EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

Comparative Scintigraphic Study of ^{99m}Tc Ciprofloxacin Pharmacokinetics after Intravenous and Lymphotropic Administration in Experimental Pulmonary Suppuration

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Intravenously injected ^{99m}Tc ciprofloxacin is rapidly accumulated and washed from the septic focus. Lymphotropic injections provide targeted and long-lasting effect of the antibiotic. After injection into the interspinous ligament the drug slowly enters the inflammation area (bypassing 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.

Key Words: *^{99m}Tc ciprofloxacin; lymphotropic injections; intravenous injections*

Acute suppurative diseases of the lungs remain a pressing medico-social problem. They are usually characterized by extensive involvement of the organ and run severe life-threatening course. The lymph system in this disease is actively involved in the inflammatory process and participates in immune defense reactions and detoxification [2].

An important pathogenetic components of pyoinflammatory process is active lymphogenic resorption of the microflora from the focus of inflammation. In this context the increase in antibiotic concentration in the lymph system can appreciably improve the efficiency of etiotropic therapy [2]. However, traditional methods of antibiotic administration fail to create sufficient stable concentration of the drug in the lymph [6]. Hence, in 1986 a method of indirect endolymphatic (lymphotropic) therapy was proposed, based on the use of substances (lidase, terrilytin, trypsin, chymotrypsin) improving permeability of lymph capillaries [3]. This created conditions for enhanced targeted transport of the drug from tissue into lymph capillaries; antibiotic concentrations in the lymph increased and lymph flow was accelerated 2-10-fold and more [3].

Numerous methods of lymphocorrection and lymphosanitation, including interspinous lymph-stimulating blockades according to M. S. Lyubarskii, are now widely used in therapeutic and preventive medicine at the empirical level [5]. However, the advantages of lymphotropic therapy over intravenous injection of antibiotics cannot be considered proven, because there are still no persuasive data on the dynamics of drug accumulation in the inflammation focus and on the pharmacokinetics and dynamics of drug clearance from the body after the use of this method.

These problems can be solved by using radiolabeled antibiotics (radiopharmaceuticals, RP), *e.g.* ^{99m}Tc ciprofloxacin [9].

We compared the kinetics of ^{99m}Tc ciprofloxacin accumulation in the focus of inflammation in the lung after intravenous and lymphotropic injection of the drug.

MATERIALS AND METHODS

Experiments were carried out on 12 adult mongrel dogs of both sexes with due consideration for the "Re-

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gulations for Handling Experimental Animals" (Order of Ministry of Health of the USSR No. 755 of August 12, 1977). These experimental animals were chosen because high quality scintigraphic images, with available resolving capacity of the equipment, can be obtained only on large objects.

The main experimental group consisted of 5 dogs with acute staphylococcal pneumonia induced by the method of G. Sh. Chachibaya (1981) [8]. To this end, *Staphylococcus aureus* suspension containing 1,000,000 bacterial bodies was injected into the lung tissue (intercostal space VII-VIII). The formation of inflammatory infiltration was evaluated clinically and by X-ray examination.

Five days after phlogogene injection, drug cocktail was prepared *ex tempore*: 2 mg (6 mCi) ^{99m}Tc ciprofloxacin, 32 U lidase, 4 mg dexamethasone, 100 mg 10% lidocaine, and 40% glucose (total volume of injected mixture 6 ml). The mixture was injected to dogs into the minor subcutaneous vein of the hind limb. ^{99m}Tc ciprofloxacin RP was manufactured at Institute of Nuclear Physics by the method of K. E. Britton *et al.* [9] in our modification; radiochemical purity of the preparation was 95%.

Scintigraphic images were recorded 1, 2, 3, 4, and 24 h after the injection.

Two days after the first study ^{99m}Tc ciprofloxacin was injected repeatedly in a drug mixture of the same composition in the same dose, not intravenously, but into the interspinous ligament at the level of Th2-Th3, Th3-Th4, Th4-Th5 vertebrae (sites of maximum presentation of surface lymph collectors). RP distribution was monitored 1, 2, 3, 4, 24, and 48 h postinjection.

