SUBSTANTIATION OF A NONINVASIVE METHOD
OF ADMINISTRATION OF DRUGS AT THE PRELYMPHATIC LEVEL

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Parenteral administration (intramuscular, subcutaneous, or intravenous injection) of drugs is widely used in clinical practice. However, this method of drug administration does not meet the requirements of modern medicine because of low productivity, problems with sterilization of syringes and needles, and the hazard of transmission of such infections as virus hepatitis, AIDS, etc. Use of jet injectors [4] is a significant improvement on this method. A high-speed jet destroys structure of biological tissues at the site of injection and saturates it with drug. This exerts a strong effect on the topographic features of the site of injection: skin, hypodermic fatty tissue, fascia of muscles, muscles, muscular fascial spaces, blood and lymphatic vessels, and capillary bed. This is especially dangerous if the site of injection lies near the focus of an inflammatory or pyo-necrotic process because of the hazard of dissemination of the infection. Besides, jet injection injures blood and lymph microcapillary bed, thereby interfering with the processes of drainage, detoxication, metabolism, and regeneration in the infection focus.

The lymphatic system is one of the main functional systems of human body [3, 5]. It provides various mechanisms of intoxication: mechanical (filtration), biochemical (catabolism of toxins), biological (immune reactions, phagocytosis). Therapy of the lymphatic system should support its function of detoxication.

On parenteral administration, a drug diffuses into the lymphatic system through adjacent tissues, which decreases its concentration and activity. This can be avoided by a lymphotropic method of administration, when a needle is introduced into the interdigital space and the drug under pressure penetrates into lymph capillaries and further into lymphonodi. The disadvantages of this method are low speed of administration and a traumatic effect on the skin and hypodermic tissues exerted by the needle, which resides at the site of injection for a long time. Direct administration of drugs into a lymphatic vessel is a difficult task because of unstable topography of lymphatic vessels. Besides, it exerts a traumatic effect on the vessel.

Taking into account all these facts, the following requirements can be imposed upon new methods of administration of drugs: they should be noninvasive (without traumatic effect on the lymphatic system); they should provide high administration rate to produce sufficient concentration of drug; the most part of administered drug should find its way into the lymphatic rather than blood vessels.

Methods of physiotherapy, such as electrophoresis, magnetotherapy, laser therapy, ultrasonic therapy (at high and low frequencies of ultrasound), etc. [1, 2, 8, 9] can be used for drug transfer activation. However, the problem of drug impregnation to a sufficient depth without injury to biological tissues cannot be solved by the use of these methods. The horny layer of epidermis is almost impenetrable for liquids applied from the outside and prevents their penetration into the lymph capillaries (V. I. Kolpakov, 1970). Besides, these methods of physiotherapy are elaborate and require sophisticated equipment.

The method of thermocontrasting adsorption of drug solution (TCADS) developed in our laboratory is a noninvasive method of local administration of drugs into biological tissues at the prelymphatic level without injury to skin [6]. The method meets the requirements listed above. It is based on increasing skin permeability by sequential stimulation and inhibition of perspiration at the site of administration of a drug. This provides the drug penetration to a significant depth without injury to skin. Perspiration is stimulated and then inhibited by a number of physical factors, including contrasting heating-cooling cycles supplemented with an additional nonthermal effect, such as exposure to low-frequency ultrasound (LFUS). This additional physical factor activates rheological and diffusion processes at the drug solution interfaces with the surface of skin, sweat duct, and walls of hair follicle cavity, thus increasing skin permeability. The drug applied to the skin surface over the focus of lesion penetrates deeply and impregnates tissues, plasma, intertissue liquid, and lymph between the skin and lesion focus, and the lesion
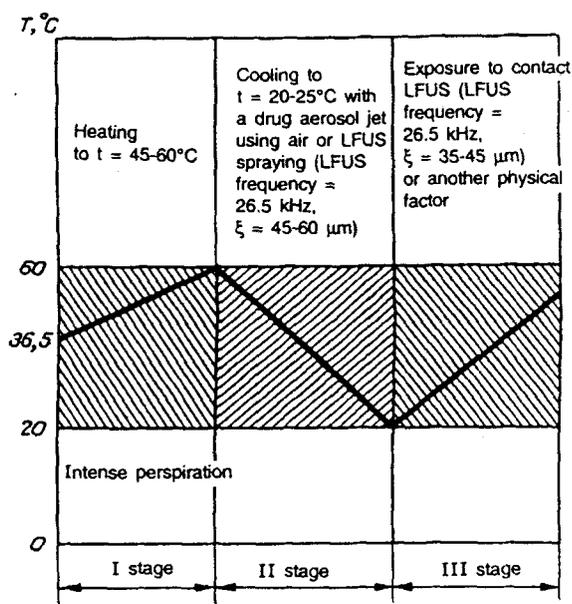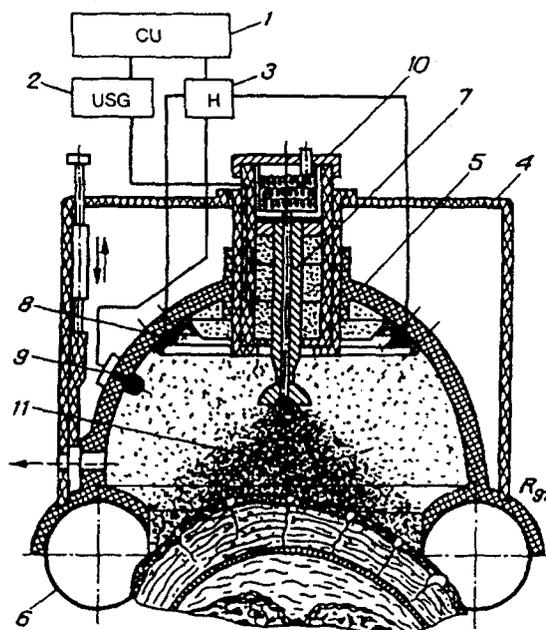
Fig. 1. Cyclogram of the heating-cooling process that increases skin permeability without injury.

