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EFFECT OF TRIMETAZIDINE PROPERTIES ON IMMUNO-INFLAMMATORY DISORDERS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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Abstract

The urgency of the problem of acute coronary pathology is determined by the growing incidence of coronary artery disease (CHD), high mortality from this disease, as well as the difficulties of timely diagnosis and differential diagnosis of exacerbations of coronary heart disease. Cardiovascular diseases occupy the first place in the structure of mortality and disability of the population. One of the forms of complications of coronary heart disease is acute myocardial infarction (AMI). AMI is one of the most threatening and life-threatening conditions in cardiology. A significant part of deaths is caused by AMI [5]. Myocardial infarction (MI) is an important medical, social and economic problem for highly developed countries due to its prevalence, mortality, and temporary and permanent disability. Among the factors affecting life expectancy and mortality in MI, acute heart failure, cardiac arrhythmias, and repeated coronary attacks are the most serious. Heart failure increases the risk of early and long-term mortality associated with MI. In patients with acute coronary syndrome and signs of heart failure, the risk of death in a hospital setting increases 4-fold [12]. In recent years, it has become generally accepted that the most real factor in both the initiation and progression of atherosclerosis and the development of its acute clinical manifestations is inflammation, and the destabilization of atherosclerotic plaque is determined by the high activity of the chronic inflammatory process in it [11]. Of great interest is the study of specific markers of inflammation, cytokines, which may be more predictively significant in determining the processes associated with the destabilization of vascular atherosclerosis. There are a number of cytokines whose action is associated with the activation of inflammation in the atherosinflammatory plaque. Some of them, for example, tumor necrosis factor α (TNF-α), interleukin-1b (IL-1b), IL-6, have pro-inflammatory properties, while others, in particular IL-10, are associated with anti-inflammatory reactions [8,9].

Introduction

Disorders of the immune status in conditions of acute coronary syndrome and its role in the development of heart failure dictate the need to use immunotropic drugs in such patients, primarily direct-acting immunomodulators, the appointment of which will increase the high pharmacological load and increase the likelihood of side effects. Currently, in cardiology, along with traditional antianginal, antiplatelet, and anticoagulant drugs, myocardial cytoprotectors have

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been used with sufficient effectiveness in patients with angina and acute coronary syndrome [2]. In this regard, the use of cardiocytoprotectors with proven clinical efficacy in acute coronary pathology [4], capable of having an immunotropic effect according to experimental data [4], seems promising. Drugs of this class provide a reduction in the oxygen demand of an ischemic myocardium by optimizing energy exchange at a certain residual level of blood supply (including in the periinfarction zone), which allows maintaining the viability and functional activity of the myocardium in the ischemic zone [2]. Of particular interest is the cardiocytoprotector Trimetazidine, which redirects energy metabolism in myocardial cells from fatty acid oxidation to glucose oxidation and has a direct cardioprotective, antihypoxic effect. At the same time, the use of trimetazidine as an immunocorrector in the clinic remains practically unexplored, there are only convincing experimental studies on this problem [2].

Thus, these issues are relevant and require detailed study, since their solution involves the possibility of improving the effectiveness of treatment of this patient population.

Data from our own research

In connection with the above, we conducted studies aimed at: determining the role of immuno-inflammatory reactions in the development of unstable angina (NS), acute myocardial infarction in patients with coronary heart disease and to establish the immunocorrective properties of trimetazidine in patients with acute myocardial infarction.

MATERIALS AND RESEARCH METHODS

The methodology of our research was planned taking into account modern principles of scientific knowledge and organized adequately to the set goal. Planning and conducting research aimed at solving the tasks set were carried out on the basis of general scientific and specific methods. The work analyzes the data of case histories for 3 years of the intensive care unit of the Bukhara branch of the Russian National Research Center (Bukhara), clinical (collection and detailed analysis of anamnestic data, determination of severity, as well as clinical and immunological studies were used to determine the effectiveness of the therapy).

The study included 176 men (average age 52.4±3.8 years) with various forms of coronary artery disease. 93 patients with ACS were observed, 60 of them with HC and 33 with AMI. The comparison group consisted of 83 patients with stable angina pectoris of functional class II-IV. The diagnosis of coronary artery disease was established on the basis of clinical and instrumental data. Attention was paid to the typicality of angina syndrome, the specificity of ECG changes at rest, during daily monitoring and under load on a bicycle ergometer (VEM); echocardiography (ECHOCG) data were recorded. Patients with grade II arterial hypertension, congestive heart failure, complex cardiac arrhythmias, decompensated diabetes mellitus, severe liver, kidney, lung, and blood diseases were not included in the study. Patients with active inflammatory processes, oncological and immunopathological diseases were excluded from the study.

