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The Prediction of the Bisoprolol Effectiveness in Patients with Stable Coronary Artery Disease with Post-Infarction Cardiosclerosis

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ABSTRACT

The article shows the benefits of treatment with bisoprolol in achieving optimal heart rate at rest (55-60 per 1 minute) and identifies the prediction markers of its achievement in patients with stable coronary artery disease with post-infarction cardiosclerosis, taking into account clinical and genetic data: physical examination, 24-hour ECG monitoring, 5-minute study of heart rate variability, Arg389Gly polymorphism of the ADRB1 gene. The article proved that when a heart rate of 55-60 in 1 minute is reached, the antianginal effect of bisoprolol is expressed better, the markers of the prognosis in the achievement of this heart rate are determined.

Keywords: heart rate, stable coronary artery disease, post-infarction cardiosclerosis, heart rate variability, Arg389Gly polymorphism of the ADRB1 gene.

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INTRODUCTION

In the latest edition of the international guidelines for the diagnosis and treatment of stable coronary artery disease (CAD), β-blockers (BAB) have maintained their position as antianginal drugs (1). Categories of patients with the expected prognostic benefit from the appointment of BAB (patients who have had a myocardial infarction (MI) and / or those with heart failure) were selected. Dose, choice of drugs and the mode of administration depends on the clinical features and is selected individually (2). Particular attention is paid to a simple way to assess the effectiveness of this class drugs action. Thus, the dose of BAB can be considered optimal if, during the treatment, the heart rate (HR) alone is steadily reduced to 55–60 beats / min. This circumstance is extremely important, since the anti-ischemic effect of the drug is most pronounced with such HR (3, 4). The hypothesis about the role of HR as a modifiable risk factor is convincingly confirmed by studies on the pharmacological correction of HR, which show a direct relationship between HR reduction and mortality in the treatment of BAB in patients with MI (5 -7).

In the Russian Federation, one of the most optimal and frequently prescribed BAB in patients with CAD is bisoprolol. The tolerability profile, the minimum number of side effects and contraindications makes it possible to use it in conditions of multimorbidity (8). The pulse-reduction and anti-ischemic effects of bisoprolol are dose-dependent, but the individual sensitivity to it varies widely and has not been studied to date. Individual pharmacodynamics of BAB may be affected by changes in the genes responsible for the synthesis of β-adrenoreceptor (β-AR) molecules. There are polymorphic variants of the β-AR genes, in particular the ADRB1 gene. Arg389Gly polymorphism of this gene is of the greatest interest, since they are located in the coding region of the gene (9). However, there is no consensus on the degree of this polymorphism influence on the activity of the BAB. There are only a few studies on the effect of the Arg389Gly polymorphism of the ADRB1 gene on the use of BAB after undergoing MI (10, 11).

Optimal HR during treatment with bisoprolol is achieved by suppressing the activity of the sympathetic nervous system, an indicator of the state of which is heart rate variability (HRV). Patients with reduced HRV are limited in their ability to counteract sympathetic activation by vagal mechanisms (12).

All the above prompted the authors to identify and analyze the main factors affecting the efficiency of achieving optimal HR in bisoprolol treatment in patients with stable CAD with post-infarction cardiosclerosis, taking into account clinical parameters, HRV and Arg389Gly ADRB1 gene polymorphism.

AIM

Determination of factors affecting the effectiveness of treatment with bisoprolol in patients with stable coronary artery disease with post-infarction cardiosclerosis.

MATERIAL AND METHODS

In an open, observational, comparative study with a cross-sectional element, 107 ethnically homogeneous patients of the Caucasians who are not related by blood, with CAD, who had had MI at the age of 35-65 years(average age 54.7 ± 6.2 years)were examined. The study complied with the provisions of the Helsinki Declaration and was approved by the Ethical Committee of Omsk State Medical Universityof the Ministry of Health of the Russian Federation (Protocol No. 63 dated October 9, 2014). The sample size was calculated using the Altman nomogram for a power of 80% and a two-sided significance level of 0.05, which is minimal enough to obtain evidence. The number of men was statistically significantly more than women ($p < 0.001$). Inclusion criteria: age from 35 to 65 years; underwent MI with a stable course of CAD for six months preceding the point of inclusion in the study; steady sinus rhythm; moderate and high adherence to treatment (3-4 points according to Morisky-Green questionnaire), taking the selected optimal maximum tolerated dose of bisoprolol, the absence of decompensated diseases, diabetes mellitus and absolute contraindications to taking BAB.

