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Lymphotropic administration of photosensitizer as a model of target therapy of testicle inflammation: Experimental and clinical data

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ABSTRACT

Background: The existence of zones of humoral skin–subskin tissue linkage with internal organs as well as the possibility of targeted administration of preparation into the affected organs were studied.
Methods: An experimental study of preparation and distribution in the bodies of mice was held by both intravenous and lymphotropic methods of administration. By means of detection with a photosensitizer (as a marker), the study was conducted on healthy mice and mice with testicle inflammation.

Based on the experimental results, the study has been implemented into the clinical practice of treatment of acute inflammatory diseases of testicle and its epididymis. Patients were administered antibiotics either by the lymphotropic method, or by traditional methods.
Results: The concentration of the preparation, administered by the lymphotropic method, maintained in target organs (testicles) at a high level for a longer time, while the intravenous injections provided fast achievement of high concentrations. Moreover there was a lower level of accumulation of the photosensitizer in parenchymal organs after subcutaneous (lymphotropic) administration.
Conclusions: The presence of humoral connection of certain areas of skin and subcutaneous tissue with testicles and their epididymis was proved. It was found that the lymphotropic administration leads to earlier clinical improvement and normalization of laboratory indices, and, thus, to significant reduction in hospital stay. Such results open the possibility of targeted drug delivery to the diseased organs. In perspective, the method may be used in treating patients not only in urology, but also in surgery, as well as for many acute, chronic or cancer diseases.

1. Introduction

Targeted delivery of medicinal preparations and maintenance of their high concentrations in the affected organs and tissues are among the most urgent problems of modern medicine. Traditional methods of drug delivery to the organs (intravenous, intramuscular, oral) do not cover all the medical necessities for fast, safe and successful treatment. Thus it is extremely important to find and develop new ways of drug administration. One of the methods of injection, providing high concentrations of preparations in target organs and maintaining a high concentration for a long period of time, is endolymphatic administration. At the present time several methods of endolymphatic administration such as lymphovascular [1], intranodular [2], lymphotropic [3], extracorporeal lymphosorption [4], lymph reinfusion [5], and controlled drainage of the thoracic duct [6–8] are known. Experimental searching and clinical impressions allowed the definition of two main methods of endolymphatic drug administration: direct endolymphatic administration through catheterized peripheral lymphatic vessel and indirect saturation of lymphatic system. The main advantages of the second method are: it is less invasive so there is no need for direct surgical intervention or for special surgical skills [9], and thus accessibility for doctors of different specialties. Administration of a drug in a certain part of the body allows obtaining the saturation only of a lymphatic area which drains this part of the body. This is the basic idea of regional lymphotropic therapy [10].

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It is considered that the most effective and simple method of drug saturation of a lymphatic system is lymphotropic therapy which provides high and long-lasting concentration of preparations in pathological areas and in local lymphotropic capillaries and nodes [11].

Driven by the influence of the factors disrupting lymph transport (such as diseases and pathological states of lymphatic system, various diseases of inflammatory, tumorous and sclerotic gneisses, endogenic intoxication, surgical operations etc.) certain compensatory-adaptive mechanisms "turn on". These mechanisms are: enhancement of propulsive activity of lymphangions, inclusion of redundant routes, opening of collaterals, capacity expansion of a lymphatic channel, and retrograde lymph flow [12]. These mechanisms give perspective on using reverse lymph flow, which appears at acute inflammation and other pathological conditions of organs and tissues, as a basis for lymphogenous drug therapy (by both, direct and indirect, ways of preparation saturation of a lymphatic system).

Lymphological methods are successfully applied in some medical fields: surgery [2,13–15], gynecology [16], urology[1,5], therapy [17,18], phthisiology [19,20], oncology [10,21], and others. One can find information on preparation accumulation in liver, kidneys, pancreas and other organs at lymphotropic administration [4,11]. However, using the above mentioned methods of endolymphotropic administration there is a side effect of the preparation penetrating healthy organs and tissues. Nevertheless the lymphotropic and "epicentric therapy" methods allow a significant decrease in such penetration. Several assumptions, like the existence of zones of humoral skin–subskin tissue linkage with certain inner organs, influence interstitial humoral transport and tissue lymphatic drainage, interconnection of lymphatic paths with inner organs on the surface of skin [12,22,23] play particular roles in the perspective of successful lymphotripoc therapy. Herewith the daily dose and the duration of treatment significantly decreases [12,22,23]. The delivery of the preparation to target organs in lymphotropic therapy is carried out either by tissue and lymphovascular transport (tissue → lymphatic system → organ-epicenter of accumulation) or passing it (tissue → tissue (another type) → organ-epicenter of accumulation).

