Effect of Trekrezan on Lipid Peroxidation in Patients with Chronic Heart Failure

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The effect of the new Russian-manufactured immunomodulator trekrezan in combination with isosorbide dinitrate on lipid peroxidation is studied in patients with chronic heart failure associated with ischemic heart disease, arterial hypertension, and dilated cardiomyopathy. Trekrezan reduces blood content of malonic dialdehyde and diene conjugates and the index of peroxide production and increases the content of vitamin A. Trekrezan can be recommended for clinical use.

Key Words: *lipid peroxidation; trekrezan; chronic heart failure; diene conjugates; catalase*

Chronic heart failure (CHF) is a terminate stage and outcome of practically all cardiovascular dis-orders. Epidemiological studies demonstrate a growing contribution of CHF to mortality, while the treatment of CHF is associated with many problems. Lipid peroxidation (LPO) plays an important role in the development of CHF and determines the resistance of severe heart failure to therapy [5,6,8]. Lipoperoxides attack cell membranes and cause serious tissue damage. These processes affect functional systems regulating muscular contraction [1].

They can be prevented by synthetic and natural antioxidants [7,13]. The aim of the present study was to evaluate the effect of trekrezan, a new Russian-manufactured immunomodulator and adaptogen (Reg. 94/151/2; temporary pharmacopoeic item 42-2351-94) on the content of LPO products and serum antioxidant enzyme activity in patients with CHF, since this preparation exhibits a wide spectrum of biological activities and is characterized by low toxicity [2].

MATERIALS AND METHODS

Fifty-three CHF patients aged 30-65 (28 males and 25 females) were examined; of them stage IIA was found in 32 and IIB in 14 patients. In most cases CHF was caused by ischemic heart disease, arterial hypertension, and dilated cardiomyopathy. Control group comprised 20 healthy individuals of the same age. Diagnosis was confirmed by echocardiography, tetrapolar transthoracic rheography, and polarography. Blood content of diene conjugates (DC) was measured spectrophotometrically by specific light absorption at 232 nm. Malonic dialdehyde (MDA) was assayed by reaction with 2-thiobarbituric acid (acidic medium, heating) yielding colored trimethine complex with an absorbance maximum at 532 nm [11]. Some low-molecular-weight compounds also form colored complexes with 2-thiobarbituric acid; therefore, this reaction revealed the sum of thiobarbituric acid-reactive substances. The tissue peroxidation potential was determined as described previously [12]. Erythrocyte catalase was preinactivated with sodium azide. This procedure 50-fold enhanced the oxidative potential of hydroperoxide and improved reproducibility of experimental results. The activity of superoxide dismutase was measured by the enzyme competition with nitroblue tetrazolium for superoxide anions formed in the reaction between $NADPH_2$ and phenazine methosulfate [3]. The antioxidant system activity was assessed by serum contents of vitamins A and E [9] and reduced and oxidized glutathiones [10], as well as by glutathione

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TABLE 1. Parameters of LPO and Antioxidant System in Patients with CHF ($M\pm m$)

Parameter	Group of patients		
	control	stage IIA	stage IIB
MDA, μmol/liter	2.25±0.03	3.19±0.05*	3.22±0.04*
DC, μmol/liter	17.5±0.67	17.8±0.8	18.8±0.5
Production of peroxide, μmol/liter	26.4±0.6	34.0±0.4*	33.9±0.6*
Superoxide dismutase, % of blockade	9.68±0.13	10.90±0.13*	10.30±0.15*
Glutathione, μmol/liter:			
reduced	1.33±0.015	1.23±0.013*	1.23±0.012*
oxidized	2.20±0.012	2.41±0.014*	2.38±0.018*
Vitamin E, mmol/liter	21.07±0.56	16.5±0.7*	16.3±0.8*
Vitamin A, mmol/liter	2.82±0.03	2.36±0.03*	2.38±0.03*
Glutathione reductase, nmol/liter	79.0±0.2	74.1±0.5*	76.0±0.7*
Glutathione peroxidase, μmol/liter	0.222±0.008	0.210±0.008	0.220±0.01
CP, mmol/liter	14.32±0.22	14.1±0.24*	15.0±0.3*