At the time of inclusion in the study, all patients received bisoprolol, its dose was selected to the optimum maximum-tolerated. The median time for the selection of such a dose

was 7.5 (2.5; 10.0) weeks, and ranged from 2 to 15 weeks. Then two main groups of respondents were formed: Group I with the optimal HR reached (n = 46) and Group II with unreached (n = 61) optimal HR (55-60 in 1 minute). In addition, respondents were stratified into subsamples according to the presence of the Arg389Gly polymorphism of the ADRB1 gene: group G with Gly polymorphic allele in homo- and heterozygous form in their genotype (n = 43) and group A - without it (n = 64).

The diagnosis of stable CAD with post-infarction cardiosclerosis was carried out in accordance with clinical guidelines (1). The functional class (FC) of angina pectoris was determined using stress tests (bicycle ergometry and stress echocardiography). Patients with angina pectoris of FC II and III (45.8% and 33.6%, respectively) prevailed in the total sample, patients with FC I of angina were significantly less (20.6%), and there were no patients with FC IV. I and II groups, when included in the study, before the optimal dose of bisoprolol was selected, were comparable in clinical characteristics (by age, coronary interventions in history, number of respondents with FC I, II and III of angina pectoris, by stage and degree of chronic heart failure (CHF), by such anthropometric data as height, weight, body mass index), in all cases p> 0.05.

HR was measured at rest twice with an interval of 5 minutes, in a calm atmosphere. All patients underwent general clinical research methods (complete blood count, biochemical blood test, blood lipid spectrum, echocardiography, 24-hour ECG monitoring). The studied groups of respondents were comparable in all laboratory parameters and EchoCG indicators (Mann-Whitney U test, p> 0.05).

Special research methods were conducted - a study of 5-minute HRV to determine the signs of hypersympathicotonia as a marker of insufficient effectiveness of bisoprolol and the determination of the polymorphism of the ADRB1 gene (Arg389Gly, rs1801253). HRV was studied by registering short 5-minute ECG intervals at rest using the "VNS-micro" hardware-software complex (NeuroSoft, Ivanovo). HRV analysis was performed taking into account current recommendations (13). The polymorphism of the ADRB1 gene (Arg389Gly, rs1801253) was detected by real-time PCR.

The studied patients received concomitant treatment with bisoprolol (ACE inhibitors or ARA blockers, antiplatelet agents, statins, non-dihydropyridine calcium antagonist, mineralocorticoid receptor antagonists, diuretics). The doses of concomitant drugs at the time of cross-section in the study, after the selection of the maximum-tolerated optimal dose of bisoprolol, were comparable (p> 0.05).

Quality of life in groups I and II was studied according to the SF-36 questionnaire and the Seattle Questionnaire (SAQ).

During statistical processing the probability α less than 0.05 were established as significance level. Material processing was performed in certified software packages Stat Soft Statistica 6.13 for Windows (StatSoft Inc., USA), Deductor Studio.

RESULTS AND DISCUSSION

Patients of groups I and II were comparable in the selected maximum tolerated dose of bisoprolol and blood pressure (BP), but significantly differed in HR, in group II it was higher (Table 1).

Table 1: Doses of bisoprolol and indicators of HR and BP during treatment in patients of groups I and II

Indicators	I group.n=46Me (P25.75)	II group.n=61 Me (P25;75)	p (Mann-Whitney)
Bisoprolol dose. mg	5 (2.5;7.5)	5 (2.5;5.0)	0.31
Systolic BP.mm Hg	110 (105;115)	105 (100;110)	0.12
Diastolic BP.mm Hg	70 (65;70)	65 (60;70)	0.16
HR at rest per 1 min	59 (58;60)	68 (65;72)	<0.001

The studied patients of group I more often complained of palpitations and interruptions of the heart rhythm (p = 0.003), the frequency of cardiac pain episodes (p = 0.02), noted a greater need for nitrates (p = 0.03) and significantly more often sought medical help with worsening of the course of CAD (p = 0.001).

In all studied patients, FC of angina pectoris was again determined after selecting the optimal doses of bisoprolol. In group II, III FC of angina pectoris was significantly more frequently recorded (p = 0.02), which is probably due to the fact that some patients from group I of FC III managed to be transferred to FC II when the optimal HR was reached. The proportions of patients with FC I and II still did not significantly differ in both groups.

