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Pharmacogenetic testing by polymorphic markers G1846A (*CYP2D6*4*) and C100T (*CYP2D6*10*) of the *CYP2D6* gene in coronary heart disease patients taking β-blockers in the Republic of Sakha (YAKUTIA)

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Abstract

Background: The aim of this study was to determine carrier frequencies of the polymorphic markers G1846A (*CYP2D6*4*) and C100T (*CYP2D6*10*) of the CYP2D6 gene in coronary heart disease (CHD) patients in Russian and Yakut ethnic groups. The association between the administration of higher doses of bisoprolol and metoprolol and the carriage of these polymorphic markers related to the decreased function of the haplotype of CYP2D6 was also studied.

Methods: The study included 201 CHD patients (aged 66 ± 8.7 years) receiving metoprolol in titrated dose (12.5–150 mg), bisoprolol (2.5–10 mg) or atenolol (50 mg). Ninety-three patients were Russian (30 men and 63 women), and 108 patients were Yakut (54 men and 54 women).

Results: In genotyping CHD patients in the Russian and Yakut ethnic groups, there was no significant difference in the prevalence rate of the polymorphic markers G1846A (10.8 vs. 10.2; p = 0.871) and C100T (16.1 vs. 16.2; p = 1). In patients carrying the polymorphic marker G1846A, the dose of bisoprolol was established to be lower than that in the control group (p = 0.0289).

Conclusions: The carriage frequency of polymorphic markers, which theoretically should differ between Russians and Yakuts as representatives of two different races, in practice turned out to be the same.

Keywords: bisoprolol; CYP2D6*4; CYP2D6*10; metoprolol; pharmacogenetics; Russians; Yakuts.

Introduction

β-Blockers are an important class of drugs currently used to treat ST-segment elevation acute myocardial infarction [1], arterial hypertension [2], stable angina [3], heart rhythm disturbances (sinus tachycardia, ventricular and supraventricular arrhythmias, including paroxysmal tachycardia, supraventricular tachycardia, extrasystole, atrial flutter and fibrillation and atrial tachycardia) [4] and hypertrophic cardiomyopathy [5], as well as for the prevention of migraine and the complex treatment of thyrotoxicosis. β-Blockers without internal sympathomimetic activity, such as bisoprolol, metoprolol and atenolol, are widely used in cardiological practice.

From the standpoint of the pharmacogenetics of these drugs, polymorphisms of the b1-adrenoceptor encoding by the *ADRB1* gene and the CYP2D6 isoenzyme, encoding by the same name gene, are of the greatest interest. In such a way, metoprolol, an active substance in the form of succinate or tartrate, undergoes a pre-systemic metabolism in the liver with the CYP2D6 isoenzyme of the cytochrome P450 system, resulting in 50% bioavailability of the drug upon oral administration [6]. About 70%–80% of the drug undergoes exclusive metabolism with the CYP2D6 isoenzyme, which plays a decisive role in the pharmacokinetics of metoprolol [7]. In its turn, the gene encoding this isoenzyme has a large number of polymorphisms: at the moment there

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are about 100 variants [8]. In connection with the characteristic of genotyping, this variety of polymorphisms is generally classified according to the haplotypes, which form the basis for determining the metabolic rate of substrates of the CYP2D6 isoenzyme. Traditionally, four groups are distinguished: ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers and poor metabolizers.

In ultrarapid metabolizers, most of the drug is inactivated when it is first passed through the liver, especially when administered orally, which leads to a low concentration of metoprolol in the blood and the lack of the necessary therapeutic effect. A feature of this group is the amplification of the original gene in the amount of 2–13 repetitions, which leads to a significant increase in enzyme activity [9].

