ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Cardio Protective Action of Thioctic Acid Combined with Rosuvastatin in the Combined Hypoestrogen and L-Name-Induced Nitrogen Oxide Deficiency.

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ABSTRACT

the study performed proves that the combined use of thioctic acid featuring antioxidant properties and Rosuvastatin belonging to the category of anticholesterol drugs has a cardio protective effect as exemplified by the model of hypoestrogen-L-NAME-induced deficiency of the nitrogen oxide consisting in the prevention of the increase in adrenoreactivity and maintenance of the myocardial contractility reserve.
Keywords: ovariectomy, *L*-NAME, endothelial dysfunction, thioctic acid, Rosuvastatin, nitrogen oxide.

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ISSN: 0975-8585

INTRODUCTION

According to the statistical figures of the recent year in the structure of mortality from the cardiovascular diseases (CVD) 85,5 % fall to the share of the coronary heart disease (CHD) (46,8 %) and cerebral stroke (38,7 %). These two kinds of pathology that are to a large extent determined by atherosclerosis are assigned the priority by development of the CVD prevention program [1]. One of the pathogenic links in the genesis of CVD is imbalance of vasodilators and vasoconstrictors produced by the vascular endothelial cells. First of all, the nitrogen oxide (NO) belongs to them. The main effects of NO including, first of all, the vasodilatating and anti-platelet one are exercised by means of activation of K+Ca2+ -channels. The opening of the numerous potassium and calcium channels located on the cell membrane is mediated by the cGMP-dependent proteinase that is activated under the action of cGMP the production of which is stimulated by the nitrogen oxide. Besides, the cGMP reduces the concentration of the calcium ions in the smooth muscle cells, thrombocytes affecting in such a way all the hemostasis stages and processes of the myofibrils contraction [2].

The failure of endothelium function resulting in the decrease in the production or bioavailability of NO was named the endothelial dysfunction [3, 4]. One of the ED markers is the heart disease consisting in the development of the cardiomyocyte hypertrophy, increased adrenoreactivity, reduced myocardial contractility [5, 6].

This is why one of the main tasks of the modern pharmacology is searching for drugs, their combinations that are able to correct the endothelial dysfunction featuring not only the endothelium protective but also the cardio protective effect as well.

According to the literature sources and results of the own studies one of the chemicals featuring an endothelium protective effect is the lipoic acid ([alpha]-LA) [7] being the coenzyme in the oxidative decarboxylation of the pyroracemic acid to acetyl-CoA and a-ketoglutaric to syccinil-CoA (in the Krebs cycle) [8]. The main biologic properties of the LA are decarboxylation of [alpha]-keto acids which is important for energy supply of a cell and prevention of development of ketoacidosis as well as reduced concentration of the fatty acids, total cholesterol and its ethers in the plasma. The antioxidant effect consisting in binding of free radicals, free tissue iron, glutathione recovery allows assuming the importance of the lipoic acid for the ED correction in pathogenesis of which one the oxidative stress plays one of the major parts. Besides, the LA inhibits the synthesis of the nitrogen oxide through hepatocytes arresting the flow disorders and vascular abnormalities and features a radioprotective effect.

These effects underlie the protective action of the di-hydro-lipoic acid ensuring its curative effect and determining a wide nosological range of application of the [alpha]-lipoid acid products [9].

Taking the above into account, the objective of the present study was the analysis of the cardio protective properties of the [alpha]-lipoic acid in the tableted form thioctacid (thioctic acid) BV (600 mg) and the combination thereof with the anticholesterol drug from the statin group Rosuvastatin (10 mg) as one of the possible effective combinations at the endothelial dysfunction as exemplified by the model of the hypoestrogen-L-NAME-induced deficiency of the nitrogen oxide.

PROCEDURE

The experiments were performed on the white male Wistar rats weighing 200-250 g. For stimulation of the endothelial dysfunction in rats at the age of 3,5 months were anesthetized with chloral hydrate (300 mg/kg) and the bilateral ovariectomy was performed. On the 43d day (6 weeks after the surgery) the inhibitor of NO-synthase N-nitro-L-arginine methyl ether (L-NAME, Sigma) was administered intraperitoneally once a day in the dose of 25 mg/kg 1 ml/kg during 7 days (n=10 animals) [10, 11, 12]. The animals from the intact group received the normal salt solution NaCl in the same amount (n=10 animals). The thioctic acid and Rosuvastatin as well as the combination thereof are administered daily intragastrically (through the gastric tube) in the doses of 50 mg/kg/day and 0,85 mg/kg/day, respectively, during 7 days simultaneously with L-NAME.

