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CLINICAL RESEARCH

ROSUVASTATIN AND FENOFIBRATE INFLUENCE ON ECHOCARDIOGRAPHIC AND BIOCHEMICAL PARAMETERS OF ENDOTHELIAL REACTIVITY DEPENDING ON POLYMORPHISM OF PPARG И PPARA GENES IN OBESE PATIENTS WITH ESSENTIAL HYPERTENSION

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ABSTRACT

The aim of study was determination of rosuvastatin and fenofibrate influence on echocardiographic and biochemical parameters of endothelial reactivity depending on polymorphism of PPARG u PPARA genes in hypertonic patients with obesity.

Totally 352 patients were examined, 332 of them with hypertonic disease of I-II stage, 1-2 grade and obesity, forming the experimental group and control group, consisting of 20 practically healthy individuals. The level of total cholesterol, triglycerides, high, low and very low density lipoproteins, uric acid, C-reactive protein and immunoreactive insulin were determined in serum levels of examined patients. Polymerase chain reaction was used to study polymorphism of PPARA and PPARG genes. Vasomotor endothelial function was investigated using ultrasound diagnostic complex Vivid-3 by the method of D. Celermajer with analysis of flow-mediated dilatation and index of peak flow. In turn, the experimental group was divided into 2 subgroups, 172 patients from those were treated with rosuvastatin in dose of 5-40 mg per day, and 160 patients – with fenofibrate of 200 mg per day.

A significant decrease of hyperlipidemia, insulin resistance and systemic inflammation parameters as well as their intercorrelation was found in both groups. Both preparations significantly increased post-ischemic hyperemia level (indices of flow-mediated dilatation and peak flow). Genotype Pro12Ala/Ala12Ala of PPARG gene was found more favorable for rosuvastatin treatment as well as genotype Leu162 Leu of PPARA gene for fenofibrate treatment. The best efficacy was found in patients with genotype Pro12Ala/Ala12Ala of PPARG gene during treatment with rosuvastatin and genotype Leu162Leu of PPARA gene in the group treated with fenofibrate.

Thus, it can be concluded, that rosuvastatin and fenofibrate on have positive impact on hyperlipidemia and insulin resistance in hypertonic patients with obesity. Dependency of treatment efficacy from gene polymorphism was also proved: for PPARG in terms of treatment Pro12Ala/Ala12Ala genotype was more favorable, as well as for PPARA – Leu162Leu.

KEYWORDS: *hypertonic disease, endothelium, rosuvastatin, fenofibrate, endothelium-dependent vascular reactivity, gene polymorphism.*

INTRODUCTION

There is a growing body of evidence that endothelial dysfunction worsens the course of hypertension disease and causes the progression of atherosclerosis in patients with the presence of cardiovascular risk factors, such as obesity. The main functional consequences are the reduction of the bioavailability of nitric oxide, increasing of expression of cytoadhesive molecules and components involved in the processes of thrombosis and fibrinolysis. Connection of endothelial dysfunction is well-proven with the increase of choles-

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terol, low density lipoproteins, which are accompanied by the increase of triglycerides, insulin resistance [*Bocharova K, 2010; Babak O et al., 2011; Konopleva L, 2011; Belovol A et al., 2013*]. Destructive vascular effect of hypertriglyceridemia is mainly due to the prevalence of atherogenic small dense particles of low density lipoproteins that was proven for the level of triglycerides above to 1.5 *mmol/l* [*Malik J et al., 2001; Teragawa H et al., 2005; Uenoa H et al., 2011*].

Chronic inflammation of vascular paries is also connected with endothelial dysfunction. The levels of C-reactive protein, interleukin-6 decreased while conducting lipid-lowering therapy [*Malik J et al., 2001; Huang Y et al., 2003; Teragawa H et al., 2005; Uenoa H. et al., 2011*].

The treatment of endothelial dysfunction in this group of patients also remains a not fully identified issue. There is evidence that statins improve endothelial function in patients with hypercholesterolemia [*Chazova I et al., 2006; Drapkina O et al., 2012*]. There are less data regarding to the influence of fibrates on the improvement of endothelial function, there is information only about the population of patients with diabetes. Overall, the data on the effect of lipid-lowering therapy on endothelial function in combined hyperlipidemia is not enough. Pleiotropic metabolic effects of fenofibrate are mediated by PPARα receptors, which can partially explain the influence of fenofibrate on vascular reactivity [*Malik J et al., 2001; Huang Y et al., 2003; Teragawa H et al., 2005*].

