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CARDIOPROTECTIVE EFFICACY OF ZOFENOPRIL MONOTHERAPY IN ASSOCIATION WITH THE CYP11B2 C-344T POLYMORPHISM IN UZBEK HYPERTENSIVE PATIENTS

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ABSTRACT

Objective: The present study aimed to evaluate pharmacogenetic aspects of the antihypertensive, cardioprotective efficacy and clinical safety of 12-week Zofenopril monotherapy in association with the CYP11B2 C-344T polymorphism in Uzbek hypertensive patients. **Materials and Methods:** In order to study prevalence of CYP11B2 C-344T polymorphism there were selected 150 Uzbek hypertensive patients with Stage I-III of arterial hypertension (ESH/ESC, 2013), as well as 58 healthy Uzbeks aged from 30 to 70 years. The clinical efficacy of 12-week Zofenopril monotherapy in association with the CYP11B2 C-344T polymorphism was studied in 39 Uzbek hypertensive patients with Stage I-II of AH (ESH/ESC, 2013) (mean age 44.5±9.9 years, mean duration of AH was 4.3 ±4.4 years). **Results:** The prevalence of CT-heterozygotes and T-allele of the CYP11B2 C-344T polymorphism in Uzbek hypertensive patients was determined. The analysis in the subgroups with various carriers of CYP11B2 C-344T polymorphism revealed advances of the antihypertensive and cardioprotective efficacy of Zofenopril monotherapy in patients-carriers of TC+CC genotypes in comparison with carriers of TT-genotypes. The intensity of LVH and LVDD was associated with carrying of TT-genotype of CYP11B2 gene. **Conclusion:** The advanced antihypertensive and cardioprotective effect of Zofenopril monotherapy in hypertensive patients is associated with TC+CC genotypes.

KEYWORDS: Arterial hypertension, CYP11B2 C-344T polymorphism, Zofenopril.

INTRODUCTION

Understanding the mechanisms of the arterial hypertension (AH) is of high importance due to widely spread disease being one of the main reasons of disability and mortality among the population of the Earth. The methods developed in the last decays allowed to transfer from empiric description to elucidation of deep genetic and biochemical causes underlying the hypertonic disease as well as understanding that the spectrum of these causes is multiform. The genetic factors make a valuable contribution to the regulation of arterial blood pressure (BP): it is suggested that 30-60% of the variations observed in the BP are identified by genotype. Genetic factors both play integral role in the development of AH and effect on the response during pharmacotherapy. Besides, the multiform role of renin-angiotensin-aldosterone system (RAAS) has been confirmed in the formation of AH. It is known that aldosterone controls sodium balance in the body and volume of circulating blood and thus participates in the regulation of BP. It stimulates collagen synthesis and fibroblasts proliferation in the heart and vessels through activation of local receptors of mineralocorticoids.[1] The presence of aldosterone receptors in the large arteries, particularly in aorta,[2] and endogenic synthesis of aldosterone in the vessels.[3,4] suggests that aldosterone plays a role in the regulation of the structure and function both of heart and large arteries,[5] resulting in hypertrophy and hyperplasia of the smooth muscle cells, damage of vascular matrix and endothelium dysfunction.[6,7]

One of the polymorphisms of aldosterone synthase gene (CYP11B2), rs1799998, is located −344 bp upstream in promoter region and consistent with either T or C (C-344T), may influence the cardiovascular system through the effects of aldosterone, because the C allele binds to the steroidogenic factor-1 (SF-1) site five times stronger than does the T allele.[8] Thus, study of CYP11B2 C-344T polymorphism as a candidate gene for AH, particularly in the pharmacogenetic aspect is of special importance.

The angiotensin-converting enzyme inhibitor (iACE) including SH-group – Zofenopril, having some special characteristics in comparison with previous captopril, have been synthesized and clinically studied over the last 30 years. Calcium zofenopril is a high lipophilic iACE, which converts into its active form – zofenoprilate both in the blood serum and in the various tissues. This is an important difference of zofenopril from other drugs such as ramipril, enalapril, which are rather activated only in the blood serum and kidneys. Zofenopril, as the other representatives of this class, inhibits ACE in the plasma and tissues and interferes with bradykinin degradation, which is connected with vascular and renal effects of preparation. Individual variation in drug response, caused by genetic differences of various populations, is widely spread and is a part of important clinical problem.[9] The most important principle of molecular medicine is the strong selection of the individual medicinal treatment subject to special genetic characteristics of a patient. This problem has to be resolved by the personalized therapy - the leading part of molecular medicine.

