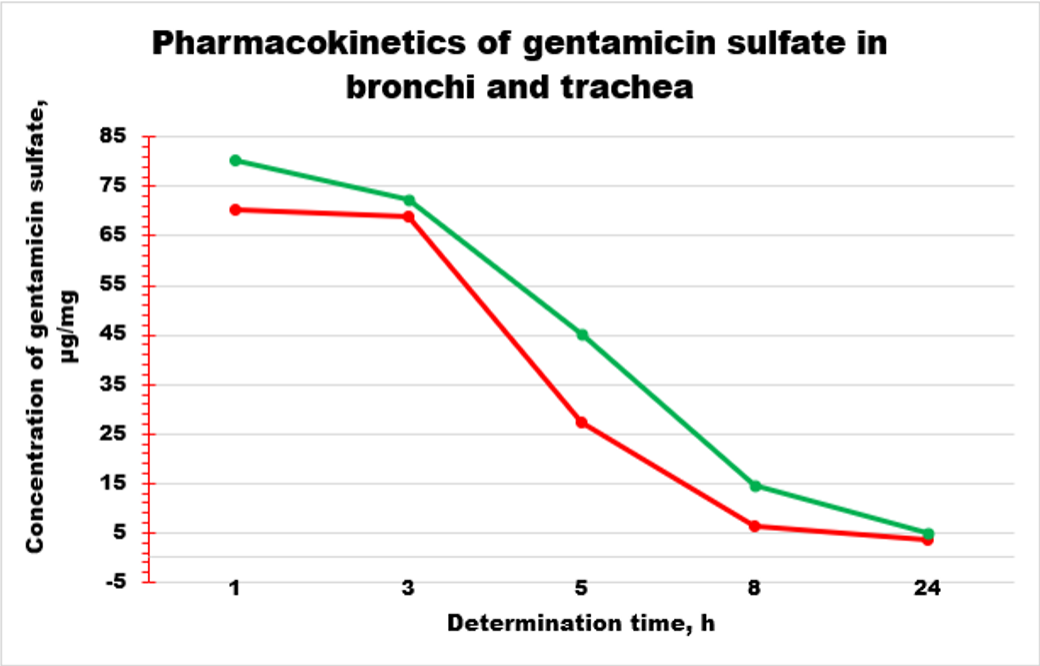

Figure 4. Pharmacokinetics of gentamicin in the bronchi and trachea with intramuscular (red colour) and pretracheal (green colour) administration

Source: Compiled by the author.

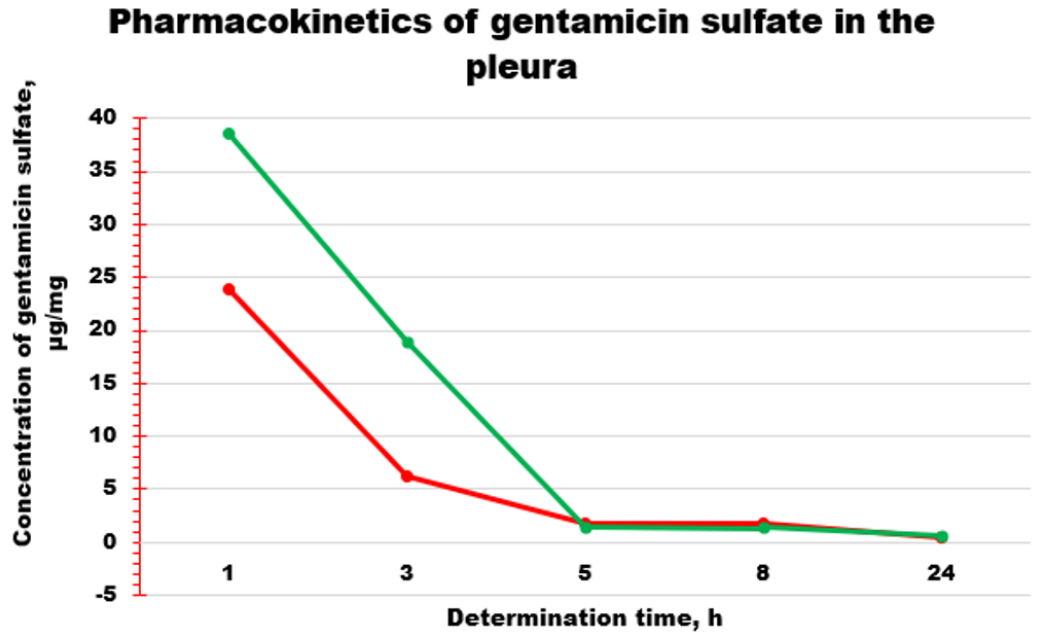

Figure 5. Pharmacokinetics of gentamicin in bronchi and trachea with intramuscular (red colour) and pretracheal (green colour) administration

Source: Compiled by the author.