For poor metabolizers, the inactivation of the drug will be reduced, resulting in a high concentration of it in the blood at the time of the next dose. For bisoprolol, the lack of influence of the polymorphism of the *CYP2D6* gene on pharmacokinetics and pharmacodynamics was proved, although this drug is metabolized by 40%–60% by this isoenzyme [10]. In recent studies, it was found that the frequency of carriage of allelic variants of the *CYP2D6* gene is mediated by the ethnogenetic features of the population. In the representatives of the Caucasoid race, the polymorphic marker G1846A of the *CYP2D6* gene (*CYP2D6*4*) is most often found, and in the Mongoloid race – C100T (*CYP2D6*10*) [11]. Both these polymorphic markers are referred to the *CYP2D6* haplotype associated with a reduced enzyme activity. Such ethnopharmacogenetic features must be taken into account in such a multinational country as the Russian Federation, numbering 194 different nationalities [12]. From these positions, the Republic of Sakha (Yakutia) is a unique region in which the majority of the population is made up of representatives of two different races: the Yakuts (Mongoloid race, 49%) and the Russians (European race, 37%) [13]. It should be noted that the study of the G1846A and C100T polymorphic markers in Yakut representatives is being conducted for the first time. The data obtained will make it possible to determine the position of the Yakuts among other representatives of the Mongoloid race from the standpoint of ethnopharmacogenomics.

The aim of this study was to determine the carrier frequency of the polymorphic markers G1846A (*CYP2D6*4*) and C100T (*CYP2D6*10*) of the *CYP2D6* gene in coronary heart disease (CHD) patients in the Russian and Yakut ethnic groups. The association of the carriage of these polymorphic markers related to the decreased function of the *CYP2D6* haplotype with an administration of higher doses of bisoprolol and metoprolol was also studied.

Materials and methods

The research was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki and was approved by the local ethics committee of the Federal State Budgetary Institution "Yakut Science Centre of Complex Medical Problems." The objectives of the study and its possible complications were explained to the patients in a manner that they could understand. Written informed consent was obtained from all participants prior to entering the study.

Study population

The study included 201 patients (average age of 66 ± 8.7 years) who were admitted to the "Republican Hospital No. 3" in Yakutsk with a CHD diagnosis and received metoprolol with a titrated dose (12.5–150 mg), bisoprolol (2.5–10 mg) or atenolol (50 mg). Of these patients, 93 (46%) were Russian (30 [32%] men and 63 [68%] women) and 108 (54%) were Yakut (54 [50%] men and 54 [50%] women). The ethnicity of the participants in the study was established using the method of self-determination. The inclusion criterion was self-determination in at least two generations, with both parents representing a single ethnic group.

Genotyping

A total of 4 mL of venous blood of patients obtained with the VACUETTE vacuum system (Greiner Bio-One, Kremsmünster, Austria) was collected in tubes with K3-EDTA (3-substituted potassium salt of ethylenediaminetetraacetic acid). Mutations of G1846A and C100T were determined in the Laboratory of the Center for Personalized Medicine of the State Bank of the Republic of Sakha (Yakutia), Republican Hospital No. 3. Isolation of genomic DNA from whole-blood leukocytes was carried out using a set of laboratory reagents "DNA-EXTRAN-1" (CJSC "Sintol," Moscow, Russia). The frequencies of the polymorphisms of the *CYP2D6* gene (G1846A, rs3892097 and C100T, rs1065852) were determined by an allele-specific polymerase chain reaction in real time using commercial reagent kits (CJSC Sintol, Moscow, Russia). Genotyping was carried out using a Real-Time CFX96 Touch Amplifier (Bio-Rad Laboratories, Inc., Hercules, CA, USA). The total volume of the reaction mixture was 25 μL: 100–200 ng of DNA solution, 300 nmol of the forward primer (3′-CGGGAGACCAGGGGGAGCATAGG-5′ for G1846A; 5′-TCAACACAGCAGGTTCA-3′ for C100T), 300 nmol of the reverse primer (3′-GACCGTTGGGGCGAAAGGGGGGT-5′ for G1846A; 5′-CTGTGGTTTCACCCACC-3′ for C100T), 200 μmol of dNTPs, amplification buffer (650 mM Tris-HCl [pH 8.5 at 25 °C, 240 mM $(NH_4)_2SO_4$, 0.5% Tween 20, 35 mM $MgCl_2$], thermostable Taq polymerase – 0.5 unit act/reaction (CJSC "Sintol," Moscow, Russia). Amplification was performed under the following conditions: initial denaturation at 95 °C for 3 min, then 40 cycles, including denaturation at 95 °C for 15 s, annealing the primers followed by

