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Research Article

Endothelial Dysfunction Accompanying the Systemic Inflammatory Response Syndrome: the Effectiveness of Concomitant use of HMG-COA Reductase Inhibitors and Endothelial Protectors

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ABSTRACT

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

Research tasks: To study the effectiveness of the concomitant use of statins and endothelioprotectors by applying the endotoxin-induced endothelial injury model.

Methods: Cardio- and endothelioprotective effects of HMG-CoA reductase inhibitors (atorvastatin, rosuvastatin, nanozosvastatin) in combination darbepoetin were examined by means of the L-NAME- and endotoxin-induced endothelial dysfunction (EIED) model.

Results: Rosuvastatin reduces the endothelial dysfunction coefficient from 3.7 ± 0.5 to 1.5 ± 0.2 in the endotoxin-induced endothelial (EIED) dysfunction model; in the L-NAME model of induced ED, atorvastatin reduces coefficient of endothelial dysfunction (CED) from 5.4 ± 0.6 to 1.1 ± 0.1, whereas the combination of nanoparticulated rosuvostatin + darbepoetin - from 5.4 ± 0.6 to 1.6 ± 0.3.

Conclusion: It was shown that the most pronounced positive effects on hemodynamic and biochemical parameters in both models are produced by nano-rosuvastatin, atorvostatin and a combination of nanorozuvastatin and darbepoetin.

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

INTRODUCTION:

The response of the body to the phlogogenic factor is described by molecular pathophysiology through a cascade of neurohumoral reactions, formed by complex mediator and cytokine networks [4]. The active involvement of the endothelium in the formation of these networks has been known for a long time. However, recent studies have found that the endothelium is also one of the most vulnerable links in cases of systemic inflammation. This is proved by the fact that patients who have had sepsis, abdominal disasters and other pathologies associated with systemic inflammatory response syndrome develop certain further manifestations of endothelial dysfunction (ED) [1, 3, 9]. Based on the current understanding of the molecular mechanisms of systemic inflammation, a

promising pharmacological group aimed at restoring the endothelial function in case of a pathology is HMG-CoA reductase inhibitors (statins). Possessing pleiotropic effects, such as anti-inflammatory, antioxidant and anticoagulant, they are able to affect several pathogenetic links in the formation of endotoxin-induced endothelial dysfunction (EIED) and prevent complications associated with it [5]. The fact that remedies to make up NO deficiency can improve endothelial function [2, 6, 7] suggests that such drugs as L-arginine can increase the effectiveness of using statins in the pathology in question (Figure 1). In addition, the combination with darbepoetin may happen to be potentially successful, as it was shown that drugs from the erythropoietin group had a maked cardioprotective, anti-ischemic and preconditioning activity [8, 10].

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 of endothelial dysfunction: endotoxin-induced (EIDD) and L-NAME-induced. The investigated drugs - atorvastatin 4.3 mg / kg, rosuvastatin 8.5 mg / kg, and nanoparticularized rosuvastatin 11.6 mg / kg were administered intragastrically; L-arginine 200 mg / kg and darbepoetin 500 μg / kg - intraperitoneally once every 7 days. For each of the two models, the following groups of animals were identified (n = 10): 1) intact, 2) control with simulated pathology, 3) atorvastatin , 4) rosuvastatin, 5) nanorosuvastatin, 6) L-arginine, 7) L-arginine + atorvastatin, 8) L-arginine + rosuvastatin, 9) L-arginine + nanorosuvastatin, 10) darbepoetin, 11) darbepoetin + atorvastatin, 12) darbepoetin + rosuvastatin, 13) darbepoetin + nanorosuvastatin. All the studies were carried out in compliance with the principles set forth in 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 in the Russian Federation (Order No. 267 of the Ministry of Healthcare of the Russian Federation of 19.06.2003). For calculations, we used a Microsoft Excel 7.0 program for statistical analysis.

RESULTS.

Simulation of EIED leads to the development of endothelial dysfunction with an increase in CED, a decreased myocardial reserve and an increased adrenoreactivity (Table 1), as well as to an increased number of NO metabolites against an increased number of inflammatory markers of C-reactive protein (CRP) and cytokines IL-6 and TNF-α. The use of HMG-CoA reductase inhibitors on the background of EIED leads to the development of a dose-dependent endothelioprotective effect, which is expressed in the normalization of CED, prevention of increased adrenoreactivity and depletion of the myocardial reserve, as well as in normalization of biochemical parameters. The positive dynamics of NO metabolites and eNOS expression was detected. The most effective was the nanoparticulated form of rosuvastatin, which supports the hypothesis of a change in the volume of distribution of the drug (Table 1).