Control studies were carried out on 3 groups of healthy animals (3 animals per group) according to the following protocol: intravenous injections of analogous drug complex containing RP of different chemical and biological characteristics: ^{99m}Tc pertechnetate (TcO_4Na) (group 1), ^{99m}Tc, Technephyte (colloid solution of phytin-based ^{99m}Tc) (group 2), or ^{99m}Tc ciprofloxacin (group 3). After 2 days, radionuclide indicators were injected lymphotropically in the same dose according to the same protocol. Scintigraphy was carried out 1, 2, 3, 4, and 24 h postinjection (control).

Scintigraphic images were obtained on a GSK 301T gamma camera (VNIIMP) in planar and tomographic modes.

During investigation the dogs were placed with their ventral surface to the gamma camera detector, so that the whole body was in the visual field. The differential discriminator was fixed to the 140 keV photopeak at 20% window width. Scintigraphic data were processed using Scinti applied software pack (Gelmos), after which "zones of interest" were distinguished and activity—time curves were plotted.

RESULTS

One hour after intravenous injection of ^{99m}Tc ciprofloxacin its maximum accumulation was recorded in the kidneys (≅30% of the total activity) and urinary bladder (≅60% of total activity), which corresponded to normal biological distribution of RP [9]. According to the time course of the indicator accumulation in the lungs, the scintillation count in the focus of inflammation peaked after 2 h (6.9% of total activity), after which RP was slowly washed out (Fig. 1). The content of the preparation in intact lung tissue remained lower than in the focus of inflammation throughout the experiment (focus of inflammation/lung tissue coefficient was 4.2±0.7) and after 2 h did not surpass 1.6%

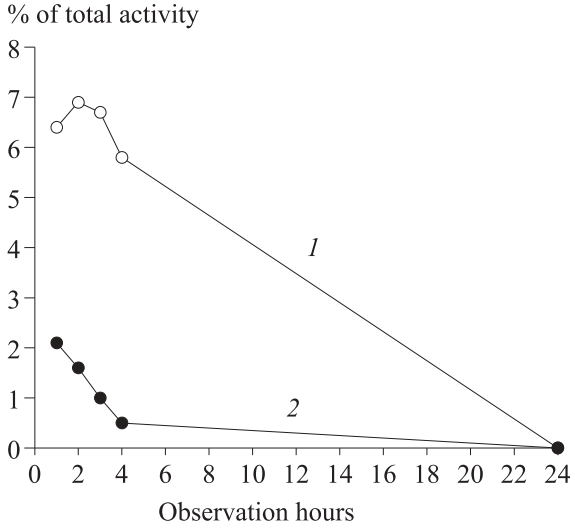

Fig. 1. Dynamics of ^{99m}Tc ciprofloxacin distribution after its intravenous injection to a dog with pneumonia. *1*) focus of inflammation; *2*) lung.

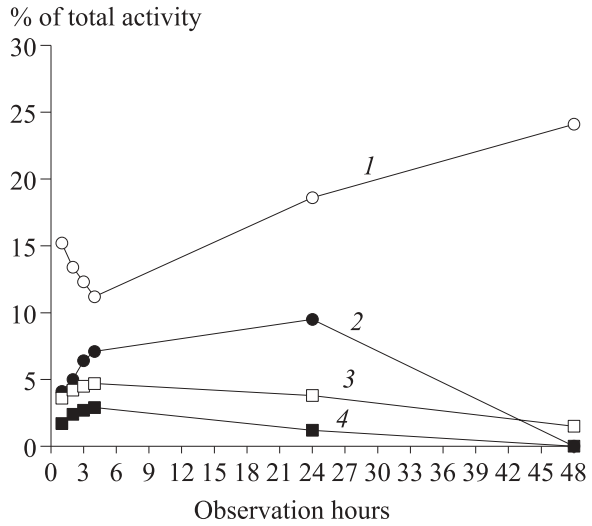

Fig. 2. Dynamics of ^{99m}Tc ciprofloxacin distribution after lymphotropic injection to dogs with pneumonia. *1*) site of injection; *2*) focus of inflammation; *3*) projection of the lung root; *4*) lung.

of total activity. By the end of the experiment (24 h) lung tissue radioactivity in the zone of interest was at the background level.

Scintigrams of the chest 2 h after lymphotropic injection of RP (into the interspinous ligament) showed the most intense (local) incorporation of the indicator at the site of antibiotic injection. This picture did not change throughout the observation period.

