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Efficacy of Ivabradine and Bisoprolol Based on the Results of Flow Mediated Dilation in Patients with Coronary Heart Disease

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Abstract

In this article, the possible application of Ivabradine and Bisoprolol in patients with stable angina based on the results of clinical and hemodynamic indices, Flow Mediated Dilation (FMD) and exercise loading tolerance (ELD) are discussed. In this study, 60 patients with stable angina II-III FC were included. Patients were randomized into two groups and given Bisoprolol and Ivabradine as the main treatment. Patients underwent a treadmill test by Bruce protocol and FMD probe by the Celermajer method. After 10—14 days of daily treatment, the patients were switched from one medicine to another, in both groups, and the results of FMD and ELD were analyzed. After treatment with Ivabradine, an increase in the chronotropic effect in the exercise tests was observed; however, the improved endothelial function, assessed by the results of the flow mediated dilation test was quite significant. IJBM 2011; 1(3):158-162.

Key words: *Ivabradine, FMD, ELD.*

Introduction

Coronary heart disease (CHD) remains the one of the most important medical and social problems in most leading industrial countries [1]. Despite the high rate of success in the treatment and management of CHD, patients suffering from stable angina (SA) are still in danger of nonfatal complications and sudden death, within one year of onset of disease [2]. Endothelial dysfunction assessed by flow-mediated dilatation (FMD) led to increased mortality, unstable angina, coronary thrombosis, LV remodeling and progression of heart failure [3].

According to COURAGE and BARI 2D trials, the optimal management and treatment of CHD in patients with stable angina is favorable and shows some degree of efficacy as well in invasive treatment [4, 5].

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Purpose

To study the reactions of the different applications of Ivabradine and Bisoprolol in patients with stable angina, based on initial clinical and hemodynamic parameters, exercise tolerance and flow mediated dilation.

Methods

In this investigation, 60 men with SA II-III FC (by CCA) were selected. The initial characteristics of the patients are shown in Table.1

The investigation included patients observed in the CHD Laboratory, of the Uzbek Republican Specialized Center of Cardiology.

Initially patients were treated on standard therapy (ASA, statins, ACE-inhibitors) for one month. The Bisoprolol dose was reduced gradually, stopping two to three days before investigation. Patients did not receive prolonged nitrates but could take nitrates short-term, if required.

After examination, all the patients were randomized into two groups in an open-label double comparative

Table 1
Clinical characteristics of patients with SA (n=60) (M±SD)

Age	46.7±8.5
Duration of CHD, years	2.9±1.8
Post STEMI, n%	6 (10)
Mild Arterial hypertension, n%	41 (68.3)
Diabetes Mellitus, n%	3 (5)
Treatment	
ASA, n%	56 (93.3)
Statins, n%	55 (91.7)
ACE inhibitors, n%	41 (68.3)

crossover study. Bisoprolol 5 mg/day and Ivabradine (Coraxan®, «Les Laboratoires SERVIER», France) 5 mg/day was given besides standard therapy. Dose titration was performed according to the individual's needs in both groups, based on achieving a 20%-25% drop in the HR from initial. The main criteria were the BP and HR levels, clinical symptoms of hypotonia (SBP<90 mm Hg), bradycardia (HR<50 beat/min) or dizziness and weakness. In such cases, the dose was lowered and accepted as particular for these patients.

The mean dose of Bisoprolol was 6.9±2.42 mg/day and Ivabradine 10.7±2.94 mg/day, respectively. After 10-14 days of treatment, patients were re-examined and switched to another medicine (from Bisoprolol to Ivabradine) using the «double Latin Square method» with re-examination after 10-14 days.

Next, the clinical state of the patients (HR, systolic and diastolic BP) was controlled, the Double Score ($SC = HR \times SBP/100$) calculated, and the rate of SA attacks and number of Nitroglycerin tablets taken were counted. Patients underwent a treadmill test according to Bruce protocol and reactive hyperemia was assessed by the D. Celermajer method [6]. Investigation was conducted in the morning 2 hours after taking Bisoprolol and Ivabradine.

Analysis of the exercise tolerance test, duration of the test, time interval prior to the SA attacks, depression of ST more than 1 mm, HR, BP, and METS were done.