The pharmacokinetics of gentamicin sulfate under the conditions of lymphotropic administration were also evaluated based on the comparison of the areas of conditional triangles under the dynamic curves: increase from zero to maximum concentration and decline to zero. Conditional areas were determined programmatically using statistical data processing software SigmaPlot.The more “stretched” the triangle, the slower the kinetics. The “narrower” the conditional triangle, the faster the decline in concentration, therefore, the faster the kinetics.

The largest area was determined for the lung tissue (51 cm2), and the areas of the trachea, bronchi, and lymph nodes (47 cm2 and 41 cm2, respectively) were comparable to the average values (Table 1). The areas of blood (15 cm2) and pleura (13 cm2) were the lowest. Slow kinetics were observed in lung tissue, respiratory organs, and lymph nodes. Due to the small area, but sufficient height of the triangle, the dynamics were fast in the pleura. At the same time, the area of the triangle for the pleural tissue sample in the experimental group was 49% larger than that of the control group. Instead, a small area was determined for blood, but the dynamics were stretched and slow.

Table 1. Areas under the curve of pharmacokinetics of gentamicin sulfate under the condition of pretracheal administration of the drug

Sample after pretracheal administration of gentamicin sulfate	Area, cm^2
Blood	15
Lymph nodes	41
Trachea and bronchi	47
Lung tissue	51
Pleura	13

Source: Compiled by the author.

This small area is due to the low peak value of the accumulated gentamicin content in the first hour after administration. Thus, with lymphotropic administration of the drug, its concentration in the samples of all investigated tissues was higher than that with intramuscular injections. Instead, the maximum concentration of gentamicin sulfate in the serum was observed in the first hour after the classic injection. This is the peak concentration from all experimental points for both studied samples. After 3 h, the antibiotic content in the blood after injection into the muscles was reduced by half. Five hours after intramuscular administration, the residual amount of antibiotics in the blood is insufficient to achieve a therapeutic effect.

If the peak concentration in the blood (238 μg/ml) under the condition of classical administration was taken as 100%, then the residual content reached 57% at the third hour, and after 5 h, it dropped to 0.2%. When the pretracheal method was used, the maximum was also observed in the first hour. This indicates a high rate of absorption of the antibiotic into the blood despite the edema caused by the action of lidase. After 3 h, the content of gentamicin sulfate in the blood was 63% of the maximum, after 5 h, it remained at 7%, and after 8 h, it was within 1%. However, 5 h after lymphotropic administration (in contrast to the classical method), the drug concentration remained at a subtherapeutic level. Based on these data, it can be stated that pretracheal administration of one dose of gentamicin sulfate provides longer and more stable blood filling with this drug. When comparing the average daily concentration of gentamicin sulfate in the tissues and its amount in the blood with pretracheal administration, the residual content of the drug in the tissues was higher than that with intramuscular injections.

Discussion:

The majority of studies on the kinetics of gentamicin in rats were conducted at the end of the twentieth century. In particular, Trnovec et al. studied the accumulation and excretion of this antibiotic during intratracheal and venous administration of 8 mg gentamicin sulfate in a single dose of 200 μl to white rats. Gentamicin content was determined in urine, blood plasma, lung, kidney, liver, and myocardial tissue homogenates. The change in concentration was monitored at different time intervals from 2.5 min to 2 hours. The half-life of intravenous gentamicin sulfate was 21 min, whereas that after tracheal injection was 23 min. Regardless of the administration method, gentamicin was completely eliminated from the plasma within 2 h from the liver and myocardium within 1 h. However, in the kidneys, the residual concentration of the antibiotic after 120 min remained at 48 μg/ml and 32 μg/ml after venous and tracheal injections, respectively (Trnovec et al., 1978). Under the conditions of the current experiment described in the results, the half-life for the lymphotropic route averaged 4 h, and that for intramuscular injection ranged from 2 to 5 h. Obviously, this difference is

related to the method of injection (when injected into the blood and trachea, the antibiotic is excreted faster).