elongation at 63 °C for 40 s, each step being accompanied by the registration of the fluorescent signal via the appropriate channel: FAM, HEX or FAM and HEX.

Statistical analysis

The statistical analysis of the results was carried out in the GraphPad InStat program. The averages are represented as mean ± standard deviation. To establish differences in the carriage of minor allelic variants between Russians and Yakuts and to verify the observance of the Hardy-Weinberg equilibrium, the exact Fisher test (two-tailed p) was used. To establish the difference in doses between the groups of patients taking metoprolol and bisoprolol, the Mann-Whitney U-test was used. Differences were considered statistically significant at $p < 0.05$.

Results

In both ethnic groups, Hardy-Weinberg equilibrium was followed in the distribution of alleles and genotypes in the population ($p > 0.05$): what gives evidence about the accordance in the frequency distribution of alleles and genotypes in the studied groups in the general population and the data sample. It should be noted that the study groups differed significantly in sex composition ($p = 0.014$).

Based on the results of genotyping, patients were divided into three groups: those who had only the G1846A polymorphic marker, those who had only the C100T polymorphic marker and those who had both polymorphic markers (1846GA/100CT). There were no homozygous patients with regard to these polymorphic markers. When genotyping by the G1846A polymorphic marker, 159 (79.1%) patients had the GG genotype, and 10 (5.0%) patients had the GA genotype. When genotyping by the C100T polymorphic marker, 136 (67.6%) patients had the CC genotype, and 33 (16.4%) patients had the CT genotype. Thirty-two (15.9%) patients had the GA genotype by the G1846A polymorphic marker and the CT genotype by the C100T polymorphic marker; therefore, the share of this group was taken into account when calculating the other two groups.

When genotyping patients with CHD in the Russian and Yakut ethnic groups, there was no significant difference in the incidence of the polymorphic markers G1846A (10.8 vs. 10.2; $p = 0.871$) and C100T (16.1 vs. 16.2; $p = 1$).

The main characteristics of the population and the results of the genotyping are presented in Table 1.

In the second part of the study, the dependence of the dose of bisoprolol and metoprolol on the carrier of the polymorphic markers G1846A and C100T of the *CYP2D6* gene was evaluated.

Thirty-two patients received bisoprolol, six (18.7%) of which were carriers of the polymorphic marker G1846A. When comparing the titrated dose of the drug in these two groups with the help of the Mann-Whitney U-test, a significant difference was found ($p = 0.044$). It was also reliably established that the dose of bisoprolol was lower in patients carrying the polymorphic marker G1846A than in the control group ($p = 0.029$). Ten (31.3%) people were carriers of the polymorphic marker C100T. When comparing the titrated dose of the drug in these two groups with the help of the Mann-Whitney U-test, no significant difference was found ($p = 0.156$). Also, it was not reliably established that the dose of bisoprolol was lower in patients carrying the polymorphic marker C100T than in the control group ($p = 0.244$). Fairly significant differences in the dose of the

Table 1: The frequencies of polymorphisms and alleles of the *CYP2D6* gene in the Yakut and Russian ethnic groups.