Table 1. Effect of therapy with HMG-CoA reductase inhibitors and their combination with endothelioprotectors on endothelial dysfunction and biochemical markers of inflammation in endotoxin-induced endothelial dysfunction (EIED)

EIED						
	CED	NOx	eNOS	CRP	IL-6	TNF-α
Intact	1.1 ± 0.1	116.8±10.3	5.4±0.21	0.05±0.01	0.43±0.17	8.42±2.51
EIED	3.7±0.5*	82.3±12.4*	0.04±0.01*	0.38±0.01*	6.87±1.93*	17.83±3.39*
EIED+Statins						
Atorvastatin	2.1±0.3*#	130,0±10,9*#	2.07±0.21*#	0.09±0.01*#	1.27±0.33*#	9.89±1.79*#
Rosuvastatin	1.7±0.5*#	122.1±9.9#*	3.04±0.35*#	0.11±0.01*#	1.17±0.33*#	10.80±1.99*#

Nanorosuvastatin	1.5±0.2*#	132.1±10.3*#	4.01±0.56*#	0.18±0.01*#	1.48±0.24*#	9.56±1.87*#
EIED+L-arginin+Statins						
L-arginin	2.1±0.3*#	132.7±11.3*#	2.14±0.22*#	0.17±0.02*#	2.23±1.67*#	10.23±2.08*#
L-arginin + Atorvastatin	1.5±0.3*#	121.7±9.5*#	4.23±0.69*#	0.07±0.02*#	0.90±0.13*#	9.97±1.36*#
L-arginin + Rosuvastatin	1.7±0.4*#	119.5±9.3*#	4.47±0.72*#	0.06±0.02*#	0.78±0.11*#	10.54±1.72*#
L-arginin + Nanorosuvastatin	1.5±0.2*#	117.8±10.0*#	4.92±0.86*#	0.06±0.02*#	0.63±0.10*#	8.20±2.26*#
EIED+Darbepoetin+Statins						
Darbepoetin	1.9±0,2*#	122.5±10,5*#	4.19±0,72*#	0.17±0,01*#	1.72±0,97*#	8.20±2.26*#*
Darbepoetin + Atorvastatin	1.5±0,1*#	120.1±7,6*#	4.59±0,49*#	0.15±0,11*#	3.89±0,17*#	9.89±1.42*#
Darbepoetin+ Rosuvastatin	1.6±0,1*#	119.4±7,7*#	4.67±0,48*#	0,16±0,10*#	4.02±0,21*#	10.40±1.04*#
Darbepoetin + Nanorosuvastatin	1.5±0,1*#	109.5±7,3*#	4.95±0,53*#	0.20±0.11*#	4.09±0,24*#	10.60±1.50*#

CED- endothelial dysfunction coefficient, 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 (pg / ml), * - significant difference from the group of intact animals (p <0.05), # - significant difference from the EIED group (p < 0.05)

Table.2. Effect of HMG-CoA reductase inhibitors and their combination with endothelioprotectors on endothelial dysfunction and NO metabolism in L-NAME-induced endothelial pathology

L-NAME			
	CED	NOx	eNOS
Intact	1.1 ± 0.1	114.1 ± 10.5	72.9 ± 3.8
L-NAME	5.4 ± 0.6*	61.2 ± 8.5*	21.4 ± 4.7 *
L-NAME + Statins			
Atorvastatin	1.1 ± 0.1	84.3±9.6*#	35.6±4.2*#
Rosuvastatin	2.1 ± 0.1*#	65.7±9.3*#	35.1±4.2*#
Nanorosuvastatin	1.9 ± 0.6*#	63.6±8.7*#	43.6±4.5*#
L-NAME + L-arginin+statins			
L-arginin	1.5±0.3	73.2 ±8.1	42.1 ±3.1
L-arginin + Atorvastatin	1.6±0.3*#	59.3 ±7.1#	58.2 ±6.3#
L-arginin + Rosuvastatin	1.6±0.3*#	59.2 ±7.2#	59.7 ±6.9#
L-arginin + Nanorosuvastatin	1.5±0.3*#	59.3 ±7.3#	59.0 ±6.8#
L-NAME + Darbepoetin+statins			
Darbepoetin	1.8±0.3	90.2 ±5.4	48.4 ±4.2
Darbepoetin + Atorvastatin	1.8±0.4*#	99.0 ±6.3#	58.3 ±4.1#
Darbepoetin+ Rosuvastatin	1.7±0.3*#	97.8 ±5.7#	59.2 ±4.0#
Darbepoetin + Nanorosuvastatin	1.6±0.3*#	98.5 ±5.8#	57.3 ±4.8#

CED coefficient of endothelial dysfunction, c.u., NOx-final metabolites of nitric oxide, μmol / L, eNOS-expression of endothelial NO synthase, * - significant difference from the group of intact animals (p<0,05); ** - significant difference with the control group (p <0.05), # - significant difference from the L-NAME group (p<0,05).