Huy et al. conducted an experiment on white rats with the detection of accumulation of gentamicin in the inner ear (due to ototoxicity of the drug), kidney cortex, myocardium, liver, spleen, and lungs. A single intramuscular injection of an antibiotic was administered at a dose of 100 mg/kg. The maximum concentration in plasma was 168 μg/ml 30 min after injection, the half-life was approximately 4 h, and no residual amounts were detected after 5 days. Only 0.06-0.09 μg/mg gentamicin accumulated in the tissues of the inner ear, liver, spleen, and lungs, and 4 μg/mg in the kidneys (Huy et al., 1986). The ototoxicity of antibiotics is apparently due to the penetration of the compound into the compartments of the inner ear, which slows down its half-life (Ferreira et al., 2022). The authors observed such an average concentration between lymphotropic and muscle administration of three times smaller dosage for the first hour; the half-life time of gentamicin also converged in the current experiment. In contrast, in this experiment, an order of magnitude higher maximum accumulation in the organs was observed.

When studying the residual amounts of gentamicin in the plasma and cerebrospinal fluid of white rats, it was found that the peak concentration in the plasma was reached 2 h after injection. At the same time, the antibiotic content was approximately 70 μg/ml. In the cerebrospinal fluid, the maximum was reached 75 min after arterial administration and was only 3.2 μg/ml. Such an insignificant concentration is related to the difficulty of overcoming the hematoencephalitis barrier: only 5% of the antibiotic penetrates the cerebrospinal fluid from the blood (Meulemans et al., 1986).

The pharmacokinetics of gentamicin sulfate in the blood are excellent in various model objects of its research, which can be traced by comparing the results of this study with the data of Wilson et al. The experiment was conducted with Equus caballus under anesthesia and without anesthesia. Gentamicin was administered at a rate of 6.6 mg/kg of the animal's body weight, and the residual amount was monitored in plasma and synovial fluid samples at 1 and 6 h after administration. The gentamicin concentration was determined using high-pressure liquid chromatography and mass spectrometry. The minimum concentration of gentamicin in the plasma without the effect of an additional anesthetic factor was 1.9 μg/ml. These data are consistent with those obtained for white rats 24 h after intramuscular administration. Instead, the maximum concentration of gentamicin in the blood for the first hour after administration differed by an order of magnitude: in E. caballus, it was 20 μg/ml (Wilson et al., 2023), while in the current experiment, it was more than 200 μg/ml. In the blood of E. caballus, a higher titer of gentamicin was found than in the synovial fluid (as in the data of the current experiment, the absolute value in the blood was the highest compared to other tissues). Obviously, gentamicin metabolized faster in E. caballus than in Rattus sp.

The half-life of an antibiotic depends on its volume of distribution and clearance. Therefore, time varies for different species of animals. In particular, it is directly proportional to body weight; the greater the mass, the longer the half-life. The antibiotic is removed from the organism of large animals more slowly than from the organism of small model objects because the relative size of the kidneys and liver in comparison with the size of the body is smaller in larger objects. Half-life is also affected by the percentage of water and fat in the body. (Steger et al., 2020). Therefore, the kinetics were similar for animals of the same weight. Studies described by Soh et al. on budgerigars, the mass of which is commensurate with the mass of white rats, state that the half-life of gentamicin is 0.53 hours, and the kinetics is linear (Soh et al., 2022). The authors observed this type of kinetics in the conducted experiment when determining the content of gentamicin in the tissue of the respiratory organs under the condition of lymphotropic administration; however, the average half-life time in white rats with pretracheal injection was 4 h. The difference in half-life is probably due to the difference in the starting concentration and methods of injection.

In addition to the traditional methods of injecting antibiotics, there are many new options for their administration to improve the effectiveness of the action. One such method is the delivery of antibiotic-loaded lipid granules to target cells (Huck et al., 2022). E. C. Umeyor et al. (2012) used solid lipid microparticles with a solid reversed micellar solution containing gentamicin for the intramuscular administration of antibiotics to white rats. After injection of 2, 3, and 4 mg/kg gentamicin, more than 50% of the drug was released into the blood. The maximum plasma concentration was observed 25 min after administration. Chitosan-based nanoparticles have also been used to deliver gentamicin

to target biocomposites. The base is a polymer with a positive charge (cationic polysaccharide). It is easily biodegraded and exhibits antimicrobial activity against gram-positive and gram-negative bacteria and fungi (Alavi and Nokhodchi, 2020). The cationic polymer easily binds to the negatively charged groups of the bacterial cell wall, breaking its integrity and thus can deliver the antibiotic inside the cell. When using nanoparticles with 50 mg of gentamicin for wound healing, the treatment efficiency was higher than that when using the antibiotic without nanoparticles (Asgarirad et al., 2021).

