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The comparison of intravenous and lymphotropic routes of ^{99m}Tc ciprofloxacin in experimental pulmonary suppuration

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ABSTRACT

Intravenously injected "^{99m}Tc-ciprofloxacin" is rapidly accumulated and washed from the septic focus. Lymphotropic injections provide targeted and long-lasting effect of antibiotics. After injection into the interspinous ligament the drug slowly enters the inflammation area (by-passing the urinary organs and liver), where it is maximally accumulated only after 24 h, which allows to reduce the number of injections and the total dose of the antibiotic.

Keywords: Pulmonary Suppuration; Lymphotropic Route; ^{99m}Tc Ciprofloxacin

1. INTRODUCTION

Acute suppurative lung diseases are one of the most actual medical-social problems, because they are characterized by massive organ injury and severe, life-threatening clinical course. It is well-known, that lymphatic system plays an important role in this pathology and is actively involved into protective reactions of immune system and detoxification [1,2]. Since the resorption of tissue fluid in suppurative-inflammatory process is attended with considerable enhance of endolymphatic concentration of pathological microorganisms, the directed increasing of antibiotic concentration in lymphatic system may result in the therapeutic effectiveness strengthening of such kind of drugs [2]. However, traditional routes of antibiotics are enabling to accumulate these drugs in sufficient concentrations in blood [3]. In this connection, Levin Yu.M. *et al.* [4] in 1986 proposed "method of indirect endolymphatic therapy". It is based on using drugs (tripsin, chemotrypsin, *et al.*) which are able to change lymphatic vessels permeability making possible to increase drug delivery into lymph capillaries. It was shown, that such kind of pharmacological intervention not only increases lymphatic concentration of antibiotics in 2 - 10 times, but also stimulates lymph outflow from organs [5].

Numerous methods of limfocorrection and limfosanitation, including limfostimulatory interspinal injections suggested by M.S. Lubarsky [6] are now widely used in practical medicine.

Nevertheless, the advantage of endolymphatic therapy to intravenous route of administration of antibiotics is not conclusive, because there is still no convincing data on the dynamics of drug accumulation in the inflammatory foci, as well as the pharmacokinetics and washout.

Recently, a new radiopharmaceutical - antibiotic ciprofloxacin labeled with ^{99m}Tc, have been proposed for diagnoses of infective inflammation [7]. In our opinion, it can be used in experimental studies to trace the dynamic of antibiotic accumulation in the lung inflammatory foci and to compare the effectiveness of intravenous and endolymphatic routes of this medicine.

To compare the extent of ^{99m}Tc-ciprofloxacin accumulation in the lung inflammation after intravenous or endolymphatic route.

2. MATHERIALS AND METHODS

Experiments were carried out on 12 adult mongrel dogs of both sexes, and kept before and after the experiment in normal vivarium conditions. All experiments were performed under general anesthesia. The main series of experiments were performed on 5 dogs, with preliminarily modeled acute staphylococcal pneumonia (method of L. A. Mamedov) [8].

To this purpose the suspension containing 1,000,000 microbial cells of Staphylococcus aureus was injected into the lung tissue of animals at the level of VII-VIII intercostal space on the right. The process of the inflammatory infiltrate formation was evaluated by clinical

and X-ray methods. In 5 days after experimental contamination in a strictly aseptic conditions at the level of Th_2-Th_3, Th_3-Th_4, Th_4-Th_5 (places of the greatest representation of superficial lymph collectors) dogs were injected with prepared ex tempore drug mixture consisting of 32 units lidazy, 4 mg dexamethasone, 100 mg, 10% lidocaine, up to 6 ml of 40% glucose and 2 mg 200 - 300 MBq ^{99m}Tc-ciprofloxacin (Institute of Organic Synthesis, Ural Branch of Russian Academy of Science). The radiopharmaceutical, with radiochemical purity 95% was synthesized in Tomsk Polytechnic University []. Registration of scintigraphic images was performed at 1, 2, 3, 4, and 24 hours post injection.

In 2 days after the first study 99mTc-ciprofloxacin with the same drug mixture was injected to animals intravenously (into the small subcutaneous vein of the hind limb). Tracing of the radiopharmaceutical's distribution was performed at 1, 2, 3, 4, and 24 hours post injection.

For control studies we used three groups of healthy animals (3 dogs each), which initially were intravenously injected with even drug complex, containing radiopharmaceuticals with different chemical and biological properties: for animals of the first group—^{99m}Tc-pertechnetate (TcO_4Na), for the second—^{99m}Tc-radioactive colloid, for the third—^{99m}Tc-ciprofloxacin. Two days later the same radiopharmaceuticals were injected by lymphotropic route with hereinabove method.

