VOLUME LXXV, ISSUE 7, JULY 2022

ISSN 0043-5147
E-ISSN 2719-342X

Wiadomości Lekarskie

Official journal of the Polish Medical Association

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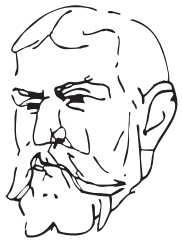

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CONTENTS

ORIGINAL ARTICLES

ORIGINAL ARTICLE

LYMPHOTROPIC ADMINISTRATION OF ANTIBACTERIAL DRUGS – A METHOD OF RATIONAL ANTIBIOTIC THERAPY

DOI: 10.36740/WLek202207115

Igor D. Duzhyi, Volodymyr V. Shymko, Halyna P. Oleshchenko, Hennadiy I. Piatykop
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ABSTRACT

The aim: To explore the possibilities of rationalizing antibacterial therapy by comparative analysis of the accumulation of ceftriaxone administered lymphotropically and intramuscularly.

Materials and methods: The research used a method of studying the sensitivity of microorganisms to antibacterial drugs, which is based on the diffusion of antibacterial drugs from the carrier (homogenate of the test organ) in a dense nutrient medium, which, depending on the sensitivity of microorganisms, inhibits the growth of the studied culture and is accompanied by the formation of a growth inhibition zone (GIZ) in the nutrient medium. For control purposes, a commercial disk with ceftriaxone was used, which caused GIZ of microorganisms at the level of 27.05 ± 0.9 mm.

Results: The homogenate of organ samples obtained from rabbits administered with the antibiotic lymphotropically, inhibited the growth of test cultures around the discs in all cases. The inhibition was slightly less than the control inoculation, but the result clearly indicated the presence of antibiotics in the test material in the quantity sufficient to inhibit the growth of the pathogen. Concurrently, after intramuscular administration of the antibiotic, biopsy specimens from various growth inhibition organs of test cultures were either not induced at all or were induced in small amounts, which was certainly insufficient for the inhibitory action of the drug administered by this method.

Conclusions: The administration of the antibiotic lymphotropically promotes its accumulation in all organs in the quantity sufficient for antibacterial action, which allows us to recommend lymphotropic therapy as a rational method of antibiotic therapy.

KEY WORDS: lymphotropic therapy, antibiotic therapy, ceftriaxone

Wiad Lek. 2022;75(7):1688-1692

INTRODUCTION

Recently, the issue of optimizing antibacterial therapy has become acute. This is primarily due to the growing number of infectious and suppurative and inflammatory diseases and their complications, as well as increasing the resistance of pathogenic microflora to antibiotics accompanied by a decrease in the effectiveness of the latter and the growth of various complications [1]. Unfortunately, it becomes clear that the development of new antibiotics does not solve this problem. Therefore, to achieve the desired result, the antibacterial drug dose should be increased, which, accordingly, increases the number of toxic and allergic manifestations. Complications mostly occur with the use of expensive most advanced antibacterial drugs, which, among other things, are not available to all patients [1]. Given the above, the issue of rational antibiotic therapy, which can reliably maintain a sufficient inhibitory antibiotic concentration in the body (bacteriostatic or bactericidal), without causing toxic stress and other adverse effects in the patient is very important, raises many questions.

Many authors, in particular, R. T. Panchenkov, Yu. E. Vyrenkov and I. V. Yarema [2] highlighted the role of the lymphatic system in the pathogenesis of suppurative and inflammatory diseases. The authors emphasize that the lymphatic system is the first to react to any «regional» aggression, including the inflammatory process of any localization [3, 4]. The hemolymphatic barrier in each region of the human body is represented by a system of blood and lymph vessels and lymph nodes, which create mechanical, physicochemical, and biological protection of organs and tissues of this region due to the active functioning of the endothelium of blood vessels, capillaries, and interstitial layers from the penetration of pathogens into the relevant organs. Metabolic processes between blood, interstitial fluid, and lymph, as well as cells of organs and systems, are in close active interaction. The change in the intercellular substance during inflammation affects its permeability and changes according to the course of pathological processes [5-7]. Spasm in the microvascular bed, slowing of blood flow, and inhibition of metabolic processes, which results in the accumulation of acidic metabolic products in the interstitium and leads to reduced outflow on the background of dilatation of precapillary sphincter mechanisms and, consequently, increased hypoxia and acidosis accompanied by tissue edema and dysfunction of cellular structures [5, 8]. Disruption of blood flow in the region helps to go beyond the vascular bed of fluid and blood-formed elements leading to increased blood viscosity, activation of adhesion, and aggregation of formed elements. The above-mentioned is accompanied by sludge formation and causes