In group I, at the time of cross-section, there were significantly fewer patients with daily attacks of angina (p = 0.02) and significantly more with rare attacks (less than 1 time per month) of angina (p <0.01); and less need for short nitrates (pp = 0.03), they were less likely to complain of palpitations and interruptions in the heart rhythm(p = 0.01).

Significant differences between groups were obtained at the time of the cross section in the study on the 24-hour ECG monitoring: the number of patients with myocardial ischemia episodes in group I was significantly less(p = 0.005), the average (0.009) and minimal (p = 0.004) daily HR were less, the number of ventricular extrasystoles (p = 0.01) in this group were less.

The quality of life of patients, depending on the achievement of the target resting HR, according to the SF-36 and SAQ questionnaires in the studied groups, significantly differed in all scales (p <0.05). Moreover, in group I it was higher, which is most likely associated with a lighter course of CAD on the background of the achieved HR values.

The study of HRV parameters showed a decrease in the total power (TP) of its spectrum in both groups of respondents, with the prevalence in the spectrum of very low frequencies (% VLF), indicating an increase in neurohumoral influences in all patients with stable CAD

with post-infarction cardiosclerosis. Such spectral and temporal parameters of 5-minute HRV as LF norm, n.u. (p = 0.02); LF / HF (p = 0.01); HF,% (p = 0.02), pNN50,% (p = 0.02) RRNN, ms (p <0.0001) were significantly different. There were significant differences in the indicators of variational pulsometry of the HRV: group II respondents showed higher values of parameters reflecting the activity of the sympathetic section of the autonomic nervous system (AM-amplitude of the mode of RR intervals, IVB-index of vegetative balance, VIR-vegetative index of rhythm, IT-index of theregulatory systems tension, p <0.05 in all cases). Thus, hypersympathicotonia in terms of 5-minute HRV can serve as an unfavorable marker in achieving optimal HR in patients with post-infarction cardiosclerosis receiving bisoprolol.

When comparing the frequencies of the Arg389Gly polymorphism of the ADRB1 gene in the respondents of the studied groups, a significant (p = 0.0001) prevalence of the Gly allele carriers in the I group compared to the II was found.

To identify possible differences in response to treatment with bisoprolol, depending on the carriage of the Gly allele, the antiarrhythmic, pulse-reduction and anti-ischemic effects of bisoprolol in subgroups A (without the polymorphic allele) and G (with the carriage of the polymorphic Gly allele) (table 2) were evaluated, it turned out that the HR in group G was significantly lower than in group A, including on HRV and 24-hour ECG monitoring.

Table 2: Indicators of the bisoprolol effectiveness depending on the carriage of the polymorphic Gly allele of the Gly389Arg ADRB1 gene polymorphism

Indicators	Group A389 n=63	GroupG389 n=44	p
FC of angina pectoris I/II/III, n (%)	12(19.1)/29(46)/22(34.9)	10(22.7)/20(45.5)/14(31.8)	0.6/0.9/0.7[2]
Systolic BP mm Hg, Me (P25;75)	105 (100;110)	110 (100;112,5)	0.54[1]
Diastolic BP mm Hg, Me (P25;75)	65 (65;70)	65 (60;70)	0.76[1]
HR at rest per 1 min, Me (P25;75)	67 (60;70)	60 (58;66.5)	0.002[1]
Number of responders with HR at rest 55-60 в 1 мин., n= (%)	17(26.9)	29 (65.9)	0.0001[2]
HR min. 24-hour monitoring of ECG, Me(P25;75)	53 (48;57)	51 (48.5;54.5)	0.38[1]
HR max. 24-hour monitoring of ECG, Me (P25;75)	115 (103;125)	115 (104;128.5)	0.99[1]
HR med. 24-hour monitoring of ECG,Me (P25;75)	73 (66;80)	70 (65.5;73)	0.06[1]
Number of responders with SVT paroxysms, n= (%)	9(14.3)	13(29.6)	0.06[2]
Number of VE, Me (P25;75)	88 (10;523)	11.5 (3;94)	0.007[1]
Number of responders with ischemia episode, n= (%)	23 (36.5)	6(13.6)	0.009[2]
Ischemia duration, minutes, Me (P25;75)	15 (7.5;26.8)	7.2 (4.0;25.0)	0.16[1]
Number of ischemia episode on 24-hour monitoring of ECG,Me (P25;75)	3 (1;3)	1(1;2)	0.07[1]
Number of responders with achieved optimal HR in HRV background sample (55-60 per 1 min) , n= (%)	18(28.6)	22(50.0)	0.03[2]

Note: SVT-supraventricular tachycardia, SVE-supraventricular extrasystoles, VE-ventricular extrasystoles, p1- Mann-Whitney significance of differences; p2 - $\chi 2$ significance of differences

At the same time, groups A and G were comparable by sex, age and selected maximum tolerated doses of bisoprolol (p> 0.05). Thus, the presence of the Gly allele of the Arg389Gly polymorphism of the ADRB1 gene can be regarded as a favorable prognostic marker for achieving optimal HR.

