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Research Article

Experimental Syndrome of Systemic Inflammatory Reaction: Effectiveness of Concomitant use of HMG-KOA-Reductase Inhibitors and S- (2-Boro-Ethyl) -L-Cysteine (BEC)

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ABSTRACT

Introdution: Endothelial dysfunction (ED) is a serious complication of systemic inflammation. At the moment, one of the most promising drugs for the prevention of cardiovascular disasters are statins and endothelioprotectors.

Research tasks: study of endothelioprotective properties of several statins and their combination with S-(2-boro-ethyl)-L-cystein (BEC) on the models of endotoxin-induced and L-NAME-induced endothelial dysfunction.

Methods. Male Wistar rats weighing 200-250 g were used in the experiment. Cardio-and endothelioprotective activity of the drugs was studied on two models: endotoxin-induced endothelial dysfunction (EIED) and L-NAME-induced endothelial dysfunction. The investigated drugs: atorvastatin 4.3 mg / kg, rosuvastatin 8.5 mg / kg, nanoparticularized rosuvastatin 11.6 mg / kg were administered intragastrically; BEC (S-(2-boroethyl)-l-cysteine) 10 mg / kg - intraperitoneally once a day, for 7 days. Endothelium dysfunction modelling was accompanied by increased CED–coefficient of endothelial dysfunction, NO metabolites levels increased with decreasing eNOS expression level.

Results: Atorvastatin 4.3 mg / kg, Rosuvastatin 8.5 mg / kg, and Nano-rosuvastatin 11.6 mg / kg contribute to reducing CED 1.76, 2,2 and 2.5 times, respectively. Also statins monotherapy showed normalization of eNOS expression up to 38% (Atorvastatin 4.3 mg / kg), 56% (Rosuvastatin 8.5 mg / kg) and 74% (Nano-rosuvastatin 11.6 mg / kg) from that of the intact group. At the same time, the concomitant use of these statins with BEC demonstrated an increase in expression of the enzyme to 44% (Atorvastatin+BEC), 46% (Rosuvastatin+BEC) and 55% (Nano-rosuvastatin+BEC), conceding monotherapy for a positive effect on the endothelium.

Conclusion. The concomitant use of HMG-CoA reductase inhibitors with BEC concedes to monotherapy with statins by the effectiveness of normal endothelial function recovery.

Key words: HMG-CoA reductase inhibitors, endothelial dysfunction, systemic inflammatory response syndrome, statins

INTRODUCTION:

The range of programs used to treat the syndrome of the systemic inflammatory response (SIRS) does not include remedies to correct endothelial dysfunction (ED). At the same time, the endothelium is one of the most vulnerable parts in case of systemic inflammation. This dictates the need to consider it as an important target in the pharmacological correction of SIRS to prevent delayed cardiovascular complications [2, 3]. Since modern pharmacology is known for a wide arsenal of agents with endothelioprotective properties, it seems reasonable to choose the most appropriate [4, 6, 7, 8, 9].

Based on the pathogenetic principles, to correct ED associated with inflammation, it seems

appropriate to use drugs from the group of statins. In addition to the classical hypolipidemic, they have anti-inflammatory, antioxidant and antithrombotic properties, which is of great importance in case of cytokine imbalance and nitric oxide (NO) deficiency [5, 10,]. The combination of statins with other remedies aimed to restore the function of the endothelium, such as S- (2-boro-ethyl) -L-cysteine (BEC), can have a positive effect when treating and preventing ED in SIRS [1]

MATERIALS AND METHODS

Male Wistar rats weighing 200-250 g were used in the experiment. Cardio- and endothelioprotective activity of the drugs was studied in two models: endotoxin-induced endothelial dysfunction (EIED) and L-NAME-induced endothelial dysfunction. The drugs under study: atorvastatin 4.3 mg / kg, rosuvastatin 8.5 mg / kg, and nanoparticularized rosuvastatin 11.6 mg / kg were administered intragastrically; S-(2-boro-ethyl)-L-cystein (BEC) 10 mg / kg, was administered intraperitoneally once a day for 7 days. There were nine groups of 10 animals each for both models: 1) intact without a modelled pathology, 2) untreated, 3) ED (endothelial dysfunction) + atorvastatin, 4) ED + rosuvastatin, 5) ED + nanorosuvastatin, 6) ED + BEC, 7) ED + BEC + atorvastatin, 8) ED + BEC + rosuvastatin, 9) ED + BEC + nano-rosuvastatin. All studies were carried out in compliance with the principles set forth in the the Convention for the Protection of Vertebrates used for experimental and other purposes (Strasbourg, France, 1986) and in compliance with the rules of laboratory practice of the Russian Federation (Order No. 267 of the Ministry of Healthcare of the Russian Federation of 19.06.2003). A program for statistical analysis of Microsoft Excel 7.0. was used for calculations.