tissue necrosis of varying prevalence. The pressure in the affected tissues and lymph nodes increases, which blocks capillary blood flow and the entry of anti-inflammatory and antibacterial drugs into the area of inflammation, as well as the excretion of products of pathological metabolism. Considering this, the leading role in maintaining the proper functional level of homeostasis in the inflammation zone should be played by the regional lymphatic system, which is also affected [8, 9]. Taking this into account, it becomes obvious that by influencing the physiological state of the lymphatic system and its rehabilitation, it is possible to prevent homeostasis in the relevant part of the human body, which is identical to the prevention or reversal of the inflammatory process.

It has been studied that the current method of lymphotropic antibiotic therapy can be used for targeted delivery of antibiotics to the affected organ against the background of effective rehabilitation of the lymphatic system [10, 11]. At the same time, a stable therapeutic concentration of the antibiotic in the relevant tissues is maintained for a long time, even when used in small doses. Given this, we believe that there are all prerequisites for studying the targeted supply of antibacterial drugs to the selected region or diseased organ by applying our proposed method of lymphotropic supply of antibiotics and other anti-inflammatory drugs to various organs, which determines the relevance of the issue.

THE AIM

To explore the possibilities of rationalizing antibacterial therapy by comparative analysis of the accumulation of ceftriaxone administered lymphotropically compared to intramuscular administration of the drug to specific organs.

MATERIALS AND METHODS

We experimentally studied the accumulation of the antibiotic in the tissues of various organs after its lymphotropic administration in comparison with the accumulation of the drug after intramuscular administration. The antibiotic ceftriaxone was chosen for the study, which according to the literature is most often used in surgical hospitals and has a fairly high (59%) inhibitory capacity for intra-abdominal microflora, including the microflora of the pancreas and retroperitoneal tissue with resistance to 32% [12].

RESULTS

In the course of the research, the method of studying the sensitivity of microorganisms to antibacterial drugs was used according to the order of the Ministry of Health of Ukraine № 167 of 05.04.2007 «On the approval of guidelines of «The determination of the sensitivity of microorganisms to antibacterial drugs».

During the experiment, ceftriaxone was lymphotropically administered in experimental rabbits regionally in five different parts of the body according to the organ to be studied: in the right iliac region, left iliac region, right paravertebral region, left paravertebral region. The essence of the lymphotropic method of antibiotic administration was the regional sequential administration of drugs that stimulate lymph secretion to antispasmodics, anticoagulants, anti-inflammatory drugs, and antibiotics.

The drug was injected intramuscularly into the posterior-upper quadrant of the left gluteal muscle. One hour after the drug administration, the animals were removed from the experiment after overdosing on the analgesic drug.

Eight tissue samples were obtained from different abdominal organs from each rabbit: the body of the stomach, the middle part of the small intestine, blind intestine, sigmoid intestine, omentum, the body of the pancreas, parietal peritoneum in the right hypochondrium, liver.