The level of the indicator accumulation in the focus of inflammation in the lung was 5% of total activity after 2 h, which was 1.4 times lower than after intravenous injection under similar conditions (Fig. 2). After 24 h the concentration of ^{99m}Tc ciprofloxacin in the inflammatory zone reached its maximum (9.5% of total activity). Accumulation of the preparation in the perifocal area and projection of the lung root remained low 1-24 h postinjection (2.2 and 4.5% of total activity in the body, respectively).

Scintigrams recorded 24 h after indicator injection clearly show increased radioactivity at the site of drug injection and local medium-intense accumulation of ^{99m}Tc ciprofloxacin in the focus of inflammation in the right lung. Later, the rate of scintillation above the lungs gradually decreased, and no RP was detected there after 2 days.

As soon as 1 h after lymphotropic injection of ^{99m}Tc pertechnetate to healthy dogs RP rapidly redistributed in the body with maximum accumulation in the stomach (2.2% of total activity; Fig. 3, *a*). The presence of the indicator in the projection of the root of the lung during the same period was minimum (1.1% of total activity). Later ^{99m}Tc pertechnetate was washed out from the site of injection, which was paralleled by an increase in its concentration in the stomach. After 4 h the preparation distribution was as follows: 0.8% of injected activity at the site of injection, 1.4% in the lung root projection, 3.2% in the stomach, and the rest evenly in the whole body. No activity was recorded in the chest after 24 h.

One hour after injection of ^{99m}Tc Technephyte into the interspinous ligament virtually the entire (96.3%) volume of the injected preparation remained at the site