According to the classification [9], NS patients were divided into 2 groups: 32 people with class I HC and 28 with class II-III HC. The criteria for inclusion of HC patients in the study were clinical manifestations of HC upon admission to the intensive care unit in the form of resting angina (lasting more than 10 but less than 30 minutes); angina pectoris (under stress that had not

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previously caused angina pectoris); increased frequency of seizures in combination with transient ECG changes in the form of ST segment depression (more than 0.1 mV) and/or inversion of the T wave in two or more leads without the appearance of new Q waves on the ECG.

The diagnosis of AMI was established in 33 patients based on WHO criteria in the presence of two of the following three signs: anginal pain > 30 min and/or elevation of the ST segment >0.2 mV in two thoracic leads, or elevation of the 5T segment > 0.1mV in standard leads, or the development of acute blockage of the left leg of the Gis bundle; the appearance of abnormal Q waves on the ECG and/or an increase in the level of creatine phosphokinase (CFRP) (2 times higher than normal), troponins T and J. Basic therapy for stable angina included antiplatelet agents, beta-blockers, calcium antagonists, nitrates, statins, angiotensin converting enzyme inhibitors; additional anticoagulants were prescribed for HC, and thrombolytic therapy was performed in 26.6% of cases of AMI.

The control group included 25 healthy male volunteers (average age 49.9±6.2 years) who underwent VEM (to exclude latent coronary insufficiency), ECHOCG (to exclude myocardial damage), duplex scanning of the carotid arteries (to exclude non-coronary atherosclerosis), and blood lipids.

In patients with stable angina pectoris, VEM was performed to verify coronary heart disease and determine exercise tolerance; daily ECG monitoring was performed to record episodes of myocardial ischemia. Intracardiac hemodynamics was studied using ECHOCG with an assessment of linear and volumetric parameters, myocardial mass index and left ventricular remodeling parameters according to the method recommended by the American Society of Echocardiographers.

To characterize immuno-inflammatory reactions, the levels of C-RB, proinflammatory (IL-1b, IL-6, TNF-α) and anti-inflammatory (IL-4, IL-10) cytokines in blood serum were studied by enzyme immunoassay using Protein Contour LLC test systems (St. Petersburg).

Statistical data processing was performed using the programs Microsoft Excel 7.0 and Statistica for Windows 6.0. The data is presented in the form of M±T. The correlation analysis of quantitative values was carried out with the calculation of the Pearson correlation coefficient. Differences at the level of $p<0.05$ were considered significant.

THE RESULTS OF THE STUDY AND THEIR DISCUSSION

The level of SRB in patients with class I and II-III NS was significantly increased compared to healthy men and stable angina pectoris patients (Table 1). When comparing SRB concentrations in patients with different course of NS, the highest values were observed in NS of II-III classes. The maximum values of SRB were registered in AMI, their values significantly exceeded not only parameters in control (7 times) and stable angina (3.8 times) groups, but also significantly differed from those in patients with NS of both I and II-III classes.

IL-6 indices in patients with class I and II-III NS were 1.7 and 2.5 times higher than in the control group. The increase in IL-6 level was registered in class II-III NS and exceeded the similar index in patients with stable and progressive angina pectoris. Extremely high level of IL-6 was found in AMI: its values were 3.6 and 2.6 times higher than parameters in healthy individuals and stable angina patients, and also significantly differed from those in NS of I and I-Sh classes. Correlation

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analysis performed in patients with NS and AMI revealed expected close correlations between IL-6 content and C-RB level (r=0,56; p<0,01). A significant increase in IL-1 p content was found in patients with NS of I and II-III classes compared to controls (47.5%, 2.2-fold; p<0.01). In severe course of NS (class II-III) IL-6 level significantly exceeded the parameters in patients with stable angina pectoris and class I NS. A significant increase in IL-1β concentration was registered in AMI; its values were 3 and 2.3 times higher than in healthy subjects and stable angina patients, and also significantly differed from the values in patients with class I and II-III NS.

Table 1 Levels of C-reactive protein, pro- and anti-inflammatory cytokines in patients with acute coronary syndrome

Index (M±t)	Control	Stable angina	Unstable angina		Myocardial infarction
	(n=25)	(n=83)	I (n=32)	II-III (n=28)	(n=33)
CRP, mg/l	2,2±0,36	4,2±0,52[a]	6,4±0,72[ab]	9,2±0,84[abd]	16,3±3,16[abc]
IL-1 β, pg/ml	35,6±4,14	48,9±4,26[a]	52,5±3,82[a]	78,3±8,14[abd]	112,3±11,01[abc]
IL-6, pg/ml	42,5±3,92	58,8±4,02[a]	72,4±6,36[a]	108,2±10,23[bd]	154,18±14,22[abc]
TNF-α pg/ml	21,2±2,89	33,7±3,88[a]	52,3±5,07[ab]	84,2±8,33[abd]	109,2±9,22[abc]
IL-4, pg/ml	122,6±11,90	128,2±10,73	96,5±9,17[ab]	62,4±7,05[abd]	50,1±6,36[abc]
IL-10, pg/ml	15,3±0,88	16,0±1,32	11,3±0,95[ab]	7,2±0,64 [abd]	6,1±0,58[abc]

Note: a - the significance of differences with control; b - stable angina; c - HC; d-between HC I and II-III classes (at p<0.05).