In present study we aimed to evaluate antihypertensive, cardioprotective efficacy and clinical safety of 12-week monotherapy with Zofenopril (Zocardis, "Berlin-Hemi", Germany) subject to CYP11B2 C-344T polymorphism in Uzbek hypertensive patients.

MATERIALS AND METHODS

The total number of 150 Uzbek hypertensive patients with Stage I-III of arterial hypertension (ESH/ESC, 2013), as well as 58 healthy Uzbeks aged from 30 to 70 years were genotyped to determine the overall distribution of the CYP11B2 C-344T variants in Uzbek population.

The clinical efficacy of 12-week Zofenopril monotherapy in association CYP11B2 C-344T polymorphism was studied in 39 ethnic Uzbek patients (mean age of 44.5±9.9 years) with untreated AH of Grade 1 and 2 (ESH/ESC, 2013) and average AH duration of 4.3 ±4.4 years. The diagnosis of AH conducted according to 2013 ESH/ESC Guidelines for the management of arterial hypertension. Exclusion criteria were symptomatic hypertension, clinical evidence of cerebrovascular or coronary heart diseases, cardiac arrhythmia, heart failure, renal impairment, diabetes mellitus, metabolic and other background diseases, alcohol intake greater than 30g of pure ethanol per day, and smoking.

Echocardiography and Doppler sonography conducted according to standard methods described in recommendations of the American Society of echocardiography.[10] The following parameters were measured and calculated: interventricular septum thickness (IVST), posterior wall thickness (PWT), left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), ejection fraction (EF), and left ventricular mass (LVM)**.** The LVM was calculated using the formula.[11] LVM was indexed to body surface area (LVMI). Left ventricular hypertrophy (LVH) was defined as LVMI of >95 g/m^2 (for women) and > 115 g/m^2 (for men).

The ratio of peak early filling velocity to peak atrial filling velocity (PE/PA) was calculated. The isovolumic relaxation phase (IRP) was also measured.

Genomic DNA was extracted from peripheral blood using the Diatom^{TM} DNA Prep 200 Kit according to the manufacturer's protocol. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique was performed according to previously described methodologies to determine the CYP11B2 C-344T polymorphism.[12]

Zofenopril was prescribed as monotherapy for 12 weeks in average dose of 32.7±18.1 mg.

Statistical analysis was performed using the statistical software «Statistica» (v6.0, StatSoft, USA). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±SD for continuous variables. Student's unpaired and unpaired t-tests were used to compare two groups for data with normal distribution. For small sample sizes and inconsistencies in numerical data with the normal distribution, non-parametric Mann-Whitney and Wilcoxon criteria were used.

Relative risk ratio (RR) was calculated using genetic models. The calculations were performed using the "Calculator for calculating statistics in case-control studies", developed by the State Scientific Center of the Russian Federation available at http://gen-expert.ru/calculator_or.php. Deviation from Hardy-Weinberg equilibrium and differences in allele distributions between the two groups were assessed by χ^2-test. Two-tailed *P* values <0.05 were considered statistically significant.

RESULTS

Among the patients with AH the distribution of the genotypes of CYP11B2 C-344T polymorphism was as follows: TT- 24(16%), p=0.000, χ^2 =31.9, T- 184 (61.3%), C- 116 (38.7%), p=0.000, χ^2=29.9. The significant prevalence of T-allele and TC-genotype of CYP11B2 C-344T polymorphism in Uzbek hypertensive patients was shown (Tab.1).

In healthy persons the distribution of CYP11B2 C-344T polymorphism showed also high frequency of TC-genotype in 30 individuals (51,7%) and almost even distribution of TT- and CC- genotypes: TT- 15 (25.8%), CC-genotype – in 13 (22.4%), p=0.000, χ^2=13.4. There were no differences in distribution of T- and C-alleles (Tab.1).

The above-described data in controls and patients with AH are in Hardy-Weinberg equilibrium.