Registration of scintigraphic images in control groups was performed at 1, 2, 3, 4 and 24 hours post injection.

At the time of the study, all dogs were located ventral surface of the detector γ-camera so that the field of view proved to the whole body.

Scintigraphic studies were carried out on the gamma camera "Philips-Forte". Pprocessing of scintigraphic data was performed using a package "Jet Stream® Workspace Release 2.5" (Philips) following by isolation of zones of interested and making "time-activity" curves.

3. RESULTS AND DISCUSSION

After 1 h after intravenous injection of ^{99m}Tc-ciprofloxacin maximum of its accumulation was registered in the kidney (≅ 30% of total activity) and bladder (≅ 60% of total activity) that corresponds to the normal biodistribution radiopharmaceutical [7].

The dynamics of accumulation of ^{99m}Tc-ciprofloxacine in lungs is shown on **Figure 1**, which follows that radioactivity in the inflammation foci reached its maximum after 2 hours (6.9% ± 0.3% of total) post injection with further slow washing-out of the indicator. Concentration of the drug throughout the experiment in the intact lung tissue remained significantly lower than in the area of damage (the index "inflammatory foci/lung tissue" has averaged 0.7 ± 4.2) and after 2 hours did not exceed 1.6% ± 0.2% of the total activity. By the end of the experiment (24 hours), the radioactivity of lung tissue in the zone of interest was not different from background values.

On scintigrams of animal's chests obtained 2 hours after the lymphotropic introduction (into the interspinous ligament) of the radiofarmaceutical, the most intensive (local) accumulation of the indicator was marked at the site of antibiotic's injection (**Figure 2**). This pattern persisted throughout the study. In the perifocal area and in

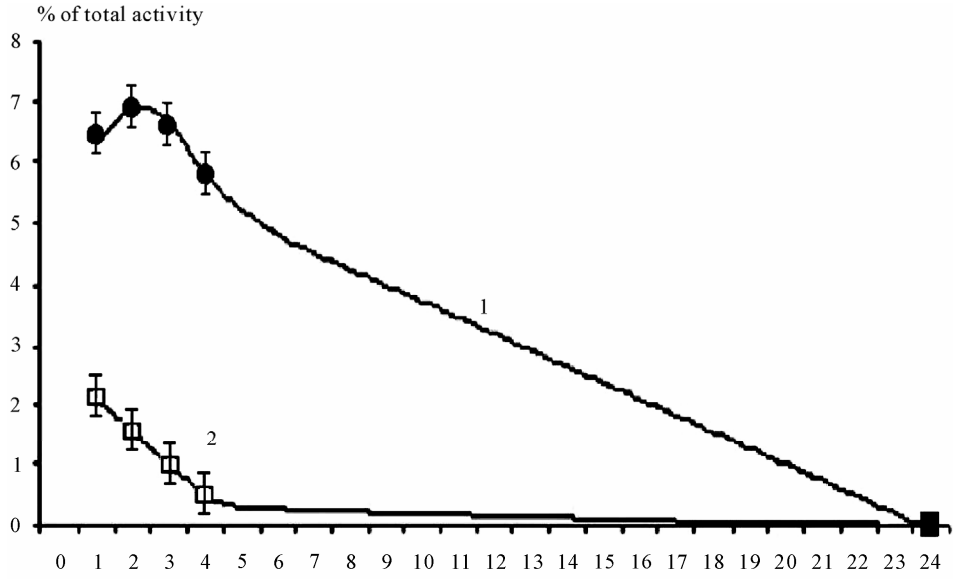

Figure 1. The dynamics of accumulation of ^{99m}Tc-ciprofloxacine in lungs after intravenous injection. (1: radioactivity in the inflammation foci; 2: radioactivity in the intact tissue).

