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EXPERIMENTAL TREATMENT OF ACUTE RENAL FAILURE WITH PROSTENON, A SOVIET PROSTAGLANDIN E_2*

R. M. Glants, B. V. Kachorovskii, V. L. Turchin, I. O. Kushch, B. R. Kotsai, and L. V. Mudrovskaya

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KEY WORDS: acute renal failure; prostaglandin E_2.

As a result of the use of hemodialysis, hemoperfusion, and gravitational surgery [3] the treatment of acute renal failure (ARF) has improved considerably, but even now the mortality from this disease is 40% [12]. Hence the importance of developing methods of treatment of ARF which would restore kidney function.

One cause of ARF is transfusion of patients with incompatible blood. Under these circumstances blood transfusion shock develops and goes on to ARF. Moreover, blood transfusion shock is regarded as the first stage of ARF [1] and, consequently, experimental heterologous transfusion provides a model of ARF which corresponds to the clinical form. The writers showed previously that during complications of blood transfusion, changes take place in all renal and extrarenal factors controlling kidney function: The adrenalin concentration in the kidney rises and this correlates with an increase in functions of the blood clotting and fibrinolysis system (the sympathico-adrenal system) [7], changes take place in the function of the endocrine system (anterior and posterior lobes of the pituitary, adrenal medulla, and cortex, endocrine part of the pancreas) [4], and metabolism is disturbed [9]. Heterologous blood transfusion causes changes in all components of the kinin system [2] and raises the serum ADH level in dogs [8]. Prostaglandin (PG) E_2, which has a selective vasodilator action on vessels of the renal cortex and medulla, so that not only is the total blood flow increased but it is redistributed, with a relative decrease in cortical blood flow, also has maximal activity in the kidney. PG released under the influence of catecholamines are their physiological antagonists and, like ADH and ACTH, PG interact with the kinin system and the sympathicoadrenal system [13]. They restore normal metabolism, especially protein metabolism, in the organs and tissues and depress the functional state of the sympathicoadrenal system in the kidney [10].

The facts described above are the basis for the use of PGE_2 in the experimental treatment of ARF.

EXPERIMENTAL METHOD

PGE_2 of Soviet origin (prostenon), synthesized in the Sector of Pure Substances, Academy of Sciences of the Estonian SSR (Professor J.E. Lille) was used. ARF was induced in dogs by a method developed in the laboratory: After massive blood loss (20-25 ml/kg) heterologous blood (human blood, 25-30 ml) was transfused. The animals developed heterologous transfusion shock, which turned into ARF, as shown by the severe oliguria or anuria, the sharp rise in the blood urea (to 64.185 mM), an increase in the plasma potassium concentration (to 6.477 mM), and a decrease in the sodium concentration (to 127.000 mM) and the blood alkaline reserve (to 126.10 meq/liter) [6]. Experiments were carried out on 20 female mongrel dogs weighing

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Experimental Department, L'vov Research Institute of Hematology and Blood Transfusion.
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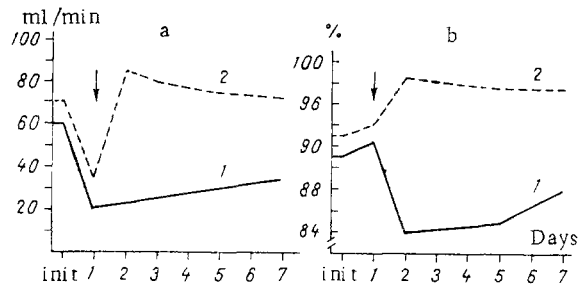

Fig. 1

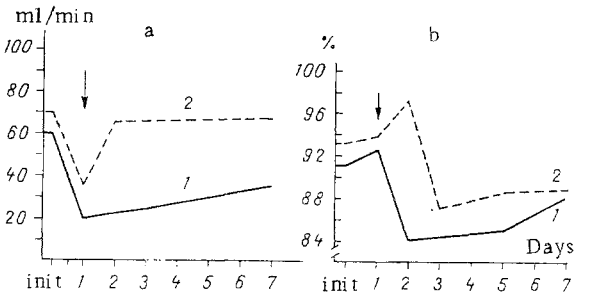

Fig. 2

Fig. 1. Effect of intra-arterial injection of prostenon on glomerular filtration (a) and tubular reabsorption (b). 1) Control, 2) experiment. Arrows indicate time of injection of prostenon. init — initial value.

Fig. 2. Effect of intravenous injection of prostenon on glomerular filtration (a) and tubular reabsorption (b). Legend as in Fig. 1.