At the present time there are no fundamental data certifying the humoral connection between skin–subskin tissue and certain organs. The application of photosensitizers (PS) as markers for detection can be used in order to confirm or disprove this theory. Thus we can summarize that the purpose of this paper is the study on the existence of the zones of humoral skin–subskin tissue linkage with certain inner organs. In order to achieve this purpose we have to accomplish the task of analysis of specifics of distribution and accumulation of PS at its lymphotropic (subcutaneusely) and intravenous administration to healthy laboratory animals and animals with an experimental model of pathological process at different time intervals.

2. Materials and methods

2.1. Experimental part

Inverse flow in the lymphatic system can occur only when there is pathology in an organ so we have performed an experimental model of inflammation. Testicle inflammation has been selected as the most convenient model.

Experimental study of distribution, accumulation and excretion of the PS in organs and tissues of male white laboratory mice was carried out in two stages. At the first stage the study was conducted on organs of healthy mice, and at the second stage on organs of mice with inflammation of the testicle. As a marker for spectral measurements of preparation accumulation a PS of a Chlorin [24–26] E6 derivative "Photoditazin" [27] was used.

A 20 μL volume of the PS was administered into the mice at a concentration of 5 mg/kg. The mice were divided into two groups according to the method of administration: a main group and a control group. In each group there were 35 mice for the first stage of the study, and 25 mice for the second stage. The Photoditazin was administered to the animals of the main group by a lymphotropic mean (subskinly, at the inguinal region), and of the control group-by a tail vein injection.

Acute aseptic inflammation was provoked by administration of 10 μL of 10% formalin solution to the testicles of white laboratory mice. In 2 days after the formalin administration the PS was injected to the mice.

After cervical dislocation of laboratory animals at certain time points (from 15 min to 24 h) the mice were fixed and their abdominal cavity was dissected layer by layer.

The measurements of back-scattering and fluorescence signals from mice organs (testicles, liver, kidneys, and spleen) were carried out by spectrum analyzer «LESA-01-BIOSPEC». He–Ne laser with the wavelength of 632.8 nm and the output power of 5 mW at the fiber end was used as an irradiation source for fluorescence excitation. A fiber-optic probe with one illuminating and six receiving fibers (each of 200 μm diameter) was attached to the spectrometer. During the spectra measurements the probe was "in contact" with mice organs. The spectra were registered in the range of 400–900 nm. The output of the signal processing were fluorescence indices (in relative units) obtained by division of the fluorescence signals and backscatter signals. The maximal signals for each organ at every time point were selected for further analysis.

2.2. Clinical part

We have implemented the target lymphotropic administration in clinical practice for the treatment of patients with acute inflammatory diseases of testicle and epididymis. The basic idea was to estimate the effectiveness of the application of such an administration method in comparison with traditional methods.

As the basis of this research the results of a complex examination and treatment of 72 patients aged from 16 to 85 years with acute inflammatory diseases of testicle and epididymis were used. The patients were at in-patient treatment at the Urology Department of Moscow City Clinical Hospital №51. The patients of the most sexually active age (from 16 to 35 years) formed 26.38% of the group; 9.74% was formed by the patients aged 36–45 years; 30.55% of the age 46–60 years, and 33.33% of the patients older than 61 years. The patients of the most working age formed 66.67% (18–60 years old).

The clinical trial included patients' complaints, life anamnesis and anamnesis of the disease, physical and instrumental examinations. Ultrasound investigation of the scrotum was carried out for all the patients after being admitted to the hospital, and the dynamic monitoring was conducted during the entire course of treatment. The investigation was made using an ultrasound device «Aplio» MX SSA-780A, TOSHIBA. In order to control and to determine the effectiveness of the administered therapy the body temperature of all the patients was measured every day. Furthermore, the presence or absence of leukocytosis and its dynamics were estimated during the complete blood analysis, and were conducted at the time of hospitalization, then after 2–4 days, 4–6 days, 7–9 days and after 10–13 days (and more often if necessary). Clinical urine analyses were done according to the standard methods.

For our study the patients were divided into two groups: main and control. The main group included 25 patients (34.72%), the control group—47 patients (65.28%). Due to the ineffectiveness of the conservative therapy 6 patients out of 72 underwent the surgical