The use of concomitant use of L-arginine with HMG-CoA reductase inhibitors shows a protective effect, the results of which did not differ from those of the intact group. The concomitant use of recombinant darbepoetin with statins showed the additive effect with respect to CED and BP. The values were even slightly higher than with monotherapy with statins, but statistically they were significantly different from those of intact animals (Table 1).

Persistent hypertension was observed in the model of L-NAME-induced endothelial

dysfunction, the myocardial reserve was depleted 1.2 times, CED increased to 5.4 + 0.6 units, there was observed an increased number of NO metabolites and decreased eNOS expression. The cardioprotective effect of HMG-CoA reductase inhibitors also showed in the improvement of the contractility indices under the resistance load, which is significantly higher than that in the control and does not differ from the values in intact animals. HMG-CoA reductase inhibitors caused a dose-dependent endothelioprotective effect, expressed in preventing an increase of the values of the final NOx metabolites and reduction of the eNOS expression (Table 2). The combination of L-arginine with HMG-CoA reductase inhibitors shows a protective effect, improvement of contractility, hemodynamics and normalization of NO metabolism. An additive effect was shown when combined with darbepoetin, which in the case of a combination of nanoparticulated rosuvastatin + darbepoetin brought the hemodynamic parameters in the EIED group closer to those in intact animals.

CONCLUSION:

The study showed that HMG-CoA reductase inhibitors demonstrate their effectiveness in the correction of EIDD, both in monotherapy and in combination with endothelioprotectors. At the same time, among the studied statins, the greatest efficacy was shown when using nanoparticulated rosuvastatin at a dose of 11.6 mg. In addition, for all drugs of the group, an additive effect was shown when combined with darbepoetin, which in the case of a combination of nanoparticulated rosuvastatin + darbepoetin brought hemodynamic parameters in the EIED group to those in intact animals.

REFERNCES

1. Fastova, I.A. 2011. Factors Affecting the Development of Multiple Organ Failure and Increased Risk of Death in Peritonitis. Vestnik novyih meditsinskih tehnologiy.18(2): 80-83. [in Russian]
2. Khadieva, T.A., Dovgan, A.P., Pokroskaya, T.G. 2016. Method of Correction of Endothelial Dysfunction with Combination of Ademetionine and Taurine. Research Result: Pharmacology and Clinical Pharmacology. 2 (2): 36-40.
3. Malkova O.G., Medvedeva S.Yu., Leyderman I.N. 2011. Interrelation of Lipid Metabolism Disorders and Endothelial Dysfunction in Patients with Severe Sepsis. Vestnik Uralskoy meditsinskoy akademicheskoy nauki. 3(36):17-22. [in Russian]
4. Mezhirova N.M., Danilova V.V., Ovcharenko S.S. 2011. Pathophysiological and Diagnostic Aspects of Systemic Inflammatory Response Syndrome. Medical Emergency Conditions. 1(2):32-33. [in Russian]
5. Molchanova, O.V., Pokrovskaya, T.G., Povetkin, S.V., Reznikov, K.M. 2016. Endothelioprotective Property of the Combination of the Thioctic Acid and Rosuvastatin Shown in the Endothelial Dysfunction Models. Research Result: Pharmacology and Clinical Pharmacology. 2 (1): 9-15.
6. Shakhno, E.A., Savitskaya, T.A., Pokrovskaya, T.G., Yakushev, V.I., Pokrovskii, M.V., Grinshpan, D.D. 2016. Use of L-arginine Immobilised on Activated Carbon for Pharmacological Correction of Endothelial Disfunction. Research Result: Pharmacology and Clinical Pharmacology. 2 (1): 30-35.
7. Peresypkina, A.A., Gubareva, V.O., Levkova, E.A., Shabelnikova, A.S. 2016. Correction of Retinal Angiopathy of Hypertensive Type by Minoxidil, Sildenafil in Experiment. Research Result: Pharmacology and Clinical Pharmacology. 2 (4): 34-44.
8. Reznikov, K.M., Gorbunova, N.S., Kolesnichenko, P.D., Tverskoy, A.V., Kostina, D.A., Bashkatova, D.A., Nikitina, V.A. 2017. Search of New Pharmaceuticals on the Basis of Darbepoetin in the Treatment of Ischemic Stroke (review of literature). Research Result: Pharmacology and Clinical Pharmacology. 3 (1): 125-136.
9. Savelev V.S., Petuhov V.A. 2010. Lipid Distress Syndrome: a Guide for Doctors. 3rd

ed. Moscow: MAKS Press, 658 p. [in Russian]

10. Shabelnikova, A.S., Peresypkina, A.A., Gubareva, V.O., Levkova, E.A., Dolzhikov, A.A., Nikolaev, S.B., Stepchenko, A.A. 2016. Pharmacological Preconditioning by Recombinant Erythropoietin as the Possibility of Increasing the Stability of Tissue of the Retina to Reperfusion Ischemia in Experiment. Research Result: Pharmacology and Clinical Pharmacology. 2 (1): 25-29.