Thus, the significant accumulation of T-allele of the CYP11B2 C-344T polymorphism among Uzbek hypertensive patients was revealed. On the basis of genetic models, a tendency to associative link of T- allele of the CYP11B2 C-344T polymorphism with AH in Uzbeks was found (Table 1).

After genotyping, all patients (n=39) were divided into two groups: Group 1 –TT- genotype carriers (n=10) and Group 2 –TC+CC genotypes carriers (n=29). The carriers of TC- and CC-genotypes were combined to one group TC+CC since a few carriers of CC-genotype were identified. According to the initial level of BP the TT-genotype and TC+CC genotypes carriers of the CYP11B2 C-344T polymorphism showed no difference from each other. At the same time there was association of intensity of LVH and LVDD with TT-genotype in comparison with TC+CC genotype carriers of CYP11B2 gene (LVMI was 133.2±32.2 g/m^2 vs. 118.1±23.8 g/m^2, respectively, P>0.05 and IRP was 0.127±0.02 sec vs. 0.110±0.02 sec, respectively, p<0.05). The IVST was significantly higher in the TT-genotype patients in comparison with TC+CC genotype carriers (1.16± 0.19 cm vs.1.03±0.12 cm, respectively, P<0.02).

Table 1: Genotypes and alleles distribution frequencies of the CYP11B2 C-344T polymorphism among the patients with AH and healthy individuals in Uzbek population.

Inheritance models	Alleles/Genotypes	Controls	Cases	χ^2	p	OR	
		n=150	n=58			value	95%CI
Multiplicative (test χ^2 , df=1)	T	0.613	0.565	3.19	0.07	1.48	0.96-2.28
	C	0.387	0.435			0.68	0.44-1.04
Dominant (test χ^2, df=2)	TT	0.387	0.259	3.28	0.19	1.81	0.92-3.54
	TC	0.453	0.517			0,77	0.42-1.42
	CC	0.160	0.224			0.66	0.31-1.40
Additive (Cokhran-Armitadge for trend, xi=[0,1,2], df=1)	TT	0.387	0.259	3.10	0.08	1.81	0.92-3.54
	TC	0.453	0.517			1.33	0.42-1.42
	CC	0.160	0.224			0.88	0.31-1.4

Estimation of antihypertensive efficacy of Zofenopril

A 12-week monotherapy with Zofenopril in average dose 32.7±18.1 mg showed the high antihypertensive efficacy resulted in a reliable decrease in absolute values of SBP and DBP independently of the C-344T polymorphism (Table 2).

In two studied groups, the high level of BP reduction estimated by the degree of reduction in mean blood pressure > 10% (-14.6±5.9% for Group 1 and -17.5±6.0 for Group 2) was noted. Positive antihypertensive efficacy was found in 90% of cases for Group 1 and 89.7% of cases for Group 2. Achievement of the target level of SBP was determined in 60% of cases for Group 1 and 96.6% for Group 2 (χ^2 =8.889, df=1, p=0.003). Achievement of the target DBP level was noted in 70% of cases for Group 1 and 86.2% for Group 2. Simultaneous achievement of target levels of SBP and DBP was noted in 70% of cases for Group 1 and 86.2% of cases for Group 2. A tendency towards a better antihypertensive response in patients with TC+CC genotypes of CYP11B2 C-344T polymorphism was observed.

Table 2: Antihypertensive efficacy of 12-week monotherapy with Zofenopril in association with the C-344T polymorphism of CYP11B2 gene.

Variable	Total	Group 1	Group 2
SBP, mmHg	147.9 ± 10.6 122.1 ± 10.6 *	152 ± 13.36 128 ± 13.17*	146.6 ± 10.1 120 ± 8.9*
DBP, mmHg	94.9 ± 5.4 79.5 ± 7.9*	96 ± 5.16 83 ± 8.23*	94.5 ± 5.6 78.3 ± 7.6*
Mean BP, mm Hg	112.6 ± 6.9 93.7 ± 8.5*	114.7 ± 7.06 98 ± 9.58*	111.8 ± 6.9 92.2 ± 7.7*
SBP, Δ%	-17.4 ± 5.6	-15.8 ± 6.9	-18.0 ± 5.6
DBP, Δ%	-16.2 ± 7.2	-13.6 ± 6.9	-17.1 ± 7.1
Mean BP, Δ%	-16.7 ± 6.0	-14.6 ± 5.9	-17.5 ± 6.0
Achievement of target levels: SBP,% DBP,% SBP and DBP,%	 34 (87.2%) 32 (82.1%) 31 (79.5%)	 6 (60%)^ 7 (70%) 6 (60%)	 28 (96.6%)^ 25 (86.2%) 25 (86.2%)