Characteristics	All patients with CHD	Russian	Yakut	Hardy-Weinberg equilibrium	p-Value
Number of patients	201	93	108		
*CYP2D6*4*(G1846A), n (%)				(p > 0.05)	0.339
GG	159 (79.1)	73 (78.5)	86 (79.6)		
GA	10 (5.0)	3 (3.2)	7 (6.5)		
*CYP2D6*4*(G1846A)/*CYP2D6*10*(C100T), n (%)				(p > 0.05)	0.442
1846GA/100CT	32 (15.9)	17 (18.3)	15 (13.9)		
*CYP2D6*10*(C100T), n (%)				(p > 0.05)	0.447
CC	136 (67.6)	63 (67.7)	73 (67.6)		
CT	33 (16.4)	13 (14.0)	20 (18.5)		
Allele frequency, %					
1846A		20 (10.8)	22 (10.2)		0.871
100T		30 (16.1)	35 (16.2)		1

*CYP2D6*4* c. G1846A (rs3892097); *CYP2D6*10* c.C100T (rs1065852). p-Values were calculated using two-sided Fisher's exact test.

drug in Russian and Yakut patients, carriers of the polymorphic markers G1846A and C100T of the *CYP2D6* gene, were not obtained (p = 0.576). It should be noted that the carriers of both polymorphic markers G1846A and C100T had statistically lower dose of bisoprolol compared with patients with wild genotype (p = 0.03). The results are shown in Table 2.

A total of 79 patients, 16 (20.3%) of which were carriers of the polymorphic marker G1846A, received metoprolol. When comparing the titrated dose of the drug in these two groups with the help of the Mann-Whitney U-test, no significant difference was found (p = 0.071). Also, it was not established that in patients carrying the polymorphic marker G1846A, the dose of metoprolol was less than in the control group (p = 0.072). Twenty-four (30.4%) people were carriers of the polymorphic marker C100T. When comparing the titrated dose of the drug in these two groups with the help of the Mann-Whitney U-test, no significant difference was found (p = 0.240). Also, it was not reliably established that in patients carrying the polymorphic marker C100T the dose of metoprolol was less than in the control group (p = 0.429). Fairly significant differences in the dose of the drug in Russian and Yakut patients, carriers of polymorphic markers G1846A and C100T gene *CYP2D6*, were not obtained (p = 1).

Discussion

The population of Yakutia is quite unique in its national composition. Thus, the indigenous population of the region was formed before the XV century: they were settlers from the Cis-Baikal and South Siberian regions [14]. Throughout the following years and up to the present, there is an active settlement and development of this region. Despite the fact that the number of Yakuts increased from 235,000 in 1926 to 466,000 in 2010, their specific number compared with other nationalities decreased from 82.64% to 48.67%. At the same time, the share of the Russian population increased from 10.56% to 36.90% over the same years [13, 15]. Given such a long coexistence of the two nationalities belonging to different races, one cannot exclude the mixing of gene pools of these two populations. As a consequence, we can expect that the frequency of carriage of allelic variants of the *CYP2D6* gene in the Russian and Yakut people living in this region will be slightly different from those of other Caucasoid and Mongoloid races. Therefore, the carrier frequency of the polymorphic marker G1846A in representatives of the Caucasoid race is 12%–21%, and in representatives of the Mongoloid race, 1%–3%; the carrier frequency of the polymorphic marker C100T in representatives of the Caucasoid race is 1%–2%, and in Mongoloid races, it varies from 5% to 7% in Chinese to 38%–41% in Japanese [16].

The first genetic study of the people of Siberia was carried out by Duzhak et al. in 1998, which showed that the frequency of the G1846A polymorphic marker among the indigenous population is intermediate between that of the original Mongoloid and European races [17]. In 2003, a study was published by Gaikovitch et al. in which they determined the carrier frequency of polymorphic markers of the *CYP2D6* gene among 290 representatives of the Russian ethnic group from the central part of Russia [18]. It should be noted that the data obtained by Gaikovitch et al. are consistent with the global ones, but they differ significantly from ours (G1846A: 18.2% vs. 10.8%, p = 0.05; C100T: 4.2% vs. 16.1%, p < 0.05). This trend can be traced in comparison with other works. So in 2015, Mustafina et al. investigated the carrier frequency of the polymorphic

Table 2: Dependence of the dose of bisoprolol on the carrier of the polymorphic markers G1846A and C100T of the *CYP2D6* gene.