The weight of each sample was determined on electronic scales AD – 200. Their weight ranged from 0.152 g. to 0.354 g. The homogenate was then prepared from the samples and pipetted into an Eppendorf tube using an automatic pipette, where a similar volume of saline was added, that is a 1:1 dilution was obtained. The study of the presence of the antibiotic was performed by the diffusion method based on the diffusion of the antibacterial drug (ABD) from the carrier (homogenate of the studied organ) into a dense nutrient medium that inhibits the growth of the studied laboratory culture. The formation of a growth inhibition zone (GIZ) was due to the diffusion of ABD from the homogenate of the test organ into the nutrient medium – Mueller-Hinton agar, prepared from a dry preparation of industrial production following the manufacturer's instructions. 90 mm diameter Petri dishes were used in the research. 20 cm^3 of the prepared medium was added to each cup, which allowed obtaining a layer of agar with a 4 mm thickness. The plates were then left at room temperature to solidify the agar. Before the inoculation of the laboratory culture of Escherichia coli, the plates were dried in a thermostat at 35 °C with the lid open for 10–20 minutes to ensure the absence of liquid condensation on the inner surface of the lids. Then, a suspension of the microorganism *Escherichia coli* ATCC 25922 was prepared using a densilameter, the concentration of the microorganism was 1.5 x 10^8 colony-forming units / cm^3, which at visual inspection corresponded to a turbidity standard of 0.5 according to McFarland. The standard inoculum was pipetted onto the surface of a Petri dish with a nutrient medium in a volume of 1–2 cm^3, distributing it evenly over the surface by shaking. The excess inoculum was removed with a pipette. The opened Petri dishes were dried at room temperature for 10–15 minutes. As a control, a standardized commercial disk with ceftriaxone was applied to each plate, which caused a zone of growth retardation on Petri dishes at the level of 27.05 ± 0.9 mm.

In the preparation of the carrier (antibacterial drug) (antibiotic), cardboard disks were immersed in the homogenate of the corresponding organ, after which sterile tweezers were applied to the agar surface. The distance between the discs and the edge of the cup was 15–20 mm. To ensure equal contact with the agar surface, the discs were gently pressed with tweezers. On each plate, 5 disks

Table I. The dynamics of growth inhibition zones of test culture

№	Samples	Growth inhibition zone (mm)					
		Intramuscular administration n=10	Lymphotropic administration				Control n=10
			Right iliac n=10	Left iliac n=10	Right paravertebral n=10	Left paravertebral n=10	
1	Stomach	Absent *	11,95±1,79 *#	13,7±1,59 *#	15,05±1,61 *#	15,65±1,66 *#	27,05±0,9 #
2	Small intestine	2,7±1,03 *	19,25±1,62 #	18,3±1,66 *#	10,55±1,85 *	13,3±1,69 *#	27,05±0,9 #
3	Blind intestine	1,95±1,1 *	19,15±2,03 #	14,8±1,74 *#	11,65±1,9 *#	9,4±1,64 *	27,05±0,9 #
4	Sigmoid intestine	2,2±1,11 *	14,25±1,97 *#	18,45±1,85 #	9,25±1,37 *	9,75±1,48 *#	27,05±0,9 #
5	Omentum	2,4±1,19 *	14,6±1,76 #	13,6±1,67 *#	12,45±1,61 *#	11,5±1,15 *	27,05±0,9 #
6	Pancreas	Absent *	9,65±1,84 *#	10±1,75 *#	17,1±1,68 *#	18,1±1,86 *#	27,05±0,9 #
7	Parietal peritoneum	2,85±1,04 *	13,85±1,93 #	11,8±2,12 *#	12,45±1,79 *#	10,7±1,69 *#	27,05±0,9 #
8	Liver	Absent *	7,65±1,63 *#	5,8±1,79 *#	9,6±1,73 *#	8,75±1,74 *#	27,05±0,9 #

Note: *- the probability of difference from the values of the control group (p <0,05),
- probability of difference from the values of the comparison group (intramuscular injection) (p <0,05)