The implementation of technologies into clinical practice of so-called personalized medicine is one of the ways to improve the effectiveness and safety of pharmacotherapy. It is known that 50% of the adverse pharmacological responses (development of side effects or lack of efficacy) depend on the genetic characteristics of the patient. That is why clinical pharmacogenetics allows the individualization of choice of medical drugs and their dosage regimes based on the study of individual patient genotype.

Peroxisome proliferator-activated receptors (PPARα, β/δ, γ) are nuclear hormone receptors, which do not only control the activity of many genes, but also are central regulators of lipid and carbohydrate metabolism, differentiation and development of adipose tissue, modulators of gene expression in many tissues including adipocytes, epithelial cells, smooth muscle, macrophages and vascular endothelium. The effectiveness of various types of PPAR agonists (fibrates, glitazones and glitazars) depending on gene polymorphism receptors PPAR is currently investigated. The ability to activate PPAR ligands of low molecular weight can effectively affect these diseases [*Lupinskaya Z et al., 2008; Sidorchuk L, 2009; Belfort R et al., 2010; Belovol A et al., 2013*]. The achievements in the study of physiology and pathology of PPAR in recent years allow us to consider this directivity as one of the most promising in controlling of the development of atherosclerosis, essential hypertension and diabetes of 2nd type. Therefore, the conduction of molecular genetic researches for the study of gene polymorphism, involved in the regulation of carbohydrate and lipid metabolism is certainly actual and necessary.

The aim of study was rosuvastatin and fenofibrate influence on echocardiographic and biochemical parameters of endothelial reactivity depending on polymorphism of PPARG и PPARA genes in obese patients with essential hypertension.

Material and methods

Contingent of surveyed patients and their clinical characteristics: The study is based on a survey of 352 patients, who were divided into groups. Experimental group was consisted of 332 patients with hypertonic disease of I-II stage, 1-2 grade and obesity, who were hospitalized in the clinic of SI "National Institute of Therapy named after L.T. Malaya NAMS of Ukraine". The control group consisted of 20 practically healthy persons who were not taking any drugs and without cardiovascular risk factors, matched by age and sex.

Among examined were 185 (55.72%) men, 147 (44.38%) women, average age was 53.0±6.5 years. Body weight of the examined patients was 91.7±12.0 *kg*, body mass index – 32.3±3.9 *kg/m*^{2}. Initial numbers of office systolic blood pressure and diastolic blood pressures were about 161.7±3.0 and 96.9±2.5 *mm Hg* respectively; heart rate was 74.6±0.7 *beats/min*.

Obesity in patients was defined according to the criteria defined in the European guidelines for the treatment of hypertension in 2013 [*ESH/ESC, 2013*]. Data were analyzed with the standard anthropometric variables waist circumference, hip circumference, fasting glucose, the value of immunoreactive insulin, triglycer-

ide levels and high-density lipoprotein cholesterol, total cholesterol and low density lipoprotein levels in accordance with the recommendations of the International Diabetes Foundation [*IDF, 2005*].

The study excluded patients with type 1 diabetes, verified symptomatic arterial hypertension, clinical signs of coronary heart disease, by the level of office blood pressure > 180/110 *mm Hg*, uncompensated liver's diseases (transaminase levels above normal in 3 times), acute or chronic renal insufficiency (serum creatinine >133 *mmol/l* for men and 124 *mmol/l* for women), myocardial infarction or acute stroke in history, pregnancy and lactation.

Hypertensive patients were divided into first and second experimental groups depending on the intended treatment. First experimental group consisted of 172 patients treated with rosuvastatin at a dose of 5-40 *mg* per day, link of treatment effectiveness with polymorphism of PPARG gene was studied in 130 of these patients. The second group was consisted of 160 patients who were treated with fenofibrate of 200 *mg*, the dependency of treatment efficacy from polymorphism of PPARA gene was studied in 126 of these patients. All patients received antihypertensive therapy in form of telmisartan 20-80 *mg* per day at early stages of treatment. Assessment of the dynamics parameters were within 6 months after therapy.

Laboratory methods: The level of total cholesterol, triglycerides, high density lipoproteins, low density lipoproteins, very low density lipoproteins and uric acid was determined in serum, which was taken from the cubital vein, after a 12-hour fast by enzymatic method photocolorimetry recruitment firm "Human" (Germany).