Dose of bisoprolol Polymorphic marker	≤2.5 mg	>2.5 mg	p-Value	Odds ratio	95% Confidence interval
*CYP2D6*4*(G1846), n = 32					
GA	5 (15.6)	1 (3.1)	0.029	11.25	1.124–112.6
GG	8 (25)	18 (56.3)			
*CYP2D6*10*(C100T), n = 32					
CT	6 (18.8)	4 (12.5)	0.244	3.214	0.6813–15.164
CC	7 (21.8)	15 (46.9)			
*CYP2D6*4*(G1846A)/*CYP2D6*10*(C100T), n = 32					
1846GA/100CT	8 (25)	4 (12.5)	0.03	6	1.248–28.851
1846GG/100CC	5 (15.6)	15 (46.9)			

*CYP2D6*4* c.G1846A (rs3892097); *CYP2D6*10* c.C100T (rs1065852). p-Values were calculated using two-sided Fisher's exact test. CI, confidence interval.

marker G1846A among representatives of the Russian (17.2%), Tatar (9.5%) and Bashkir (7.1%) populations [19]. In 2017, Sychev et al. studied the carrier frequency of this polymorphic marker among Russians (17.4%) and Nanais (1.4%) [20].

Despite the fact that the criterion for inclusion in our study was self-determination in at least 2 generations, this does not allow exclusion of inter-ethnic marriages in older generations. Therefore, the data we obtained suggest that it is not possible to extrapolate world data on the carrier frequency of polymorphic markers of the *CYP2D6* gene to representatives of the Russian and Yakut ethnic groups in the Republic of Sakha. Moreover, the carrier frequency of polymorphic markers among Russians differs from that of Russians from the central part of Russia. All these facts emphasize the importance of pharmacogenetic testing in each individual region.

The first pharmacogenetic study performed by Ramenskaya et al. in 2002 showed that the carriage of the polymorphic marker G1846A of the *CYP2D6* gene is reliably associated with a slowing of metoprolol metabolism. The administration of the drug at a dose of 50 mg, in this case, led to the occurrence of bradycardia and arterial hypotension in patients [21]. Since 2007, the influence of the carriage of polymorphic markers of the *CYP2D6* gene on the metabolism of other β-blockers, in particular, betaxolol, has been studied [22, 23].

To date, there is strong evidence that the effective response to metoprolol therapy depends more on the slow or rapid haplotype of the *CYP2D6* gene [24]. In the current study, we were unable to confirm the association between the carriage of slow alleles of the *CYP2D6* gene and the administration of lower doses of metoprolol, which may be explained by the study's shortcomings: polymorphic markers of the ADRB1 gene were not taken into account, and the titration of the drug dose was carried out empirically. At the same time, it was reliably established that in patients carrying the polymorphic marker G1846A, the dose of bisoprolol was less than that in the control group ($p = 0.029$). In any case, for a reliable answer to this question, it is necessary to conduct a volumetric study excluding the shortcomings of the current work.

Conclusions

The results of the current study, which first established the frequency of carriage of the polymorphic markers G1846A (*CYP2D6*4*) and C100T (*CYP2D6*10*) of the *CYP2D6* gene in patients with CHD in the Russian and Yakut ethnic groups, indicate the importance of pharmacogenetic testing in the regions of the Russian Federation. The carriage frequency of polymorphic markers, which theoretically should differ between Russians and Yakuts as representatives of two different races, in practice turned out to be the same. In addition, the carriage frequency of polymorphic markers among Russians in the Republic of Sakha differs from that in the regions of central Russia. The association between carriage of the polymorphic marker G1846A and the administration of lower doses of bisoprolol requires further study. The experience of pharmacogenetic testing can be used not only in the Republic of Sakha but also in other multinational regions of the Russian Federation.

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