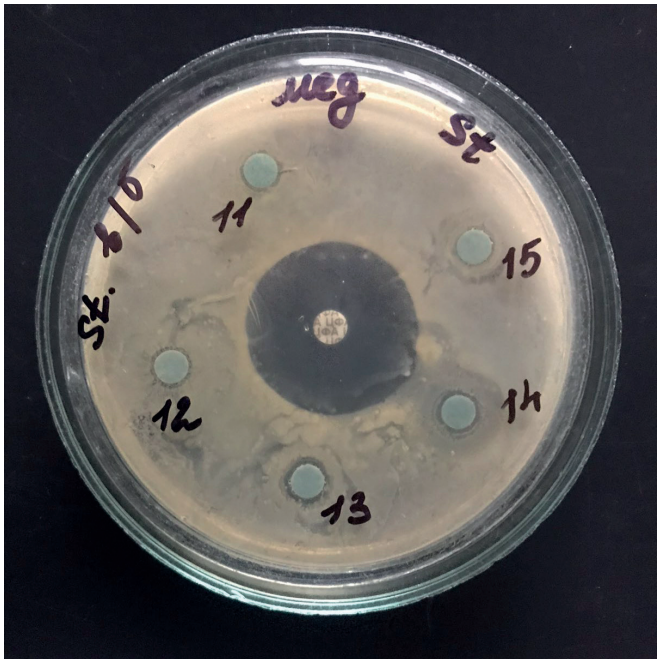

Fig. 1. Growth inhibition zones of the laboratory culture one hour after the intramuscular administration of the antibiotic

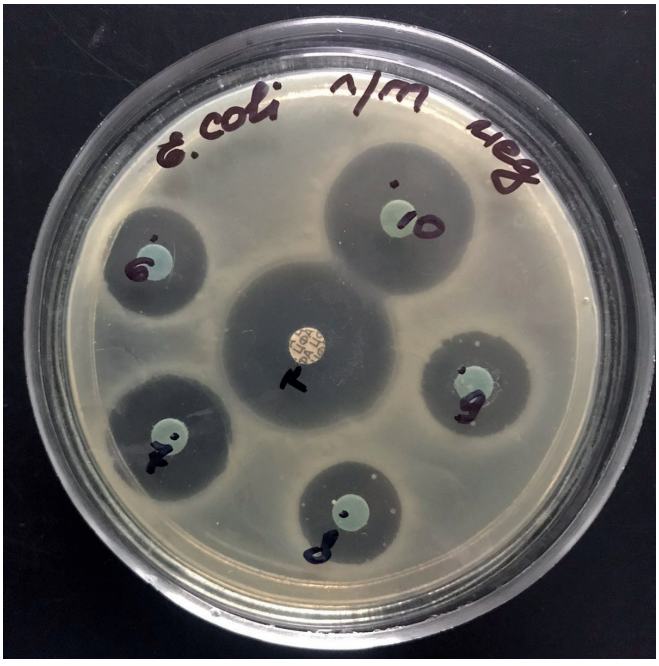

Fig. 2. Growth inhibition zones of the laboratory culture influenced by lymphotropic therapy 1 hour after the antibiotic administration

with samples of the studied organs and a control disk with ceftriaxone were placed. Immediately after the application of disks, the Petri dishes were placed in a thermostat upside down and incubated at 35 °C for 24 hours.

After the incubation, the results were determined. For this purpose, the cups were placed upside down on a dark matte surface so that light fell on them at an angle of 45°. The diameter of the growth retardation zones was measured around the disks with the investigated material to the nearest 1 mm using a caliper.

The obtained data were statistically processed according to standard formulas. Continuous data are presented as

mean ± standard deviation (M ± SD). Differences between the two groups in continuous variables were analyzed using the nonparametric Kruskal-Wallis H test. Values of $P<0.05$ were considered statistically significant.

The results are shown in Table I.

The table shows that the homogenate of the samples of the studied organs obtained from the studied animals to which the antibiotic was administered lymphotropically inhibited the growth of *Escherichia coli* in the discs' zones in all cases. The growth of the test culture under the action of homogenates of tissues obtained from animals after lymphotropic administration of ceftriaxone was inhibited slightly less than the control seeding. However, the result indicates the presence of antibiotics in the test material in a quantity sufficient to inhibit the growth of the pathogen (*Escherichia coli*).