Note: *- p < 0.001 – between before and after treatment; ^ - χ^2=8.889, df=1, p=0.003 – significance between groups; numerator – before, denominator - after treatment.

Estimation of cardioprotective efficacy of Zofenopril

The study revealed certain advantages of antiremodeling therapy depending on the genotype carrier (Table 3). We revealed no significant differences in degree of LVMI reduction, but it was less in TT-genotype carriers: -6.8±9.2% vs. -8.01±7.0 in TC+CC-genotype carriers, (p>0.05). It should be noted that only in TC+CC-genotype carriers there was reliable decrease of LVMI. Thus, in Group 2 LVMI before treatment and after treatment was 118.1±23.8 g/m^2 and 108.8±24.0 g/m^2 (p<0.001) respectively.

A significant reduction of the LVM in carriers of TC+CC genotype during Zofenopril therapy was associated with a reduction in the degree of the concentric LVH. In addition, the only Group 2 patients showed a significant increase in the EDV/LVM ratio: 0.62±0.08 ml/g before treatment and 0.66±0.09 ml/g after treatment (p<0.02) compared to Group 1 patients: 0.57±0.09 ml/g and 0.63±0.09 ml/g (p>0.05). Such positive changes in the LVM during therapy in both groups were accompanied by an improvement in LV diastolic function with significant positive dynamics of IRP.

Table 3: Cardioprotective efficacy of 12-week monotherapy with Zofenopril in association with the CYP11B2 C-344T polymorphism.

Variable	Total	Group 1°	P	Group 2
IVST, cm	1.07 ± 0.15 1.02 ± 0.14	1.16 ± 0.19 1.1 ± 0.15^	0.016	1.03 ± 0.12 0.99 ± 0.12*
PWT, cm	0.88 ± 0.09 0.84 ± 0.08	0.9 ± 0.08 0.84 ± 0.08^	НД	0.88 ± 0.10 0.84 ± 0.08*
EDV/LVM, ml/g	0.61 ± 0.08 0.65 ± 0.09*	0.57 ± 0.09 0.63 ± 0.09	НД	0.62 ± 0.08 0.66 ± 0.09*
EDD, cm	5.4 ± 0.4 5.4 ± 0.4	5.54 ± 0.42 5.63 ± 0.41	НД	5.4 ± 0.41 5.3 ± 0.42
ESD, см	0.33 ± 0.3 0.35 ± 0.3	3.36 ± 0.32 3.49 ± 0.4	НД	3.3 ± 0.34 3.3 ± 0.26
EF, %	68.3 ± 6.2 67.6 ± 3.8	69.2 ± 3.3 67.5 ± 5.06	НД	68.0 ± 6.9 67.6 ± 3.4
PE/PA	1.01 ± 0.3 1.04 ± 0.3	0.98 ± 0.36 0.97 ± 0.31	НД	1.06 ± 0.28 1.06 ± 0.28
IRP, sec	0.115 ± 0.02 0.109 ± 0.02▪	0.127 ± 0.02 0.123 ± 0.03	0.026	0.110 ± 0.02 0.105 ± 0.02
LVM, g	242.5 ± 59.2 225.1 ± 55.9▪	270.1 ± 76.9 255.2 ± 61.95	НД	233.0 ± 49.9 214.8 ± 50.8▪
LVMI, g/m²	122.0 ± 26.6 113.2 ± 24.9▪	133.2 ± 32.2 125.77 ± 24.5	НД	118.1 ± 23.8 108.8 ± 24.0▪
LVIM, Δ%	-7.01 ± 8.6	-6.8 ± 9.2	НД	-8.01 ± 7.0

Note: ^ - p < 0.05; * - p<0.02; ▪ - p<0,001 – between before and after treatment; numerator – before, denominator – after treatment. ° - due to small case number in groups the Wilcoxon Signed Rank test applied. P- significance between initial parameters in the groups.

