EFFECT OF LITONIT AND PIRACETAM ON THE COURSE OF EXPERIMENTAL MYOCARDIAL INFARCTION

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Heart lesions caused by stress and ischemia are inseparably connected, and the stress response in many cases does not simply precede ischemic heart damage, but predetermines its development [5, 6]. Accordingly, an important element of the combined treatment of myocardial infarction (MI) is the use of drugs giving effective protection of the heart not only from ischemic, but also from stress-related influences.

The aim of this investigation was to study the character of myocardial damage in a model of experimental MI and the possibility of its pharmacologic correction by piracetam* and the atypical tranquilizer litonit,† the latter produced by the N. I. Pirogov Odessa Medical Institute.

EXPERIMENTAL METHOD

MI was produced by ligation of the descending branch of the anterior coronary artery under intravenous pentobarbital anesthesia (30-40 mg/kg, 5% solution, with artificial ventilation). Experiments were carried out on 43 mongrel dogs divided into three groups: 1) control, with MI but without the use of drugs (15 dogs); 2) with MI and piracetam (14); 3) with MI and litonit (14). The ECG of all the dogs were recorded on the 1st, 3rd, and 6th days before production of MI in the traditional 12 derivations. The immunologic reactivity of the dogs was assessed by the passive hemagglutination test (PHT) [8, 10] and the lymphocyte blast transformation test (LBTT) [9]. On the 1st day after production of MI, treatment of the dogs of the experimental groups began. For 6 days piracetam in a dose of 20 mg/kg and litonit in a dose of 10 mg/kg were injected parenterally. After the end of the course of treatment the animals were killed with hexobarbital and listhenon, and pieces of heart muscle were taken for biochemical investigation. The malonic dialdehyde (MDA) concentration was determined in infarct, peri-infarct, and "intact" zones of the myocardium [7].

EXPERIMENTAL RESULTS

After ligation of the left coronary artery the electrocardiographic picture corresponded to that of an anterior septal infarct of the left ventricle. The overwhelming majority of animals developed single and multiple ventricular extrasystoles, with transition in some cases to paroxysmal tachycardia.

The use of piracetam gave an antiarrhythmic effect, and by the 3rd day of MI the extrasystoles had disappeared in 40% of the animals. By the 6th day, the rhythm was restored in all dogs treated with piracetam. Litonit, in the doses used, had no antiarrhythmic action: on the 3rd and 6th days the percentage of animals with extrasystoles was about equal.

Differences were observed in the time course of MI in the untreated dogs and dogs treated witn piracetam and litonit. Whereas toward the end of the period of observation normalization of the ECG parameters, scar changes, and disturbances of the coronary circulation were observed equally frequently, myocardial hypoxia was discovered in dogs treated with piracetem (75.0 ± 15.3%) and in the untreated dogs (33.3 ± 13.3%), but it was absent in the dogs treated with litonit. The absence of hypoxia in the dogs treated with litonit can be explained by the

*α-Pyrrolidone acetamide.

†Lithium nicotinate.

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beneficial effect of the drug on poststress disturbances of the energy supply to the myocardium, damage to membrane mechanisms, and calcium transport. Data on the normalizing action of litonit on the energy-providing function of mitochondria of the brain have been published [1, 4]. Reports on the beneficial effects of piracetam on oxidative phosphorylation in the brain of rats with ischemic necrosis of the myocardium are interesting [2, 3].

We found a decrease in the MDA concentration in the infarct, peri-infarct, and "intact" zones of the myocardium in dogs treated with litonit and piracetam compared with the control animals, evidence that these drugs inhibit free-radical lipid peroxidation in the myocardium when activated by MI. Litonit had a stronger antioxidant action. The MDA concentration in dogs treated with litonit was lower than in untreated dogs by 40% in the infarct, 42.1% in the peri-infarct, and 33.6% in the intact zone of the myocardium.

The investigation revealed a positive effect of the drugs tested on certain stages of exposure to stress during MI, including on immunologic reactivity. Litonit and piracetam were found to have a favorable action on humoral immunity. According to the results of the PHT, the highest titer of anticardiac antibodies was observed on the 3rd day of MI in all the dogs. The geometric mean titer of anticardiac antibodies in the animals after administration of the drugs was lower. Whereas in untreated dogs on the 3rd day after production of MI the antibody titer to infarct antigen rose from 1:2.5 ± 0.3 to 1:38.4 ± 4.8 (16 times higher than initially), after treatment with piracetam it rose from 1:2.6 ± 0.38 to 1:26.3 ± 5.0 (a tenfold increase; $p < 0.001$), and after administration of litonit, from 1:2.7 ± 0.4 to 1:24.8 ± 4.6 (by 9.5 times; $p < 0.001$). Toward the end of the period of observation the titer of anticardiac antibodies to antigen from the zone of MI was 1:32.6 ± 6.4 in dogs of the control group, 1:26.4 ± 5.1 after treatment with litonit, and 1:16.3 ± 2.3 after treatment with piracetam.