However, after the intramuscular administration of the antibiotic, biopsy specimens from various organs did not inhibit the growth of *Escherichia coli* at all or caused a negligible amount, which was insufficient for the inhibitory effect of the drug administered in this way.

Thus, the table shows the complete absence of growth inhibition zones after intramuscular administration of ceftriaxone in the wall of the stomach, pancreas, and liver, indicating the absence of drug accumulation in these organs. In other organs (small, blind, and sigmoid intestines, omentum, parietal peritoneum) the growth inhibition zones of laboratory test culture *Escherichia coli* were in the range of 1.9–2.8 mm, which is 7.2–10.4% of the control effect of pure antibiotic (standardized disc with the drug). After the lymphotropic administration of the antibiotic, the small intestine homogenate caused GIZ in the test culture of *Escherichia coli* in the range of 71.2–67.7% to the action of pure antibiotic; the appendix homogenate caused GIZ at the level of 70.8–54.7% to the control; sigmoid intestine homogenate caused GIZ at the level of 68.2–51.8% to the control; the homogenate of the omentum caused GIZ at the level of 54–50.3% to the control; parietal peritoneal homogenate caused GIZ at the level of 51.2–46% to the control; liver homogenate caused GIZ at the level of 35.5–32.4% compared to the control. The given sizes of GIZ of *Escherichia coli* are taken by us on their maximum values at various regional zones of lymphotropic administration of the drug.

DISCUSSION

Thus, the maximum inhibitory effect of the homogenate of samples of small, blind, and sigmoid intestines, omentum, and parietal peritoneum was manifested maximally by lymphotropic administration of the antibiotic in the right iliac region, approaching the control effect of the pure antibiotic. However, the most intense inhibitory effect of homogenates of the stomach, pancreas, and liver was observed after lymphotropic administration on the drug in the right or left paravertebral zone. An example of the clinical effectiveness of the results is our first attempt to treat acute pancreatitis by lymphotropic administration of antibiotics and anti-inflammatory drugs [12]. From the above, it can be assumed that in diseases and injuries of the abdominal cavity in case of traffic and military explosive and shooting injuries, the selective area for the lymphotropic administration of ceftriaxone should be the right or left iliac zones, and in acute pancreatitis and retroperitoneal injuries – the right or left paravertebral zones.

Because of this, it is clear that there is no or insufficient therapeutic effect under the influence of standard methods of antibiotic administration, accompanied by significant mortality, which, for example, in acute infected pancreatitis reaches 70-80% [13], because according to the data antibiotic (ceftriaxone) in these methods injection into the pancreas does not

CONCLUSIONS

1) 1 hour after the intramuscular administration of ceftriaxone in experimental animals, its accumulation is not observed in the wall of the stomach, pancreas, and liver. In other organs (small, blind, sigmoid intestines, omentum, parietal peritoneum), the antibiotic accumulates in the quantity insufficient for the inhibitory effect of the drug on the growth of *Escherichia coli*.
2) The administration of the antibiotic lymphotropically promotes its accumulation in all organs in an amount sufficient for antibacterial action.
3) Given the lymphatic link in the pathogenesis of acute inflammation of any organ, empirical rehabilitation of the area should be carried out by the lymphotropic administration of antibiotics.
4) This method of administration of antibacterial drugs should be rationally used as a preparation for surgery, starting their administration 1–2 hours before surgery and continuing in the postoperative period, or as an independent method in conservative treatment. This administration of antibiotics in the presence of retroperitoneal hematoma is especially important. In infected pancreatitis, the method of lymphotropic therapy is considered the major [12].

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The study conducted at the expense of academic research work 60.28–21/22.3П–01 «An alternative method of antibiotic therapy for injuries and wounds of the abdomen and acute appendicitis»

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Conflict of interest:
The Authors declare no conflict of interest.

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Received: 20.10.2021
Accepted: 06.05.2022

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article