Fig. 2. Scheme of a pilot model of the PROLONG-1 device: 1) control unit (CU); 2) US-generator (USG) or source of air spraying; 3) source of heating (H); 4) applicator; 5) carrier body; 6) elastic arrester; 7) spraying unit: acoustic or air sprayer (source of cooling); 8) heater (IR-radiation); 9) temperature detector; 10) system of drug administration; 11) aerosol jet.

focus itself. This provides prolonged residence of drug in the zone of lesion. The physical factors listed above produce changes in the tissue metabolism and increase the therapeutic effect of the drug.

The kinetics of the process of increasing skin permeability by the TCADS method is shown in Fig. 1.

The transglandular (rheological) route of drug penetration through the sweat ducts and cavities of the hair follicles is implemented at the first and second stages of the process. Clean and dry surface of skin is heated to 45-60°C, which initiates intense perspiration, then it is rapidly cooled to 20-25°C, and held at this temperature for 30-60 sec. There are 2-3 repeated heating-cooling cycles in one procedure. The scheme of a pilot model of the PROLONG-1 device used at this stage of the process is shown in Fig. 2.

According to [7], repeated contractions and relaxations of sweat glands induce reciprocal motion of sweat in sweat ducts, through which drug penetrates under the skin. Accumulated drug penetrates through the walls of the sweat ducts into intercellular space and cellular liquid. The mechanism of drug penetration through the cavities of the hair follicles is almost the same. Sweat ducts and hair follicle cavities are surrounded with a network of lymph and blood capillaries. At the third stage of the process, the site of impregnation is exposed to contact LFUS (Fig. 3), which increases the diffusion of the drug accumulated near sweat ducts and hair follicle cavities into the capillary bed. Exposure to LFUS increases permeability of skin and walls of sweat ducts and hair follicle cavities to ions and molecules of drug. The chemical activity of ions and molecules of drug is increased. Circulation of lymph and blood provides impregnation of the focus of a lesion with drug and prolonged residence of drug in the zone of the lesion.

A number of clinical studies were carried out for experimental substantiation of the TCADS method. Dynamics and depth of administration of drugs by various methods, morphological changes, and parameters of microcapillary bed were studied. Experiments were carried out on laboratory animals (rats weighing 300-350 g and dogs weighing 8-12 kg). The TCADS method was compared with the following methods of impregnation: application of a compress impregnated with drug; injection with a syringe; electrophoresis (current of 0.5-1 mA); high-frequency phonophoresis (HFUS-phonophoresis, f = 880 kHz); low-
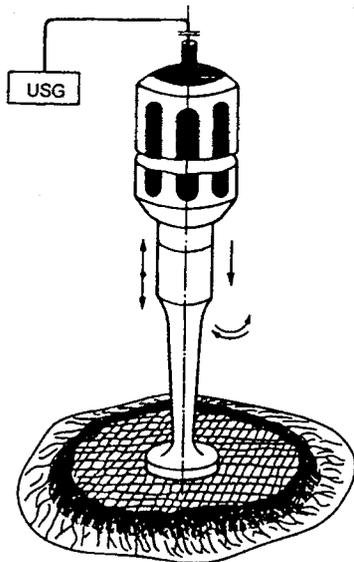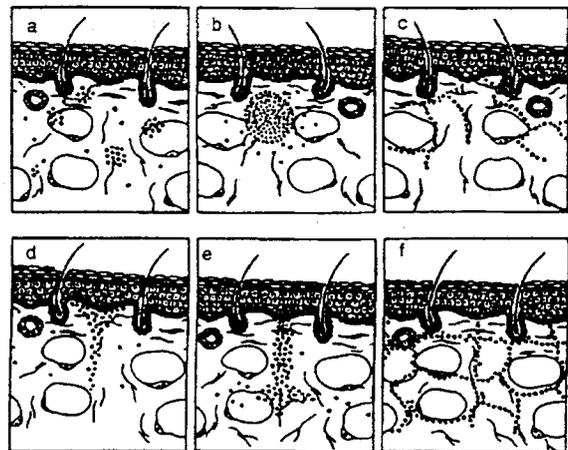
Fig. 3

Fig. 4

Fig. 3. Scheme of exposure of the site of impregnation to contact LFUS.