At the final stage of the study, we analyzed the statistically significant differences in the groups of 5-minute HRV indicators, as well as clinical and genetic data that could affect the effectiveness of bisoprolol treatment in the Deductor Studio program. A decision tree was built (Figure 1).

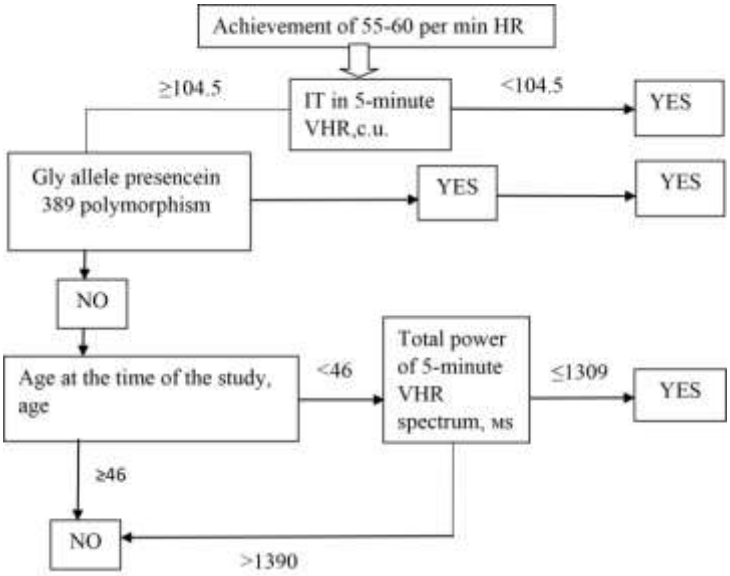

Figure 1: **Decision Tree.**

It turned out that the achievement of HR targets on the background of bisoprolol is more likely with IT<104.5 cu in the background sample of HRV. If the IT is ≥104.5 cu, it is necessary to study the Arg389Gly polymorphism of the ADRB1 gene, and if the Gly allele is present, we can also expect sufficient effectiveness of bisoprolol therapy. If the Gly allele is absent, the patient's age at the time of the study needs to be assessed, and if he is ≥46 years old, then bisoprolol will not be sufficiently effective, if less than 46 years old, then pay attention to theTP of the HRV spectrum in the background sample, and when its value is greater than or equal to 1309 ms. - the forecast is positive, but if the TP is less than 1309 - the forecast is negative.

CONCLUSION

Thus, in patients with stable CAD with post-infarction cardiosclerosis, it is not only necessary but possible to identify factors that predict the effectiveness of bisoprolol treatment in order to individualize therapy with this drug. With a positive prognosis of sufficient efficacy of bisoprolol, it is necessary to continue the titration of its dose until reaching a HR of 55-60 in 1 minute, with a negative prognosis – to use the alternative treatment regimens with other pulse-reduction drugs. The result of further research could be the development of a unified algorithm for treating such patients in real medical practice.

FINDINGS

1. In 43% of patients with stable CAD with post-infarction cardiosclerosis, an optimal HR of 55-60 in 1 minute was achieved with bisoprolol. In patients who have achieved optimal HR, the antianginal effect of bisoprolol is more pronounced (less FC of angina, p = 0.02; less angina attacks, p = 0.02; less episodes of myocardial ischemia on 24- hour monitoring of ECG, p = 0.005) and higher quality of life (p <0.05).
2. The clinical efficacy of bisoprolol is variable and depends on the Arg389Gly polymorphism of the ADRB1 gene, it can be assessed by general clinical indicators (resting HR, HR in 24-hour ECG monitoring) and by the values of a special study method: 5-minute HRV.
3. Indicators of 5-minute HRV in the background sample, the presence of Arg389Gly polymorphism, and age demonstrate high significance in prediction of the effectiveness of bisoprolol therapy in patients with stable CAD with post-infarction cardiosclerosis.

CONFLICT OF INTEREST

None

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