RESULTS

Simulation of EIED leads to the development of endothelial dysfunction, which is manifested in increased CED, decreased myocardial reserve and increased adrenoreactivity, and increased number of NO metabolites, inflammatory markers of C-reactive protein (CRP), cytokines IL-6 and TNF-α in the blood. Statins administration leads to the development of endothelial and cardioprotective action, which manifests itself in the normalization of CED, prevention of increased adrenoreactivity and the depletion of the myocardial reserve, as well as in the normalization of biochemical parameters: a decreased number of NO metabolites, normalization of eNOS expression, a decreased level of CRP and pro-inflammatory cytokines. The most effective was a nanoparticulated form of rosuvastatin. The use of a combination of a nonselective arginase BEC inhibitor with statins demonstrated an improvement in hemodynamics and myocardial contractility, but showed no additive effect (Table 1).

Table 1. Effect of monotherapy with HMG-CoA reductase inhibitors, HMG-CoA reductase + BEC on the change in the parameters studied in animals with EIED.

Groups	BDsyst	BPdiast	CED	Adrenoreactivity, mmHg	Myocardial reserve depletion,%	NOx	eNOS expression	C-reactive protein	IL-6	TNF-α
Intact	129.4± 2.2	89.2± 1.1	1.1 ± 0.1	201.5±9.4	112.7±10.9	116.8±10.3	5.4±0.21	0.05±0.01	0.43±0.17	8.42±2.51
EIED	117.6± 2.3*	85.0±2.1*	3.7±0.5*	240.3±8.7*	79.4±3.9*	182.3± 12.4*	0.04±0.01*	0.38± 0.01*	6.87± 1.93*	17.83± 3.79*
EIED+ Atorvastatin	130.0± 3.3	85.8±2.2	2.1±0.3*#	222.1±8.5*#	97.0±4.9*	130.0± 10.9*#	2.07± 0.21*#	0.09± 0.01*#	1.27± 0.33*#	9.89±1.79*#
EIED+ Rosuva statin	135.0± 3.8	83.1±2.1	1.7±0.5*#	221.0±8.4*#	109.4±5.7*#	122.1± 9.9#*	3.04± 0.35*#	0.11± 0.01*#	1.17± 0.33*#	10.80±1.99*#

EIED+Nano-rosuvastatin	129.6± 4.3	84.9±2.0	1.5±0.2 *#	219.1±8.7*#	99.9±6.3*#	132.1± 10.3*#	4.01± 0.56*#	0.18± 0.01*#	1.48± 0.24*#	9.56±1.87*#
EIED+BEC	115.3± 2.4	79.1±2.2	2.5±0.4 *	220.7±8.3*	92.4±5.7*	141.4± 12.7*#	1.97± 0.10*#	0.21± 0.02*#	2.78± 1.79*#	10.23±2.08*#
EIED+BEC+ Atorvastatin	125.3± 3.2	82.3±2.0	2.5±0.3 *	231.9±8.4*#	88.9±3.9*#	143.5±9.9*#	2.41±0.34*#	0.42±0.08*#	1.94±0.19*#	8.79±0.91*#
EIED+BEC+ Rosuvastatin	126.3± 3.1	81.9±2.1	2.7±0.4 *	223.9±9.6*#	88.5±4.9*#	139.1±9.5*#	2.52±0.41*#	0.57±0.09*#	1.89±0.21*#	8.42±0.87*#
EIED+BEC+ Nano-rosuvastatin	127.3± 3.2	84.2±2.4	2.5±0.3 *	226.5±8.4*#	90.1±5.0*#	117.8±10.0*#	2.97±0.41*#	0.83±0.09*#	1.87±0.20*#	7.56±0.79*#

BPsyst - systolic blood pressure (mmHg), BPdiast - diastolic blood pressure (mmHg), CED - coefficient of endothelial dysfunction (c. u.), NOx - final NO metabolites (μmol / L); eNOS expression (%); level of CRP-C-reactive protein (mg / l); IL-6 - interleukin 6 (pg / ml) TNF-α-tumor necrosis factor α (pg / ml), * - significant difference from a group of intact animals ($p < 0.05$).