Based on these results the chronotropic reserve was calculated using the formula:

$$ChR = HR_{max} - HR_{resting}/HR_{(age)} - HR_{resting}\ x\ 100$$

where $HR_{(age)} = 220 - age$

When ChR<80% the prognosis was «unwell» [7]. For quantitative assessment of complications the index of Duke Treadmill Score was calculated. On assessment of reactive hyperemia the FMD was estimated by the increase in diameter of the brachial artery (BA). The normal reaction of the brachial artery was an increase in diameter of more than 10% from initial. The sensibility coefficient was calculated using the formula:

$$C = (\Delta D/D0)/(\Delta\tau/\tau^{\circ}),$$

where, D0 — initial diameter, ΔD — increased diameter of the brachial artery, τ- initial tension of slope, Δτ — tension of slope.

τ° was calculated using the formula:

$$\tau^{\circ} = 4\mu V/D,$$

where, μ- viscosity of blood (≈0.05 pa) V-max speed of blood flow in D, the brachial artery diameter.

A decrease in the sensibility coefficient of the brachial artery to the tension slope (k) of less than 0.6% was considered an endothelial dysfunction [8].

Microsoft Excel Tab and the pocket of Statistical Analysis Statistica 6.0 were used for statistical analysis.

Data were reported as the mean and standard deviation values (M±SD), and the significance of data was tested using student-t test with the possibility of error (P). To compare the paired proportions in the dependent groups, the McNemar criteria was used. If pair wise differences among the groups had occurred, the Mann-Whitney test was used. If p<0.05 the index was considered statistically significant. Analysis of correlation dependence was performed using the Pearson and Spearmen coefficient of correlation.

Results

Using Bisoprolol at a dose of 6.94±2.42 mg/day and Ivabradine at a dose of 10.71±2.94 mg/day resulted in reducing the HR to 16.8±4.6 (21.8% p<0.005) and 16.4±4.8 (21.4% p<0.005), respectively (Table 2). Meanwhile, all the patients with arterial hypertension (AH) received ACE-inhibitors with a target BP<140/90 mm Hg. Significantly, a drop in BP was observed more with the Bisoprolol than the Ivabradine.

Table 2
Resting clinic and hemodynamic results in therapy with Bisoprolol and Ivabradine

	Initial	**After Bisoprolol n=60**	**After Ivabradine n=60**
HR, beat/min	76.6±4.3	59±4.1***	60.2±4.1***
SBP, mm Hg	121.8±11.8	112.3±7.3***^^^	118±7.3
DBP, mm Hg	78.4±6.7	74.7±6.8***^^	77.0±5.1
Double Score	93.3±9.6	67.2±5.8***^^^	71.5±7.0***

Notes: **** — P<0.005 vs initial test*
^,^^,^^^ — p<0.005; p<0.005 between groups

The antianginal effect of both medicines was the same based on the number of angina attacks (3.1±2.5 and 2.8±2.4) and the number of nitroglycerin tablets taken in a week.

After 10-14 days of treatment, the antianginal effect based on total exercise time more than 1 min vs initial was observed in 30 patients with Bisoprolol, and in 31 patients with Ivabradine.

As shown in Table 3, maximum HR p<0.05 and systolic BP maximum on the exercise peak was lower after Bisoprolol vs Ivabradine, while the duration of exercise time remained the same. The chronotropic reserve was statistically higher in both groups (p<0.005) compared with

Table 3
Changing of the results of exercise loading test with Ivabradine and Bisoprolol