Fig. 4. Schemes of electron-microscopic photograms (a, b, c, d, e, f) of silver nitrate distribution in tissue for various methods of impregnation.

frequency phonophoresis (LFUS-phonophoresis, f = 26.5 kHz). Silver nitrate solution was used for visualization of pathways and concentration of drug. Penetration of silver nitrate solution into lymphatic system was assessed by studying distribution of ions of silver in subcutaneous fat, blood capillaries, afferent lymphatic vessels, and tissue structures near specialized venules. The studies were carried out by the atomic-absorption method with a Perkin-Elmer analyzer, by the method of visualization of microcapillary bed according to V. V. Kupriyanov, and with the Jeol JSM-35 electron-scan microscope supplied with the Kevex accessory for semiquantitative analysis.

Analysis of experimental results showed that subcutaneous fat is enveloped with a multilevel network of blind-ended lymphatic vessels and capillaries and blood microvessels. The total surface of lymphatic vessels is many times higher than that of blood vessels. Therefore, drug is absorbed mainly by lymph capillaries. Through afferent lymphatic vessels the drug reaches the marginal sinuses of a lymphonodus. The lining of the sinuses is structured as a microsieve for filtering lymph flow. Reticular cells of the lymphonodus tissue form a coarse sieve, on which lymphoid cells settle. Inside the lymphonodus, drug is adsorbed on the surface of cells.

The impregnation efficiency depends on the amount of drug penetrated into lymphonodus. For example, determination of silver nitrate concentration in the popliteal lymphonodus of the knee joint of a dog by ultramicroscopic X-ray diffraction analysis showed that the methods of impregnation can be arranged in order of increasing efficiency as follows: electrophoresis; compress application; HFUS-phonophoresis; LFUS-phonophoresis; TCADS. The ratio between the amount of drug penetrated into lymphonodus and the amount of drug retained by subcutaneous fat is 10:1 for the TCADS method.

The process of distribution of silver nitrate in subcutaneous fat and blood and lymph microcapillary bed is illustrated in Fig. 4.

Application of a compress impregnated with the preparation induces diffusion of silver nitrate molecules into subcutaneous fat and further slow diffusion toward the microcapillary bed (Fig. 4a).

Injection of preparation with a syringe forms a globular node of silver nitrate in subcutaneous fat. The node begins to resolve and silver nitrate penetrates toward adjacent microvessels, which are traumatized by needle and an increase in hydrostatic pressure caused by an artificial edema (Fig. 4b).
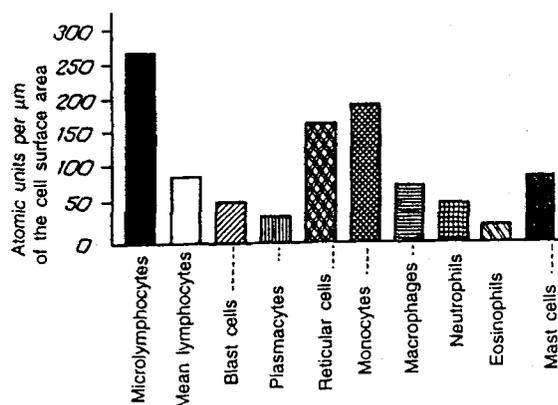
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Fig. 5

Fig. 6

Fig. 5. Concentration of silver ions at the surface of cells of a regional lymphonodus.

Fig. 6. Dynamics of lymphopoiesis rate. The abscissa is the time axis; the ordinate is the number of lymph drops issued in one minute.

If the preparation is administered by electrophoresis, a tree-like structure of silver nitrate distribution is observed (Fig. 4c). The preparation presumably penetrates along the lines of the minimum electric resistance of subcutaneous fat. Microcapillary walls containing semiconducting membrane structures lie aside from these lines.

If the preparation is administered by HFUS-phonophoresis, a cone-shaped structure of silver nitrate distribution in subcutaneous fat is observed. The preparation diffuses into the microcapillary bed (Fig. 4d).

If the preparation is administered by LFUS-phonophoresis, a fungiform structure of silver nitrate distribution in subcutaneous fat is observed. The head of the fungiform structure lies sufficiently deep. The preparation diffuses into the microcapillary bed mainly from this head (Fig. 4e).

