Lymphoprotective Effect of Perftoran

F. I. Mukhutdinova, R. Kh. Khafiz'janova, K. A. Triandafilov, and D. A. Mukhutdinov

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Experiments on rats showed that the lymphoprotective effect of Perftoran manifests in stimulation of contractile activity of myocytes in the wall and valve cusps of lymphatic microvessels, which in turn activates the pump and capacitive functions of the lymphatic system and improves central lymph outflow. These changes contribute to an increase in the resorption and transport of cell and tissue metabolites from the interstitial space.

Key Words: *Perftoran; lymphatic microvessels; lymph flow*

In modern pharmacology much attention is paid to drugs with multiple pharmacodynamics. Detection of new pharmacological properties of drugs allows us to extend the indications for therapy. This approach contributes to the avoidance of polypagmasy, reduces the cost of drugs, and stimulates the patients to comply with physician's prescriptions. Therefore, the development of new drugs for the treatment of lymphatic disorders and maintenance of the lymphatic resetting and lymphostasis under pathological conditions is an urgent problem.

Here we studied a lymphotropic component in the effect of the first oxygen-transport blood substitute Perftoran (perfluorocarbon emulsion).

MATERIALS AND METHODS

Experiments were performed on 40 outbred rats. Perftoran (Perftoran Company) in a single dose of 1 ml/100 g was injected intraperitoneally. Control rats received an apyrogenic physiological saline. Lymph flow rate in the thoracic lymphatic duct (TLD) was measured at the site of junction with the left venous angle (per unit time). The animals were anesthetized with 50 mg/kg sodium ethaminal. Contractile activity of myocytes in the wall and valve cusps, diameter of the lumen, amplitude of contractions of lymphatic microvessels (LM) in rat mesentery were estimated by means of vital microscopy [2,3]. The total number of leukocytes in 1 μl lymph was evaluated in a Goryaev chamber (5-fold dilution). Lymph smears were stained by the method of Romanovsky–Giemsa to calculate individual cells. The animals were euthanized with a narcotic drug in a lethal dose. The results were analyzed by parametric Student's *t* test.

RESULTS

Injection of Perftoran was accompanied by activation of lymphangion components in LM (Tables 1 and 2). Vasomotion frequency and contractility of valve cusps were increased by 82.1 and 75.1%, respectively. These changes contributed to an increase in the rate of central lymph flow by 81.6%. The diameter of LM lumen decreased by 20.3%. However, the amplitude of myocyte contraction in the wall increased by 41.3%. Single treatment with the drug increased leukocyte transport into systemic circulation with the lymph. At the same time, leukocyte count did not change under these conditions.

It should be emphasized that Perftoran (plasma substitute of multiple action) has the oxygen-transport, anti-acidifying, membrane-stabilizing, and thrombolytic properties. This drug improves microcirculation and stabilizes blood rheology [1,4-6,10,13]. Detoxifying and absorbing effects of Perftoran under patho-

Department of Pathophysiology and Pharmacology, Kazan State Medical University, Republic of Tatarstan, Russia. ***Address for correspondence:*** fimka54@mail.ru. F. I. Mukhutdinova

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logical conditions also contribute to a decrease in rat lymph toxicity after lymphotropic administration of the preparation [7].