Correlation analysis revealed correlations between IL-1β level and CRP (r=0.38; p<0.05), there was a correlation between IL-1α concentration and IL-6 level (r=0.44; p<0.05).

The content of TNF-α was significantly increased in class I and II-III NS compared with control (2.5 and 4.0 times; p<0.01) and stable angina (1.5 and 2.5 times; p<0.01). The maximum values of TNF-α were found in AMI; its values were significantly higher than in healthy subjects, stable angina and NS patients of both classes I and II-III. Correlation analysis revealed direct correlations between TNF-α and IL-1β parameters (r=0.42; p<0.05), correlations between TNF-α and IL-6 (r=0.39; p<0.05), C-RB (r=0.38; p<0.05). Thus, ACS is characterised by TNF-α hyperproduction, which develops against the background of increased synthesis of CRP, IL-6 and IL-1β.

Thus, IBS destabilisation and ACS development are characterized by activation of immunoinflammatory reactions with hyperexpression of proinflammatory cytokines and increased C-RB levels, which develop against the background of suppression of activity of anti-inflammatory cytokines IL-4 and IL-10.

Decreased levels of anti-inflammatory cytokines in ACS patients, accompanied by hyperexpression of IL-6, IL-1β and TNF-α, were associated with the severity of IBS course and were most significant in class II-III NS and AMI.

The next stage of our study was to investigate the immunomodulatory efficacy of trimetazidine in the correction of immune status disorders in patients with primary acute myocardial infarction.

63 patients with the diagnosis of primary acute left ventricular myocardial infarction of I-III class of clinical severity were under constant observation in the cardiac intensive care unit of Bukhara

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branch of RSCEMP in Bukhara. The diagnosis of AMI was verified on the basis of characteristic clinical picture, laboratory and ECG data. Inclusion criteria of the patients in the study were as follows: age 40-60 years; individuals who had undergone primary AMI; receiving standard conventional therapy including nitrates (nitroglycerin, nitrosorbide), β-adrenoblockers (atenolol), ACE inhibitors (enalapril), antiaggregants (aspirin) and anticoagulants (heparin). At the same time, the first control group - 29 patients received the above therapy, and patients of the second main group - 37 patients additionally received trimetazidine (Predisin 70 mg/day). Quantitative assessment of cytokine levels: TNFα, IL-1β, IL-6, IL-4, IL-10, was performed in blood serum by enzyme-linked immunosorbent assay using test systems of Protein Contour LLC (St. Petersburg).

THE RESULTS OF THE STUDY AND THEIR DISCUSSION

In the first day of admission to the hospital in AMI patients, an increase in the concentration of the studied proinflammatory cytokines, especially TNFα, IL-1β, IL-6, was registered. In the studied groups of patients an increase in plasma concentration of anti-inflammatory cytokines: IL-4 and IL-10 was observed. Traditional complex treatment by the 21st day normalised the plasma concentration of INFα, reduced, but not to the normal level, the concentrations of TNFα, IL-6, IL-4 and increased the concentrations of IL-10. The use of trimetazidine in complex treatment of AMI patients allowed to normalise plasma concentrations of TNFα, IL-6, to increase activity of anti-inflammatory cytokines - IL-4, IL-10 by the 21st day of hospital stay. On the basis of the obtained results, we came to the conclusion that the use of trimetazidine in complex pharmacotherapy of AMI patients, compared with traditional treatment, has a pronounced effective effect on cytokine pro- and anti-inflammatory status, which indicates a pronounced immunocorrective effect of trimetazidine on the disturbed parameters of immune status, especially its effect on the cytokine link.

Thus, it was revealed that destabilisation of CHD course is characterized by inhibition of anti-inflammatory cytokines activity against the background of IL-1β, IL-6 and TNF-α hyperexpression and increased SRB synthesis. The severity of immunoinflammatory reactions is associated with the severity of ACS course. Maximum levels of proinflammatory cytokines and low concentrations of IL-4 and IL-10 were found in AMI. It was determined that activation of immunoinflammatory reactions plays an important role in IHD progression and ACS formation. The use of trimetazidine has a positive effect on the disturbed parameters of immune status in AMI patients, which should be taken into account in complex pharmacotherapy of patients.

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