The determination of C-RP and immunoreactive insulin was performed by an ELISA using appropriate kits firm "DRG-Diagnostics" (USA) with ELISA photocolorimeter "HUMAREADER" firm "Human" (Germany). According to the regulations of techniques used in the study, fasting immunoreactive insulin concentration is considered normal if it does not exceed 25 *mcE/ml*.

The study of PPARG and PPARA gene polymorphism performed on the basis of the polymerase chain reaction and restriction analysis by horizontal agarose gel electrophoresis.

Instrumental methods: The vascular motor function of endothelium was measured by determining the dynamics of blood flow in the brachial artery during reactive hyperemia. The evaluation was conducted on the ultrasonic diagnostic complex Vivid-3 (General Electric, USA), 7.5 MHz linear transducer (resolution 0.01*mm*) by the procedure described by D. Celermajer and co-authors [*Celermajer D et al., 1992*]. All vasoactive drugs were canceled to patient a day before the test, diuretics – per 2 days, amlodipine - up to 5 days. On the day of study, patients refused to drink coffee, strong tea, alcohol, cigarettes. In the morning patients underwent scanning of the brachial artery on an empty stomach with air temperature + 22° C. The patient was in the supine position for 10-15 minutes, and then use of vascular sensor determined the base diameter of the brachial artery in the zone between the endothelium and media at a maximally clear image of front and rear walls of the vessel. The settings were kept constant throughout the study. Reactive hyperemia was achieved by pumping of pneumatic cuff up to 200 *mm Hg*, superimposing on shoulder for 5 minutes. All measurements were carried out in diastole. Measurement of brachial artery diameter was performed on 80 second after compression. The expansion of brachial artery testifies to the preservation of endothelial function by 10% and more, while endothelial dysfunction - less than 10%.

One of ultrasonic methods for the study of endothelial function in modern medicine is the study of endothelium-dependent vasodilation or flow-dependent dilation. But back in 2001 [*Malik J et al., 2001*], there were data that confirmed the high sensitivity and representativeness of such parameter, the maximum blood flow velocity (*ml/min*) or the index of the peak flow. It was proved that index of peak flow closely correlates with changes in blood flow induced by intra-arterial infusion of acetylcholine (a method which is widely used in the assessment of endothelial function). Unlike flow-mediated dilation, blood flow parameters reflect "average" vascular reactivity relative to large proportion of arterial network [*Malik J et al., 2001; Furuhashi M et al., 2002*].

Blood flow was measured at rest and after removal of the cuff as the average of three cardiac cycles (except the first usually deformed cycle). Index of peak flow was calculated as the integral of blood flow velocity multiplied by the cross-sec-

tion of the vessel in early postischemic period.

Statistical processing of the results was performed on a personal computer using the software package "SPSS 16.0 for Windows" on the basis of electronic database created by us. Before statistical processing, the assessment of obtained data conformity was carried out by normally distributed random variables. In most cases, the results were not consistent with the law of normal distribution, that's why nonparametric tests were used. Average values and their standard error were calculated for groups (M ± m, where M – mean value, m – its standard error). For comparison, the average values were used nonparametric Mann-Whitney test for independent samples. Correlations were evaluated by Spearman's correlation coefficient (ρ). The probability of changes in the parameters before and after treatment was evaluated by the nonparametric Wilcoxon test for dependent samples. The results, for which the level of significance (p) didn't exceed 0.05, were considered as reliable.

Results and Discussion

Ultrasonic characteristics of endothelial function

Normal significance of ultrasound indices were based on a survey of the control group. In the group of healthy volunteers vascular reactivity indices were as follows: Endothelium-dependent vasodilation – 4.75±2.52%, index of peak flow – 896.3 ± 35.6 *ml/min*.

The results of studies are shown in Table 1. The differences between the effects of drugs on ultrasound parameters were not found. A significant increase of endothelium-dependent vasodilation was found while taking these drugs. Also there was a significant change in reactive hyperemia index after treatment: index of peak flow was significantly increased after treatment with both drugs.

Biochemical parameters: The results of biochemical analysis are shown in Table 2. Rosuvastatin exceeded fenofibrate in decrease of serum levels of total cholesterol, low density lipoprotein and non-high density lipoprotein cholesterol. Fenofibrate was more effective in reduction of serum triglycerides and increase of high density lipoprotein cholesterol. Both drugs reduced C-reactive proteins and insulinemia. However, this reduction was significantly reliable only for fenofibrate.