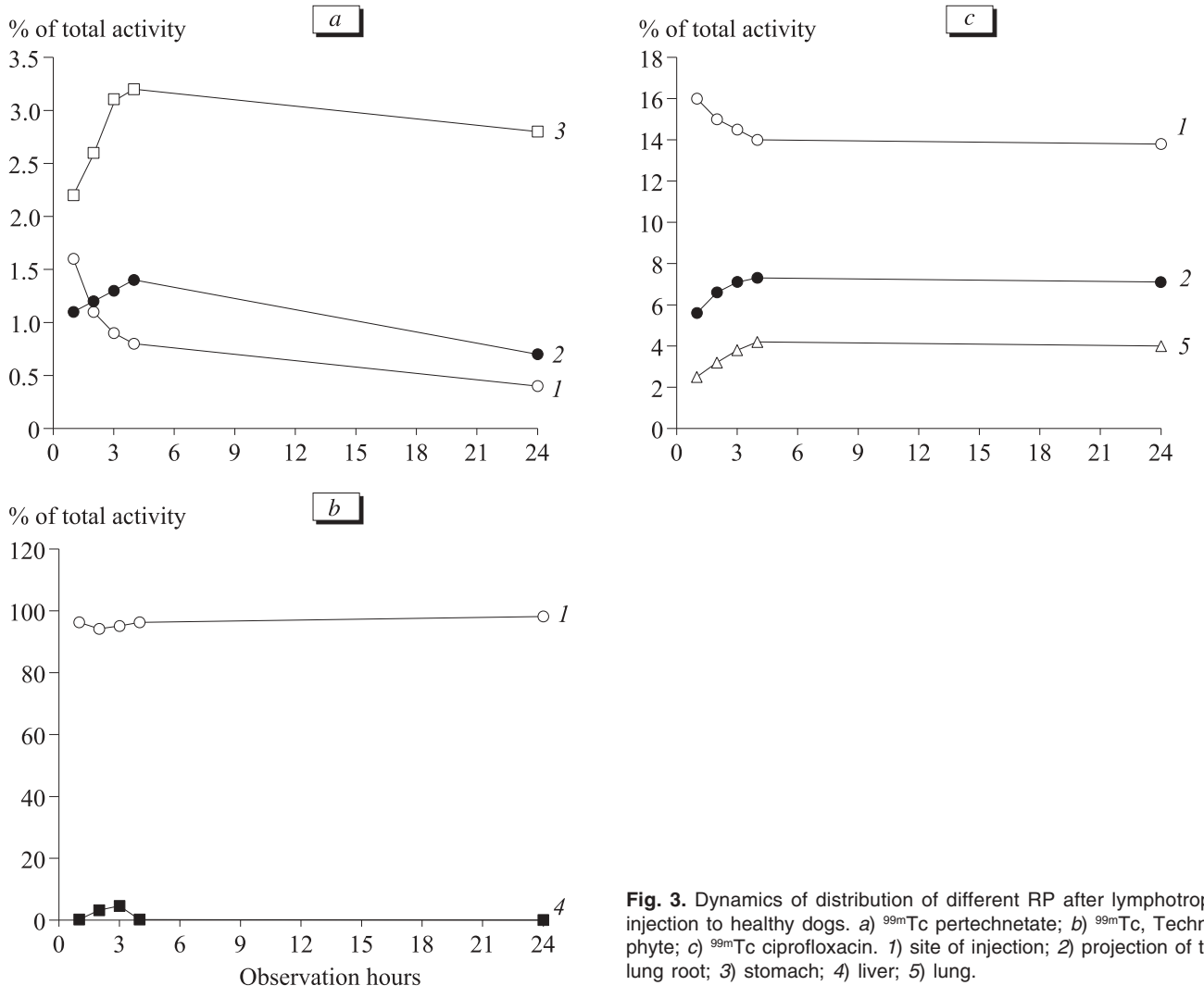

Fig. 3. Dynamics of distribution of different RP after lymphotropic injection to healthy dogs. *a*) ^{99m}Tc pertechnetate; *b*) ^{99m}Tc, Technephyte; *c*) ^{99m}Tc ciprofloxacin. *1*) site of injection; *2*) projection of the lung root; *3*) stomach; *4*) liver; *5*) lung.

of injection; after 3 h minor activity (4.6% of total activity) appeared in the liver. No accumulation of the indicator was seen in the lung root projection (Fig. 3, *b*). No changes in ^{99m}Tc Technephyte distribution in animal body were seen in later scintigrams.

One hour postinjection 16% of the antibiotic remained at the site of lymphotropic injection of ^{99m}Tc ciprofloxacin to healthy dogs (Fig. 3, *c*). Later, it was gradually washed out from this zone and its level negligibly increased in the root of the lung. After 4 h, RP was detected, in addition to the injection area, in the projection of the root of the lung; its fixation was clearly seen on tomographic sections of the chest (7.4% of total activity) and this level remained high (7.1%) after 24 h. Radioactivity at the site of injection decreased to 13.2%. Activity of ^{99m}Tc ciprofloxacin in lung tissue remained low during all periods of the study, the mean value was 3.5%.

After intravenous injection accumulation of all three RPs in dog organs corresponded to normal physiological distribution of these indicators [7].

Hence, the results indicate that intravenous injection of antibiotic leads to its rapid accumulation and washing from the septic focus. This treatment method can be justified when high concentration of the drug should be urgently delivered to the site of bacterial involvement. But active washing out of the drug from the target organ necessitates frequent injections, the number of injections depends on chemical and biological characteristics of the drug. After intravenous injection antibiotic binds to blood proteins, and high concentrations of the antibiotic are required for attaining the therapeutic effect, which is fraught with toxic side effects.

Lymphotropic injection ensures, according to our data, directed prolonged effect of the antibiotic. For example, ^{99m}Tc ciprofloxacin injected into the interspinous ligament by-passes the kidneys and liver and is slowly delivered into the focus of inflammation, where it is maximally accumulated only after 24 h; hence, only 1 injection in 24-36 h is sufficient and the total dose and toxic effect of the drug can be thus reduced. If it is necessary to deliver high concentrations of the antibiotic to the focus of inflammation urgently and prolonged antibacterial effect of the drug is desirable, both routes of administration can be combined. The following treatment protocol can be proposed: initial intravenous injection of the antibiotic is followed by lymphotropic injections until the end of treatment.

Control studies showed the absence of local incorporations of ^{99m}Tc ciprofloxacin in the lung tissue of healthy animals, this once more confirming RP capacity to selectively accumulate in tissue lesion foci. Appreciable difference between the velocities of absorption of radionuclide indicators with different physicochemical characteristics from the site of injection into the lymph system of the root of the lung indicates that the frequency of lymphotropic injections is determined by drug characteristics. For example, colloid RP ^{99m}Tc, Technephyte with its highest molecular weight virtually remained at the site of injection for 2 days and not appeared in the lymph and blood systems, while ^{99m}Tc pertechnetate was absorbed by the blood most rapidly.

The findings confirm the possibility of delivering antibiotics into the focus of inflammation by means of interspinous injections, thus reducing the daily and total doses of the drugs; however, further experimental biochemical and clinical studies of this method are needed.

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