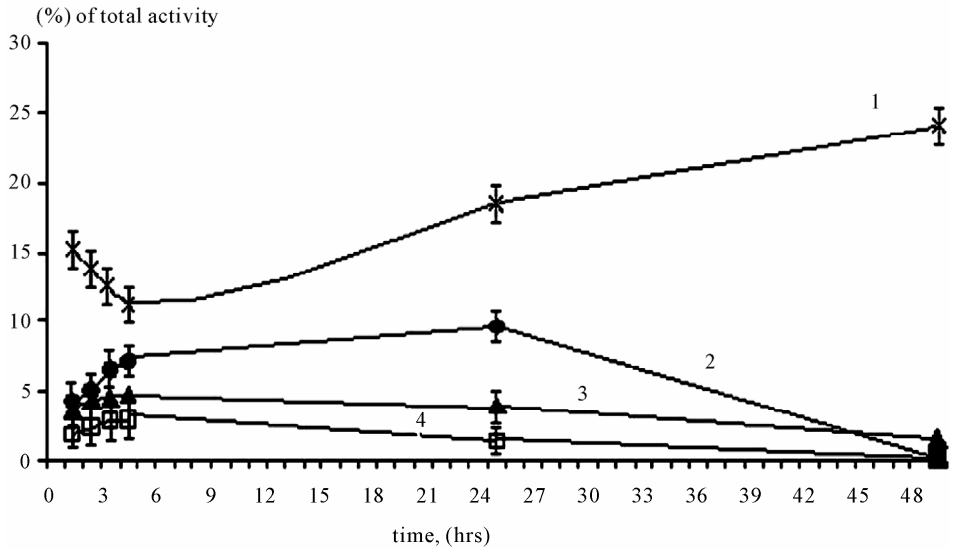

Figure 2. The dynamics of accumulation of ^{99m}Tc-ciprofloxacine in lungs after the lymphotropic injection. (1: site of injection; 2: inflammation foci; 3: lung root projection; 4: lung).

0.2% and 4.5% ± 0.4% of the total body radioactivity, respectively.

On scintigrams obtained 24 hours after injection of the indicator clearly visualized as increased radioactivity at the site of injection, and the medium-intensity local accumulation of ^{99m}Tc-ciprofloxacin in the inflammation of the right lung. Later on in concordance with radioactive decay of technetium it was the gradually slow decreasing of the rate of scintillation counting over the lung area, and two days later the presence of the radiopharmaceutical was not registered.

Distribution of "^{99m}Tc-pertechnetate" after its lymphotropic injections to healthy dogs is shown in **Figure 3(a)**. After 1 h post injection there was rapid redistribution of the radiopharmaceutical with a maximum accumulation in the stomach (2.2% of total activity). In the same period at the lung root projection the presence of indicator was minimal, averaging 1.1% of the total activity. Further 99mTc-pertechnetate washed out from the injection site with a parallel increasing of its concentration in a stomach. After 4 hours, the drug distributed as follows: 0.8% of the administered activity at the injection site, 1.4%—in the lung root projection, 3.2%—in the stomach, the rest—are uniformly throughout the body. After a day in the thorax activity was not recorded.

The distribution of ^{99m}Tc-radioactive colloid after introduction into the interspinous ligament was as follows: at 1 h post injection the main part of the drug remained at the injection site (96.3%), at 3 hours—a small activity (4.6% of the total), appeared in liver, at the same time in the lung root projection accumulation of radiopharmaceutical was not observed (**Figure 3(b)**).

Figure 3(a) shows the pharmacokinetics of ^{99m}Tc-ciprofloxacin after lymphotropic introduction to healthy dogs. At the first stage of the experiment 16% of antibiotics remained in the injection site, following by its gradual washing-out from this area and increasing in a lung root. After 4 hours at chest slices, along with the area of administration, clearly visualized fixation of the radiopharmaceutical in the lung root projection (7.4% of the total), which remained high (7.1%) also at 24 hours. In the same time radioactivity at the injection site declined to 13.2%. In the lung tissue at all stages of the study activity of ^{99m}Tc-ciprofloxacin has remained low and averaged 3.5%.

After intravenous injection each of three radiopharmaceuticals accumulated in dog's organs according to the normal physiologic distribution of these indicators [9].

Thus, the results of experiments showed that the intravenous route of antibiotic ensures its rapid accumulation and washing-out from a septic focus. Such use of the drug can be necessary when an urgent creation of a high concentration of drug in the area of bacterial lesions is needed. On the other hand, the rapid washing-out of the drug from the target organ determines the need of frequent repeated injections, the amount of which depends on the choice of drug, its chemical and biological properties. In addition, intravenous injection, as is known, is accompanied by binding of antibiotics with blood proteins, making it necessary to use sufficiently high concentrations of these drugs to achieve therapeutic effect, which is unfavorable for the organism as a whole.