The analysis of the myocardial contractility after the simulation of pathology was performed on the 8th day in the anesthetized rats under controlled respiration through catheterization of the left ventricle and

ISSN: 0975-8585

recording with the use of the hardware and software complex MP150 of Biopac System, Inc. production, USA). For assessment of the functional capabilities of myocardium in the animals the stress tests for adrenoreactivity (intravenous single-stage administration of the solution of adrenaline hydrochloride $1 \cdot 10^{-5}$Mole/L at 0,1 ml per 100 g) and resistance loading (compression of the ascending aorta for 30 seconds) were performed. By the statistical data processing the average (mean) value, deviation values were calculated. The differences were deemed to be significant at p<0,05.

FINDINGS OF THE STUDY

The test for adrenoreactivity was characterized by the expressed gain in the absolute values of the LVP, +dp/dt, -dp/dt, in response to the administration of the of the solution of adrenaline hydrochloride $1 \cdot 10^{-5}$Mole/L at 0,1 ml per 100 g. In the control group (animals that were receiving L-NAME) the left ventricular pressure (LVP), the contraction rate (+dp/dt, mm Hg/s) and myocard relaxation rate (-dp/dt, mm Hg/s) made 211,6±8,5 mm Hg, 9482,2±1125,6 mm Hg and 4691,6±857,6. mm Hg, respectively. In the animals that were receiving on the background of the hypoestorogen-L-NAME-induced deficiency of the nitrogen oxide Rosuvastatin as mono therapy the decrease in the maximum values of the left ventricular pressure to 191,7±7,0 mm Hg as well as reduced ± dp/dt was observed. By the use of the Rosuvastatin combination with thioctic acid the significant and definite reduction in the absolute LVP values under the adrenaline load to 155,8±10,3, +dp/dt, to 6324,0±1083,1 mm Hg/s, -dp/dt to 3575,9±734,1 mm Hg/s was observed (Table 1).

Table 1: The impact of Rosuvastatin, thioctic acid and the concomitant use thereof on the myocardium performance by simulation of the nitrogen oxide deficiency through administration of L-nitro-arginine-methyl ether (L-NAME) in the dose of 25 mg/kg intraperitoneally on the background of hypoestrogenia (in mm Hg, M±m, n=10).

Indicator / Group	Adrenoreactivity mm Hg				Drop in the LVP from the 5th to the 25th second of the aorta compression, %
	LVP, reference, mm Hg	LVP under adrenaline load, mm Hg	+dp/dt (relative units)	-dp/dt (relative units)	
Intact	108,6±4,3	199,2±4,3	6208±703	3973±391	16,4±4,6
Ovariectomy + L-NAME	142,5±9,4*	211,6±8,5*	9482±1604*	4691±857*	40,1±7,3*
Ovariectomy + L-NAME+ Rosuvastatin	113,6±10,7^{x}	191,7±7,0^{x}	7926±1604^{x}	4836±723^{x}	22,9±10,9^{x}
Ovariectomy я+ L-NAME+ Rosuvastatin+ thioctic acid	101,0±10,0^{x}	155,8±10^{x}	6324±1083^{x}	3575±734^{x}	16,8±4,8^{x}

Remark: * - p < 0,05 as compared to the intact group; ^{x} - p < 0,05 as compared to the L-NAME group.

By performing the test with the aorta compression and assessment of the range of drop in the left ventricular pressure (LVP) by the direct catheterization in the intact animals the drop of the LVP as of the 25th second of compression as compared to the 5th made approximately 16,4±4,6% (Table 1). On the contrary, the blockage of the NO-synthase with the use of L-NAME (25 mg/kg) resulted in the drop in the LVP at the 25 second of the aorta compression by 40,1±7,3%.

In the group of animals treated with the mono therapy with Rosuvastatin the values appeared in the intermediate position (22,9±10,9%). The concomitant use of Rosuvastatin and thioctic acid appeared to be preferable to monotherapy since the drop in the LVP at the aorta compression from the 5th to the 25th second made 16,8±4,8% (p < 0,05) which is close to the intact animals level.

ISSN: 0975-8585

CONCLUSION

Thus, the concomitant use of Rosuvastatin (0,85 mg/kg/day) with thioctic acid (50 mg/kg/day) exercised a pronounced cardio protective effect on the model of the hypoestrogen-L-NAME-induced NO deficiency which was expressed in the prevention of increase in adrenoreactivity and better maintenance of the myocardial reserve.

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