DISCUSSION

Thus, the significant accumulation of T-allele of the CYP11B2 C-344T polymorphism among Uzbek hypertensive patients was revealed. On the basis of genetic models, the association of T- allele of the CYP11B2 C-344T polymorphism with AH in Uzbeks was found. The prevalence of TC-genotype and T-allele of the CYP11B2 C-344T polymorphism in Uzbek hypertensive patients corresponded to frequencies observed in Caucasians.[13-16] and differed from Japanese population with accumulation of TT with the absence of CC-homozygotes.[17,18] and South-Africans with predominance of TT-genotype carriers and T-allele.[19] According to previous studies the association of the CYP11B2 C-344T polymorphism with AH and positive correlation with level of plasma aldosterone was found. The T allele prevalence in hypertensive patients of French population was higher than in healthy individuals and T allele was associated with AH.[20] This was confirmed in the clinical practice and in a number of studies where the significant accumulation of T allele in hypertensive patients was observed, the T allele carriers also had significant excretion of aldosterone in comparison with CC-homozygotes.[21,22] In Japanese population T allele associated with low-renin content hypertension.[23] In the Ohasama Study the frequency of T allele prevailed, and at BP monitoring there were no reliable differences between genotypes, however CC-genotype was associated with reduction of nocturnal BP

in old men.[24] In the research of G.V. Asadullina et al,[25] the frequency of T allele was higher in the patients with hypertension in comparison with healthy individuals, and carriers of TT-genotype had more intensive diastolic dysfunction of the left ventricle. In our study there was shown a negative role of T allele in AH development and TT-genotype of CYP11B2 in heart remodeling in Uzbek hypertensive patients, which is consistent with literature data. Thus, a significant accumulation of T allele of CYP11B2 C-344T polymorphism among Uzbek hypertensive patients was observed, and intensity of LVH and LVDD was associated with TT-genotype.

Organoprotective efficacy of antihypertensive drug is primary meaning for treatment of AH with target-organs damage, in achieving one of main goals of AH therapy – prevention of target-organs damage and decrease cardiovascular risk. The main distinctions of Zofenopril is high lipophility and affinity to ACE, which promotes to fast, full penetration and accumulation of the medicine in the tissues, maximal inhibition of the tissue ACE. This is connected with such pleiotropic effects of Zofenopril as cardioprotection, prevention of endothelial dysfunction, anti-ischemic, anti-inflammatory and anti-atherogenic efficacy, promotion to angiogenesis and reverse development of apoptosis. Presence of SH-group results in reduction of oxidative stress, bind to free radicals, increased production of nitrogen oxide – NO, antiatherogenic effect, that lead to increase of coronary blood flow and decrease ischemia. All this can characterize Zofenopril as antihypertensive agent with cardioprotection properties.[26]

In present work we studied antihypertensive, antiremodeling efficacy and clinical safety of 12-week monotherapy with Zofenopril in association with CYP11B2 C-344T polymorphism in AH patients. We could not compare collected information with published data on pharmacogenic peculiarities of Zofenopril due to their absence. However, high antihypertensive and cardioprotective efficacy of monotherapy with Zofenopril in the patients with AH was demonstrated, that has been also confirmed by the several SMILE studies.[27,28]

Thus, a significant accumulation of T-allele of the CYP11B2 C-344T polymorphism among Uzbek hypertensive patients was revealed. Based on genetic models, there was found an association of T- allele of the CYP11B2 C-344T polymorphism with AH in Uzbeks. There was association of intensity of LVH and LVDD with TT-genotype. The TT-genotype limits the antihypertensive and cardioprotective efficacy of Zofenopril. At the same time, we revealed certain advantages in the antihypertensive and cardioprotective efficacy of Zofenopril treatment in Uzbek hypertensive patients with TC+CC genotype of the CYP11B2 C-344T polymorphism.

Duy to the data on clinical efficacy of Zofenopril with account of the CYP11B2 C-344T polymorphism in the Uzbek AH patients was limited by short period of observation and small number of samples, an additional comprehensive clinical study should be done in the future.

Competing interests

The authors declare that they have no competing interests.

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