The detection of insulin effect on C-reactive proteins confirms the literature data about the cor-

Table 1.

Changes of ultrasonic parameters in vascular reactivity after treatment with fenofibrate and rosuvastatin

Indicators	Before	After	p
Group treated by fenofibrate			
Endothelium-dependent vasodilation (%)	2.26±0.9	2.98±0.8	<0.05
Index of peak flow (ml/min)	448.0±8.9	546.1±11.0	<0.01
Group treated by rosuvastatin			
Endothelium-dependent vasodilation (%)	2.19±0.6	2.87±0.9	<0.05
Index of peak flow (ml/min)	453.2±9.3	570.0±11.7	<0.01

Table 2.

Changes in biochemical parameters after treatment with fenofibrate and rosuvastatin

Indicators	Fenofibrate group		Rosuvastatin group	
	Initial values	After treatment	Initial values	After treatment
C-reactive protein (*mg/l*)	11.9±0.1	5.8±0.09**	10.8±0.13	8.9±0.12
Insulinaemia (*mcE/ml*)	18.2±1.2	12.9±0.72*	17.7±2.0	16.5±0.82
Uric acid (*mmol/l*)	418±2.05	308±6.0*	411±2.21	387±8.2
Triglycerides (*mmol/l*)	2.01±0.04	1.52±0.10**	2.10±0.05	1.57±0.04**
Cholesterol (*mmol/l*)				
Total	5.75±0.16	4.64±0.09**	5.96±0.12	3.44±0.05***
Low density lipoprotein	3.76±0.10	3.05±0.06	3.39±0.09	1.90±0.05***
High density lipoprotein	1.06±0.02	1.22±0.06**	1.19±0.07	1.25±0.02
Non-high density lipoprotein	4.7±0.03	3.2±0.01***	4.8±0.04	2.3±0.09***

*Notes: * p<0.05, ** p<0.01, *** p<0.001*

rection of systemic inflammation fenofibrate. Thus, fenofibrate significantly reduced high-strung C-reactive proteins in insulin-resistant patients with metabolic syndrome without diabetes on 49.5±8% (p=0.005), as well as interleukin-6 29.8±7% (p=0.03) in comparison with placebo [*Binggeli C et al., 2003*]. According to other authors, fenofibrate both in experimental and clinical studies also had the ability to adjust insulin resistance [*Florez J et al., 2007, Li P et al., 2010*]. However, the information on the reduction of insulinemia is contradictory.

Correlation of biochemical parameters and indices of vascular reactivity: Possible correlations were not found before the treatment. The analysis of treatment effects revealed a significant correlation between the decrease of insulinemia and improvement of both indicators of vascular reactivity in the treatment with fenofibrate (Table 3). Index of peak flow was significantly improved inversely proportional to changes of total cholesterol during the treatment with rosuvastatin, and endothelium-dependent vasodilation also had a similar dependence on the totals of non-high density lipoprotein cholesterol.

Study of the treatment efficacy depending on the polymorphism of genes: The efficacy of therapy depending on the genotype polymorphism of PPARG gene was studied in 130 patients of the rosuvastatin group.

Positive changes were observed among all indicators of endothelium structural and functional state on the background of the prescribed therapy. Positive effect of the treatment was more clearly established in Pro12Ala carriers of Pro12Ala/Ala12Ala genotype of polymorphism than in carriers of genotype Pro12Pro during the dynamic study of endothelium structural and functional state, which testified to the genetically determined, more directed pathogenic effect of the proposed therapies. However, while comparing, some difference were observed in carriers of genotypes Pro12Pro and Pro12Ala/Ala12Ala of Pro12Ala polymorphism of PPARG gene (Table 4).

As it can be seen from Table 4, in both subgroups changes in the indices after treatment were significant, but the values of the parameters of endothelial ultrasound in patients with genotypes Pro12Ala/Ala12Ala after the treatment were significantly higher than those in patients with genotype Pro12Pro, whereas baseline were not significantly different. That is, in case of genotypes Pro12Ala/Ala12Ala, the response to therapy with rosuvastatin was better conditioned and significantly more expressive positive dynamics in structural and functional state of the endothelium in patients with hypertonic disease, while in genotype Pro12Pro of PPARG gene the character of response to therapy with rosuvastatin was worse.