In general, there is a distinction between nanoparticles with synthetic and biological shells in which the antibiotic is located. They are often used to prevent the contamination of cardiovascular implants (Tarakji et al. 2019). In particular, M. R. Sohail et al. (2020) used synthetic and bionanoparticles containing 40 mg of gentamicin on rabbits as model subjects. When using particles with a synthetic shell, the concentration of gentamicin in the serum fell below the therapeutic level after 15 h, whereas for bionanoparticles, it remained stable for 7 days. The encapsulated antibiotic was effective against E. coli, S. aureus, S. epidermidis, P. aeruginosa, MRSA (multiresistant S. aureus) and S. marcescens. As an alternative material for the synthesis of the "shell" of the antibiotic, polycaprolactone, obtained with the help of 3D technologies, can be used. Loaded with 2-5% gentamicin sulfate, nanoparticles showed active kinetics of the drug within 14 days when studied in vitro, released at high concentrations during the first two days, and then slowly diffused in bactericidal amounts. In vivo drug was injected subcutaneously 30 minutes before the surgical insertion of the fixing staphylococcus-infected bone plate, as well as 6 and 24 hours after the end of the operation; the model object was C57BL/6/JRccHsd mice. The encapsulated 5% gentamicin sulfate diffused into the medium and completely inhibited the development of S infection. aureus (Guarch-Perez et al., 2022). Thus, in order to identify the most effective variant of the introduction of the drug from the perspective of further experiments, the pharmacokinetics of gentamicin sulfate under the condition of injection was studied using the developed nanotechnologies.

Conclusions

The Pharmacokinetics of gentamicin sulfate in white rats under conditions of lymphotropic pretracheal (test) and intramuscular (control) administration in the blood, lungs, pleura, lymph nodes, bronchi, and trachea were studied. The concentration of the antibiotic was determined by diffusion into the agar medium, followed by inhibition of growth of the test culture. In the experimental group, the concentration of antibiotics in the tissue homogenate was higher than that in the control group. The maximum drug content (238 μg/ml) was recorded in the blood plasma within the first hour after intramuscular injection. The half-life of the antibiotic after pre-tracheal administration is 4 h, and after intramuscular administration, it varies from 2 to 5 h. The smallest AUC of the antibiotic in the test conditions was in the pleura and blood (13 and 15 cm2), the same was found in the trachea, bronchi, and lymph nodes (47 and 41 cm2), and the largest was in the lung tissue (51 cm2). Kinetics during lymphotropic administration correspond to linear (respiratory organs) and logarithmic (blood, lymph nodes, and pleura) dependencies. 8 hours after lymphotropic administration, gentamicin sulfate remains at the level of 0.2-1.4 μg/ml (mg) in the blood and pleura, at the level of 14-20 μg/mg in the respiratory organs, and at the level of 7 μg in the lymph nodes/mg with intramuscular administration, the content of gentamicin sulfate rapidly decreases by two orders of magnitude during the first 5 hours, and with lymphotropic administration, it remains at a subtherapeutic level during this period of time. Within 24 h, gentamicin sulfate was almost completely removed from the tissues and blood, with the highest residual concentration (10 μg/mg) in the lungs a day after administration. The maximum concentration in all samples was observed for the first hour. Lymphotropic administration of one dose of the drug at a dose of 30 mg/1 kg of body weight provides longer enrichment of the plasma with the drug than intramuscular injection. From the perspective of further research, the pharmacokinetics of gentamicin sulfate in white rats with the introduction of nanoparticles enriched with the antibiotic should be studied to optimize further clinical experiments.

Authors' contribution

Conceptualization, B.M. and A.A.; methodology, B.M. and O.I.; software, O.I.; validation, A.A., O.I. and Sh.T.; formal analysis, B.M.; investigation, B.M. and O.I.; resources, A.A.; data

curation, O.I.; writing—original draft preparation, B.M.; writing—review and editing, A.A. and Sh.T.; visualization, O.I.; supervision, Sh.T.; project administration, B.M.; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript.

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Ethics approval

The animal study protocol was approved by the Institutional Review Board / Ethics Committee of Andijan State Medical Institute, Uzbekistan. The protocol number and date of approval will be provided upon request by the Editorial Office.

Consent for publication.

Not applicable. The study does not involve human subjects, and no identifiable personal data are included in this manuscript.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request. No publicly archived datasets were generated or analyzed during the current study.

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Conflict of interest

The authors declare no conflicts of interest.

Abbreviations

PK/PD	Pharmacokinetics/Pharmacodynamics
MIC	Minimum Inhibitory Concentration
AUC	Area Under the Curve
C_{max}	Maximum Concentration
C_{min}	Minimum Concentration
T>MIC	Time Above Minimum Inhibitory Concentration
CRP	C-reactive Protein
IL	Interleukin
TNF-α	Tumor Necrosis Factor Alpha
LB	Luria–Bertani Medium
DFT	Density Functional Theory

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