15-18 kg. As a first step the ureters were exteriorized by Tsitovich's method. The control group consisted of ten dogs, of which three died from ARF in the course of the experiment. Prostenon was injected when the animals had recovered from the manifestations of shock and hematuria and hemoglobinuria had appeared (2 h after heterologous transfusion). In the experiments of series I (5 dogs) prostenon was given by intra-aortic infusion, for which purpose a polyvinyl chloride catheter was introduced through the femoral artery as far as the origin of the renal arteries from the aorta. Prostenon in a dose of 5 mg was dissolved in 20 ml physiological saline and injected rapidly. In the experiments of series II (5 dogs) prostenon was given by rapid intravenous injection into the saphenous vein; 5 mg prostenon was dissolved in 200 ml physiological saline. Observations were made on the animals for seven days.

EXPERIMENTAL RESULTS

In all control animals glomerular filtration was sharply reduced throughout the experiment ($P < 0.05$). Glomerular filtration in all experimental dogs not only was fully restored but, after the second day of observation, it actually exceeded the initial values (Fig. 1). In the control animals tubular reabsorption was sharply reduced and was not restored even by the 7th day. Tubular reabsorption in the experimental dogs was significantly higher than its initial values at all times of observation.

Intra-arterial injection of prostenon thus completely abolished the developing ARF.

Changes in the same direction in renal function were found after intravenous injection of prostenon. In this case glomerular filtration was completely restored after the second day and changes in tubular reabsorption were less than after intra-arterial injection, but they differed significantly from those in the control animals (Fig. 2).

The relatively weaker effect of intravenous injection compared with intra-arterial can be attributed to the fact that some of the PG given intravenously is destroyed in the lungs. Meanwhile the effectiveness of intravenous injection of prostenon has also been demonstrated by the writers under clinical conditions, when it was used to induce labor [11].

The results of this investigation provide an experimental basis for the clinical use of PGE_2 (prostenon) for the treatment of patients with ARF.

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EFFECT OF CULTURE AT SUBOPTIMAL TEMPERATURE ON DEHYDROGENASE ACTIVITY OF BLOOD MONOCYTES FROM HEALTHY SUBJECTS AND LEPROSY PATIENTS

F. E. Vishnevetskii, Yu. V. Pervukhin, and Z. I. Bronfman

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The structure of the energy metabolism of macrophages and their precursors (monocytes) largely determines the functional properties of these cells [4]. The study of the mononuclear phagocytic system in leprosy is particularly important because the agent of this disease is an obligate parasite of macrophages. Functions of blood monocytes, precursors of macrophages, have been studied intensively in recent years. It has been found that blood monocytes of patients with the lepromatous type of leprosy differ from monocytes of healthy subjects and patients with other chronic diseases in their ability to carry out phagocytosis and lysis of certain bacteria [5], in their interaction with lymphocytes [3, 10], their ability to reduce nitro-blue tetrazolium (nitro-BT test) [8], and their activity in endocytosis [9].

The aim of the present investigations was to study the effect of culture at suboptimal temperatures on oxidative metabolism of blood monocytes from healthy subjects and patients with leprosy. Existing views on the affinity of *Mycobacterium leprae* for the coldest parts of the body served as the starting point: Skin lesions as a rule begin on the lobes of the ears and the dorsal surfaces of the hands and feet [2], the skin temperature on lepromatous lesions is lower than that of evidently healthy skin, in mice *M. leprae* reproduces most intensively in the foot pads [11], and the nine-banded armadillo, which has a relatively low body temperature, has been shown to be a promising animal for reproduction of experimental leprosy [7]. Information on the effect of low temperatures on enzyme activity of blood monocytes of man and animals could not be found in the accessible literature. There are reports [6] that lowering the temperature to 32°C inhibits (compared with 35-37°C) the response of lymphocytes to mitogenic stimulation. According to the authors cited, lowering the temperature of some areas of skin (of the limbs, for example) is a factor which causes insufficiency of cellular immunity, and this mechanism may be the reason why infection is localized in cooled areas of the body.

EXPERIMENTAL METHOD

Heparinized venous blood was obtained from 15 healthy blood donors and 20 patients with the lepromatous type of leprosy, in the stage of active disease. Mononuclear cells were isolated by fractionation in a Ficoll—Isopaque gradient (Pharmacia, Sweden). The monocytes were incubated on coverslips in medium 199 in Leighton's tubes for 48 h at 37 and 25°C. This last temperature was chosen because of evidence to show that multiplication of various cells

Leprosy Research Institute, Ministry of Health of the USSR, Astrakhan'. (Presented by Academician of the Academy of Medical Sciences of the USSR D. S. Sarkisov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 95, No. 5, pp. 30-32, May, 1983. Original article submitted October 27, 1982.

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