The majority of drugs are considered to be lymph-stimulating agents of indirect action. The drug-induced increase in lymph flow rate is associated with stimulation of lymph production. Under conditions of lymphatic edema, these changes can cause decompensation [11]. Our results indicate that Perftoran has a direct lymphotropic action and protective effect on lymph circulation, which is related to stimulation of myocyte contractility in the wall and valve cusps of LM. Perftoran probably maintains pacemaker activity of LM lymphangions due to improvement of blood microcirculation. Sufficient blood circulation in capillaries around mesenteric LM is required to maintain contractile activity of myocytes [14]. It cannot be excluded that the drug has an indirect lymphotropic effect and stimulates lymph production. These changes are followed by rapid filling of the lymph bed with new portions of lymph, pressure rise, and acceleration of lymph flow. At the same time, lymph pressure rise is accompanied by an increase in the mechanical influence on LM wall. Extension of the wall is followed by an increase in motor function. The lumen of the proximal lymphangion increased during constant release of fluid from the underlying lymphangions. It is probably followed by an increase in the amplitude of active contractions. Within physiological limits of intravascular pressure, the expansibility of lymphangion muscular cuff in a circular direction is mainly determined by bundles of spirally oriented smooth muscles cells (SMC). Upon a significant increase in transmural pressure in the lumen of lymphangion, elastic fibers of lymphangion connective tissue and SMC counteract the extension. In the follow-up period this process involves the straightened collagen fibers. These changes are accompanied by a significant increase in the modulus of elasticity. The involvement of elastic and collagen fibers in counteracting the extension upon high transmural pressure protects SMC of the muscular cuff from excessive extension and mechanical

TABLE 1. Effect of Perftoran on Lymph Flow Rate in TLD and Lymph Microcirculation in LM Lymphangions of Rat Mesentery (*M±m*)

Parameters	Physiological saline (control)	Perftoran
Lymph circulation rate, 10^{-2} ml/100 g/sec	0.49±0.04	0.89±0.06*
	(*n*=11)	(*n*=9)
Frequency of wall contractions, min	8.10±1.03	14.75±1.87*
	(*n*=10)	(*n*=10)
Frequency of valve cusp contractions, min	5.70±0.76	9.98±1.07*
	(*n*=6)	(*n*=10)
Diameter of LM lumen, μ	138±4	110±3**
	(*n*=10)	(*n*=10)
Amplitude of contractions of LM wall, %	23.5±6.4	33.2±4.1**
	(*n*=10)	(*n*=10)

Note. Here and in Table 2: *n*, number of animals. *p<0.001 and *p<0.01 compared to the control.

TABLE 2. Effect of Perftoran on the Cellular Composition of Rat Central Lymph (*M±m*)

Parameters	Physiological saline (control, *n*=11)	Perftoran (*n*=9)
Leukocyte number in 1 μl lymph	13 716±723	16 675±387*
Small and medium lymphocytes, %	95.71±1.69	95.40±3.58
Large lymphocytes, %	3.06±0.22	3.09±0.26
Pro-lymphocytes, %	0.51±0.10	0.60±0.13
Blast cells, %	0.11±0.03	0.13±0.05
Eosinophils, %	0.62±0.18	0.68±0.13

destruction of intercellular contacts [8]. Intravascular pressure in the lymphangion determines the frequency of spontaneous activity and amplitude and duration of phasic contractions of SMC. We believe that administration of Perftoran is accompanied by an increase in intravascular pressure in the majority of LM. Pressure elevation is followed by extension and depolarization of SMC in lymphangion circular layer. It facilitates the process of activation. Mechanical deformation of the cell membrane due to elevation of intravascular pressure serves as a trigger mechanism in activation and depolarization of pacemaker cells. Therefore, the elevation of pressure has a potentiating effect on depolarization of myocyte membranes. It contributes to an increase in the frequency of spontaneous activity of functioning pacemakers, which causes the generation of action potentials in "silent" SMC [12]. The ability of Perftoran to activate lymphopoiesis is confirmed by published data that this agent increases lymph production in the mesenteric lymph nodes of rats with peritonitis [9].

Functional activation of lymphangion components contributes to the increase in lymph flow rate in TLD. These changes promote the increase in cell transport to the systemic circulation. Leukocyte transport with the lymph increases not only due to the acceleration of lymph flow, but also due to the increase in lymphopoiesis, release of lymphocytes from lymph nodes, and decrease in cell aggregation under the influence of Perftoran.

Therefore, the lymphoprotective effect of Perftoran is associated with an increase in pump function and capacity of lymphangion components and improvement of lymph outflow and lymph circulation. These changes contribute to an increase in the resorption and transport of metabolic products of cells and tissues from the interstitial space.

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