Note. *$p<0.05$ compared with the control.

reductase and glutathione peroxidase activities [4, 10]. All the patients were divided into 2 equivalent groups according to age, sex, and severity of the disease. Group 1 patients (n=23) were treated with trekrezan (0.1 g 3 times per day, 20 days) and isosorbide dinitrate (routine scheme), while group 2 (control, n=30) patients received isosorbide dinitrate only. Patients with stage IIB CHF also received furosemide according to routine schemes.

RESULTS

Stages IIA and IIB of CHF are characterized by accumulation of primary and secondary LPO products in the blood and suppression of the antioxidant system (Table 1). In patients treated with trekrezan and isosorbide dinitrate, the content of LPO products returned to normal level (healthy donors): the content of MDA decreased from 2.98±0.05 to 2.1± 0.03 μmol/liter ($p<0.05$) and DC from 18.6±0.19 to 16.1±0.12 μmol/liter ($p<0.05$). Inhibition of LPO is probably due to activation of superoxide dismutase. Inhibition of superoxide dismutase in patients with CHF plays an important role for stabilization of the antioxidant defense system. Poorly developed antioxidant systems in the myocardium (4-fold lower superoxide dismutase activity in comparison with the liver, extremely low catalase activity, and decreased the glutathione transport system capacity) determine its high sensitivity to peroxide radicals. On the other hand, the intensity of lipid peroxidation depends on the equilibrium between generation and inactivation of peroxide radical. The index of peroxide production is an integral parameter characterizing the adequacy of the antioxidant system, i.e., the intensity of lipid peroxidation. In trekrezan-treated patients this parameter decreased from 34.5±0.5 to 26.8±0.8 μmol/liter ($p<0.05$). Trekrezan also positively changed other parameters of the antioxidant system, inducing a decrease in the concentration of oxidized glutathione (from 1.95±0.011 to 1.38±0.013 μmol/liter) and a rise in the content of reduced glutathione (from 1.95±0.011 to 2.1±0.01 μmol/liter), vitamin E (from 23.01±0.42 to 25.09±0.42 μmol/liter), vitamin A (from 2.04±0.02 to 2.41±0.02 μmol/liter), glutathione reductase (from 70.01±0.2 to 74.8±0.3 nmol/liter), and glutathione peroxidase (from 0.186±0.006 to 0.208±0.07 μmol/liter). However, the mean values of these parameters in patients treated with trekrezan did not return to normal (healthy donors). Thus, the decrease in blood concentration of primary and secondary LPO products and activation of superoxide dismutase in CHF patients treated with trekrezan attest to stabilization of free-radical oxidation and predetermine a possibility of improving metabolic processes in cardiomyocytes as well as membrane function. Monotherapy with isosorbide dinitrate (group 2) reduced the content of MDA (from 2,79±0.03 to 2.63±0.06 μmol/liter, $p<0.05$) and increased the concentration of vitamin A (from 2.21±0.04 to 2.36±0.03 μmol/liter, $p<0.05$), while other parameters remained unchanged.

Our findings agree with the data on the antioxidant effect of nitrates in patients with cardiovascular disorders [5]. However, the LPO parameters in patients treated with trekrezan did not return to normal. Moreover, a decrease in MDA content and an increase in vitamin A content were

not accompanied by a decrease in the intensity of peroxide production, which suggests only partial compensation and limited reserve capacity of the antioxidant defense system.

It can be concluded that combined therapy with trekrezan and isosorbide dinitrate improves clinical parameters, which was confirmed by echocardiography, tetrapolar transthoracic rheography, and polarography.

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