Lymphotropic route of administration provides, in accordance with our data, targeted and sustained action of antibiotic. Thus, "^{99m}Tc-ciprofloxacin" after injection

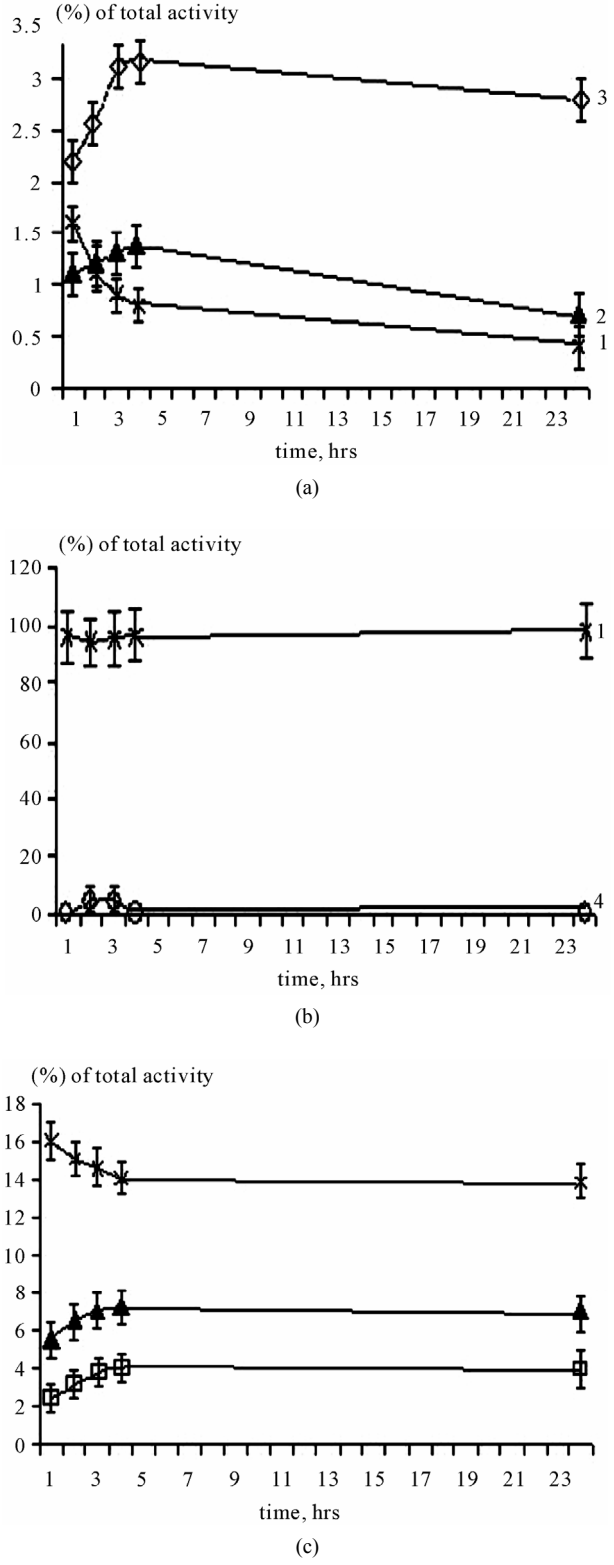

Figure 3. Distribution of different radio pharmaceuticals after limfotropic injection to healthy dogs (% of total activity). (a) "^{99m}Tc-pertechnetate"; (b) "^{99m}Tc-radioactive colloid"; (c) "^{99m}Tc-ciprofloxacin"; 1: injection site; 2: lung root projection; 3: stomach; 4: liver; 5: lung.

into the interspinous ligament, avoiding urinary tract and liver, slowly delivered to the area of inflammation, where reaches a maximum only after 24 hours. This fact suggests the possibility of reducing the number of injections to 1 in 24 - 36 hours, as well as reducing the total dose and the toxic effects of the drug. When there is a need for rapid achievement of high concentrations of antibiotic in the inflammatory foci and preservation of prolonged antimicrobial effect, in our opinion, the combination of both methods of administration is possible. This intends a treatment regimen that includes initial intravenous injection of antibiotics with subsequent transition to lymphotropic injections until the end of treatment.

Results of control studies have shown the absence of local accumulation of "^{99m}Tc-ciprofloxacin" in lung tissue of healthy animals, which once again confirms the ability of radiopharmaceutical to accumulate selectively in sites of tissue damage. Significant dependence of absorption rates of radiopharmaceuticals from the injection site to lymphatic system on theirs physicochemical properties suggests that the frequency of lymphotropic injections will depend on the characteristics of the selected drug. For example, colloidal radiopharmaceutical, which has the largest molecular weight, within two days remained in the injection site and didn't enter the lymphatic and circulatory systems, while "^{99m}Tc, pertechnetate" the most rapidly absorbed into the blood.

In conclusion, it should be noted that this study confirms the possibility of antibacterial agent's delivery into the inflammatory foci by interspinous injection and as a result reduction of daily and course dose of antibiotics. However, in our opinion, this question requires further experimental biochemical, and clinical researches.

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