Administration of preparation by the TCADS method forms a three-dimensional net-shaped structure of silver nitrate distribution. Lymph and blood capillaries are surrounded with molecules of preparation, which provides a high rate of absorption of preparation from subcutaneous fat into capillary (mainly lymphatic) bed (Fig. 4f).

When the schemes of drug distribution described above are compared with each other, it is apparent the TCADS method provides the most efficient transport of preparation from subcutaneous fat into lymphatic vessels and blood microvessels. Permeability of the walls of lymphatic vessels is increased, which provides more intense diffusion of drug into the lymphatic channel than by other methods of administration of drug.

Ultramicroscopic X-ray diffraction analysis (Fig. 5) of adsorption of ions of silver on the surface of various cells inside a lymphonodus showed that the degree of adsorption depends on the cell function. The density of ions of silver is especially high at the surface of microlymphocytes, monocytes, reticular and mast cells, mean lymphocytes, and macrophages. These cells are the first to come in contact with heterologous elements arriving into the lymphonodus from the zone of drainage. They fulfill the functions of phagocytosis and cooperation of cells in immune response. The other cells can be arranged in order of decreasing density of ions of silver at their surface as follows: neutrophilic granulocytes, blast cells, plasmacytes, and acidophilic granulocytes.

The morphometric parameters of the popliteal lymphonodus of the knee joint of a dog with experimental model of infectious arthritis were changed by TCADS. The maximum rate of lymphopoiesis (determined from the amount of lymph drops issuing from a cannula in the lymphonodus) was attained within 15-20 min of the treatment (Fig. 6). This shows that TCADS is an efficient method of stimulation of lymphopoiesis. Cell count in the cortex of the popliteal lymphonodus is shown in Fig. 7: a) control experiment; b) in a dog with experimental model of infectious arthritis after treatment by the TCADS method; c) in a dog with experimental model of infectious arthritis. It is seen from Fig. 7 (a and b) that the count of mast cells (MAST), monocytes (MON), macrophages (MAC), and mature plasmacytes (MPC) is increased by TCADS in comparison with the control experiment. The count of microlymphocytes (MLC), reticular cells (RET), plasmablasts (PB), and degenerating cells (DEG) is
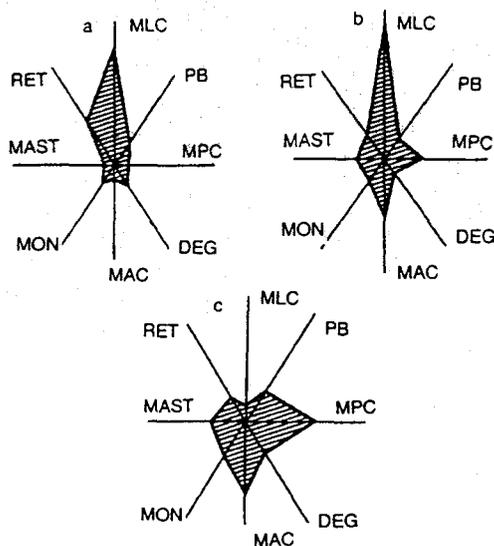
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Fig. 7. Cell counts in the cortex of the popliteal lymphonodus.

almost the same. This shows that the immune functions of lymph are activated, whereas the cell count of the knee joint is unchanged. By contrast, there is an increase in the count of DEG, MAC, MON, and MPC in the knee joint of a dog with uncured infectious arthritis (Fig. 7c).

Conclusions

1. It is shown that conventional methods of administration of drugs provide high concentration of preparation in a small volume of subcutaneous fat with a further slow diffusion into the microcapillary bed. If the method of injection with a syringe is used, the site of injection is injured by the needle and an increase in the hydrostatic pressure is caused by an artificial edema.

2. The TCADS method developed in our laboratory is a noninvasive method of local administration of drugs into biological tissues without injury to skin. It is based on increasing skin permeability by sequential stimulation and inhibition of perspiration in the contrasting heating-cooling cycle. Administration of preparation by the TCADS method forms a three-dimensional net-shaped structure of drug distribution in subcutaneous fat. Lymph and blood capillaries are surrounded with molecules of preparation, which provides a high rate of absorption of preparation from subcutaneous fat into the lymph capillary bed.

3. Exposure to contrasting temperatures during the TCADS procedure is shown to be an efficient method of stimulation of lymphopoiesis. The morphological and cytological structure of regional lymphonodi is modified by TCADS so that the immune function and morphological support of self-clearance reaction are activated.

4. The TCADS method is shown to be an efficient method of noninvasive administration of drugs at prelymphatic level without injury to skin. It is recommended to use TCADS as a clinical method of intensification of rheological and diffusion processes in the zone of impregnation with drug.

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