During the investigation of the state of the T lymphocyte system, according to the results of the LBTT in response to stimulation by phytohemagglutinin (PHA), on the 3rd day of experimental MI in all the animals the number of blast cells in a culture of stimulated lymphocytes was reduced, evidence of inhibition of cellular immunity. In dogs of the experimental groups, functional activity of the T lymphocytes to PHA showed a much greater decrease in this period than in the control group, but toward the end of the period of observation activity was increased.

The study of specific responses of T cells sensitized to infarct and "intact" antigen on the 3rd day of MI revealed stimulation of the specific immune response. During regression of MI a decrease in blast transformation was observed in all the animals with the specific antigens, and it was more marked in the dogs treated with litonit.

A comparative study of the effect of litonit and piracetam on the course of MI and on its biochemical and immunologic parameters thus demonstrated the superior pharmacotherapeutic activity of litonit.

With its stress-protective action, litonit has a favorable effect on complex interrelations of nervous reflex, humoral, and immunologic factors arising during MI under conditions of cardiogenic stress. By stimulating energy metabolism in the myocardium and stabilization of the membranes, litonit has a favorable effect on the course of MI.

The results of these obervations demonstrate depression of activity of free-radical lipid peroxidation in the infarct zone of the myocardium, an improvement in the time course of MI, and positive changes in the parameters of humoral and cellular immunity during treatment of MI by litonit.

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COMPARATIVE EFFICACY OF REGULATORY PEPTIDES IN EXPERIMENTAL ACUTE PANCREATITIS

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Traditional methods of etiotropic therapy of acute pancreatitis currently available do not enable the development of this disease to be prevented to an adequate degree. Protease inhibitors (gordox, contrykal, etc.), for instance, which do not depress pancreatic function, can only lower the circulating blood levels of pancreatic enzymes, whereas preparations acting on the synthesis of these enzymes (various cytostatics), in the optimal therapeutic concentrations used, also have a general toxic action on vital organs and systems of the body [5]. Reports have recently been published on the important role of regulatory peptides (RP) in the maintenance of homeostasis in various types of pathology, including pancreatitis [3, 6, 8]. However, in the few publications on this problem, the efficacy of peptide bioregulators was assessed mainly on the basis of biochemical tests, carried out in forms of acute pancreatitis which had already developed [1, 2]. Meanwhile there have been virtually no studies of pancreatic function during prophylactic administration of RP in the early stages of pancreatic toxemia, and equally no studies of protective factors promoting detoxication (phagocytic cells of the reticuloendothelial system – RES, fixed macrophages of the liver and spleen).

The aim of this investigation was to compare the efficacy of various RP for the prevention of experimental acute pancreatitis, using radionuclide methods to investigate functional activity of pancreatic cells and cells of RES in the liver.

EXPERIMENTAL METHOD

Experiments were carried out on 12 mongrel dogs weighing 15-20 kg, anesthetized with pentobarbital (2% solution, dose 25 mg/kg), after premedication with trimeperidine (2% solution, 0.5 ml/kg) and atropine (0.3 ml/10 kg body weight). Experimental acute pancreatitis (EAP) was induced by transduodenal injection of autologous bile into the chief pancreatic duct in a dose of 0.5 ml/kg, followed by stimulation of secretion by secretin and cerulein (2 units/kg respectively of each; from "Boots," England). A leg vein was cannulated at the same time for injection of the test preparations, including radiopharmaceuticals (RPH), and blood was taken at intervals to determine α-amylase and trypsin levels in the blood serum as in [9, 10]. EAP and hemorrhagic pancreatic necrosis developed in this model in the course of 1.5-2 h after initiation, as confirmed by morphologic and ultastructural investigations [4]. The animals were investigated by gamma-camera (Searle, the Netherlands), equipped with PDP 11/34 computer (USA). Recording began from the time of intravenous injection of RPH (a colloidal solution of ^{198}Au in a dose of 11.1 MBq and ^{75}Se-methionine in a dose of 14.8 MBq) and continued for 30 min with serial scans with an interval of 1 min, with the dog lying in the supine position. The quantitative analysis was conducted in two stages: the first consisted of identifying the "zone of interest" over the region

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