Also, the efficacy of therapy depending on the polymorphism of PPARA gene was studied in 126 patients of the fenofibrate group. Leu162Leu genotype was diagnosed in 35 of them, in 91 – Leu162Val. Therapy with fenofibrate induced positive changes of all indicators of endothelium structural

Table 3.

Correlation between biochemical and vascular effects during the treatment with fenofibrate and rosuvastatin (according to Spearman)

Indicators	Index of peak flow		Endothelium-dependent vasodilation	
	Fenofibrate	Rosuvastatin	Fenofibrate	Rosuvastatin
C-reactive protein (*mg/l*)	0.22	−0.29	0.18	0.23
Insulinaemia (*mcE/ml*)	−0.56*	−0.37	−0.40*	0.18
Uric acid (*mmol/l*)	0.24	0.15	0.04	0.05
Triglycerides (*mmol/l*)	−0.24	−0.26	−0.30	0.29
Cholesterol (*mmol/l*)				
Total	0.27	−0.42*	0.32	−0.43*
Low density lipoprotein	0.32	−0.02	0.41	0.45*
High density lipoprotein	0.06	0.08	−0.29	0.17
Non-high density lipoprotein	0.05	−0.5	0.22	0.38*

***Notes**: * Significant correlation (p<0.05); p>0.05 in other cases.*

Table 4.

Changes of ultrasonic parameters of vascular reactivity

Indicators	Before Treatment	After Treatment	p	Before Treatment	After Treatment	p	p_1
Treatment with rosuvastatin depending on polymorphism of PPARG gene							
	Pro12Pro (n=28)			Pro12Ala/Ala12Ala (n=102)			
IPF, *ml/min*	448.5±19.8	492.3±18.2	<0,05	458.6±10.2	587.5±14.3	<0.01	<0.001
EDVD, %	2.23±1.0	2.76±0.9	<0,05	2.17±0.6	3.15±0.7	<0.001	<0.01
Treatment with fenofibrate depending on polymorphism of PPARA gene							
	Leu162Leu (n=35)			Leu162Val (n=91)			
IPF, *ml/min*	453.3±12.1	562.1±14.6	<0.01	478.0±10.4	529.3±12.3	<0.05	<0.01
EDVD %	2.15±1.0	3.07±0.8	<0.01	2.28±0.7	2.86±0.9	<0.05	<0.01

Note: *IPF- index of peak flow, EDVD-endothelium-dependent vasodilatation,* p_1-difference between genotypes after treatment.

and functional state, however, while comparing, some differences were observed in such carriers of genotypes Leu162Leu and Leu162Val of PPARA gene: indicators of endothelium structural and functional state in genotype Leu162Leu were better than in genotype Leu162Val. In other words, likewise polymorphism of PPARG gene, the changes of indicators in both subgroups were significant after treatment, but the response on therapy with fenofibrate was the best in patients with genotype Leu162Leu, although this genotype was much rarer.

Therefore, rosuvastatin reduced total cholesterol and non-high density lipoprotein cholesterol, significantly higher compared with fenofibrate. Fenofibrate better reduced the level of triglycerides, C-reactive proteins and increased high density lipoprotein cholesterol. Fenofibrate also reduced the appearance of insulinemia, although no significant difference between rosuvastatin and fenofibrate on the effect of this measure was found.

Despite various metabolic effects of drugs, their effects on vascular reactivity were similar. Both drugs significantly improved endothelial state (growth of endothelium-dependent vasodilation and index of peak flow).

Reduction of manifestations of chronic inflammation and insulin resistance (the dynamics of C-reactive proteins and insulin levels) under the influence of fenofibrate significantly resulted in improved endothelial function, meanwhile, endothelium protective effect of rosuvastatin was more depended on changes in lipid levels (as evidenced by the probable correlation between vascular reactivity and levels of total and non-high density lipoprotein cholesterol ($p<0.05$)).

The best efficacy was observed in patients with genotype Pro12Ala/Ala12Ala of polymorphism of PPARG gene on the background of treatment with rosuvastatin and genotype Leu162Leu polymorphism of PPARA in the group treated with fenofibrate.

The prospect of further research can be a comparison of parameters of endothelial dysfunction and the effectiveness of hypolipidemic therapy in patients with arterial hypertension and obesity and normal body weight.

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