The model of L-NAME-induced endothelial dysfunction was characterized by persistent hypertension, a 1.2-time depletion of the myocardial reserve. QED increased from 1.1 ± 0.1 to 5.4 ± 0.6 c. u. The cardioprotective effect of HMG-CoA reductase inhibitors also showed in the improvement of myocardial contractility under resistance load, which is significantly higher than that in the control group and does not differ from the values in intact animals. HMG-CoA reductase inhibitors caused a dose-dependent endothelioprotective effect, which was expressed in preventing an increase in the values of the final NOx metabolites and reduction of eNOS expression. The concomitant use of a nonselective arginase BEC inhibitor with statins showed no pronounced pharmacodynamic interaction (Table 2).

Table 2. Effect of monotherapy with HMG-CoA reductase inhibitors, as well as combination therapy with HMG-CoA reductase inhibitors and WEB on changes in hemodynamics, myocardial contractility and biochemical blood markers in animals with L-NAME-induced pathology

Groups	BDsyst	BPdiast	CED	Adrenoreactivity, mmHg	Myocardial reserve depletion, %	NOx	eNOS expression
Intact	137.7 ± 3.7	101.9 ± 4.3	1.1 ± 0.1	199.2 ± 8.3	83.6± 4.3	114.1 ± 10.5	72.9 ± 3.8
L-NAME	190.3 ± 6.7*	145.0 ± 3.9*	5.4 ± 0.6*	247.3 ± 4.8*	66.0 ± 4.6 *	61.2 ± 8.5*	21.4 ± 4.7 *
L-NAME+ Atorvastatin	140.3 ± 9.6*	114.2 ± 6.6*	2.5 ± 0.3*#	199.0 ± 10.1#	91.7± 6.3 #	84.3±9.6*#	35.6±4.2*#
L-NAME+ Rosuvastatin	132.2 ± 7.7*#	101.1 ± 5.3*#	2.1 ± 0.1*#	187.9 ± 10.2#	92.4± 6.7#	65.7±9.3*#	35.1±4.2*#
L-NAME+ Nano-rosuvastatin	120.1 ± 6.4*#	95.1 ± 3.9*#	1.9 ± 0.6*#	186.4 ± 10.7#	93.5± 7.4#	63.6±8.7*#	43.6±4.5*#
L-NAME+ BEC	167.1±9.8	131.7±3.6	2.5±0.5	229.4 ±7.5	78.4±3.8	94.1 ±11.4	42.1 ±3.1
L-NAME+ BEC+ Atorvastatin	139.1±8.1*#	115.7±7.4*#	2.7±0.4*#	217.4 ±7.0#	77.1 ±4.8#	79.2 ±7.0#	48.1 ±5.2#
L-NAME+ BEC+	137.2±8.2*#	102.3±5.8*#	2.6±0.3*#	219.4 ±9.7#	78.5 ±5.6#	69.1 ±6.7#	49.5 ±5.8#

Rosuvastatin							
L-NAME+ BEC+Nano-rosuvastatin	135.1±9.0*#	103.7±6.8*#	2.5±0.3*#	219.8 ±10.5#	99.4 ±7.3#	68.9 ±7.1#	47.0 ±6.9#

SBP - systolic blood pressure (mmHg), DBP - diastolic blood pressure (mmHg), QED - coefficient of endothelial dysfunction (c.u.), NOx - final NO metabolites (μmol / L); eNOS expression (%); level of CRP-C-reactive protein (mg / l); IL-6 - interleukin 6 (pg / ml) TNF-α-tumor necrosis factor α (pg / ml), * - significant difference from a group of intact animals ($p < 0.05$).

CONCLUSIONS:

The use of atorvastatin HMG-CoA reductase inhibitors, rosuvastatin and nanorousvastatin against the background of modeling the EIED and L-NAME-induced pathology leads to the development of endothelial and cardioprotective action, which is expressed in CED normalization, prevention of increased adrenoreactivity and myocardial reserve depletion (nanorousvastatin); there was also identified a positive dynamics of NO metabolites (rosuvastatin), eNOS expression (nanorousvastatin), CRP (atorvastatin).

The concomitant use of a nonselective arginase BEC inhibitor with statins did not reveal a positive pharmacodynamic interaction in either model of pathology.

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