	Initial n=60	**After Bisoprolol n=60**	**After Ivabradine n=60**
HR initial, beat/min	79.1±5.3	62±3.5***	63.3±4.7***
HR max, beat/min	135.1±19.1	128±19.8^	136.5±22.3
SBP initial, mm Hg	118.3±10.2	111.8±10.6***^^	1173±8.2
DBP initial, mm Hg	77.2±9.6	73.8±6.9*	75.9±5.6
SBP max, mm Hg	150.9±15.8	145.9±15.9^	152.1±11.9
DBP max, mm Hg	85.7±8.58	82.8±10.1	86.2±8.8***
Double score resting	93.5±10.4	69.6±7.5***^^^	74.3±8.8***
Double score on peak exercise	204.5±40.1	187.8±36.5*^^	208.6±42.5
Chronotropic reserve	59.0±18.0	59.1±17.2	66.2±19.0*^
METS Total exercise time, sec Growth, sec	7.8±2.2 697.3±168.6 -	9.0±2.0** 787.0±120.5*** 89.7±87.9	9.2±2.1*** 793.7±125.9*** 96.4±98.4
Up to angina attack time, sec Growth, sec	649.3±172.3 -	744.6±127*** 95.2±79.1	756.9±130.2 107.6±89.1
Up to limited angina time, sec Growth, sec	692.21±168.0 -	780.6±19.9*** 88.5±85.5	789.4±120.4 97.3±96.4
Up to ST depression more than 1 mm, sec Growth, sec	675.7±176.1 -	769.9±120.4*** 94.2±88.0	777.5±123.6 101.8±96.9
HR restoration time, min	4.4±1.7	3.5±1.5**	3.7±1.5*
BP restoration time, min	4.2±1.5	3.3±1.1***^^^	4.1±1.4
ST restoration time, min	3.2±2.2	2.1±2.2**	1.8±2.0**
DTS index	-7.6±3.7	-4.1±4.4***	-3.6±4.7***

Notes: **,**,*** — p<0.05; p<0.01; p<0.005 vs initial results*
^,^^,^^^ — p<.05; p<0.01; p<0.005 differences between Bisoprolol and Ivabradine

the initial. The increase in total exercise time on reducing the HR by 1 beat was 63 sec with Bisoprolol and 74 sec with Ivabradine.

The DTS index improved with Bisoprolol ($p<0.005$) and Ivabradine ($p<0.005$). According to the DTS index 15 patients were at risk of developing complications zone initially, and after treatment with Bisoprolol and Ivabradine it dropped to 3 and 4, respectively.

According to the results of the FMD test, 24 patients out of 60 showed normal endothelial function and the opening of the BA>10%; 36 patients had endothelial dysfunction. As shown in Table 4 treatment with Ivabradine showed reliable improvement in the dilation of BA ($p<0.05$) and an increase in the BA sensibility coefficient to $p<0.05$.

On comparison, the rate of achieving an increase in the total exercise time of more than 1 min vs initial ($\Delta\tau>1$min) based on the results of FMD ($\Delta D>10\%$) while treating with Bisoprolol and Ivabradine, the beta-blocker was found to be more effective in patients with endothelial dysfunction ($\Delta D<10\%$) than with normal test (OR 8.6; 95% CI 2.5-9.1; $p<0.001$). The efficacy of Ivabradine was not based on the FMD test means.

Table 4
Changes in FMD test in treatment with Bisoprolol and Ivabradine

	Initial n=60	After Bisoprolol n=60	After Ivabradine n=60
BA diameter ΔD%	7.7±8.4	8.3±9.7	10.9±8.7*
BA sensibility coefficient to tension slope	0.73±9.7	0.53±0.86	1.17±1.07*

Notes: **- p<0.05 differences vs initial results*

As seen in Table 5, Ivabradine showed efficacy in 50% of the patients with normal endothelial function based on the results of FMD ($p<0.05$). Bisoprolol was effective in 20.8% patients with normal endothelial function. In patients with dysfunction, the efficacy of Bisoprolol (69.4%) and Ivabradine (52.8%) was nonsignificant.

Table 5

The growth of usual duration of loading in treatment with Bisoprolol and Ivabradine according to initial state of endothelium

	FMD<10% n=36	FMD>10% n=24
Bisoprolol growth of FMD>1min n=30	n=25	n=25
Bisoprolol growth of FMD<1min n=30	n=11	n=19
%	25/36(69.4%)	5/24(20.8%)
Ivabradine growth of FMD>1 min n=31	n=19	n=12
Ivabradine growth of FMD<1min n=29	n=17	n=12
%	19/36 (52%)	12/24 (50.0%)*

Notes: ** — P<0.05 differences between Bisoprolol group with normal endothelial function (McNamara criteria)*

Discussion

The results of this study revealed that the action of Ivabradine at a dose of 10-15 mg/day was as good as Bisoprolol, by causing a drop in the HR, total exercise time and ST depression time. At the peak of exercise, following treatment with Ivabradine, the HR and systolic BP max was higher because Ivabradine has an additional vasodilator action relating to slow spontaneous diastolic depolarization, because of which the coronary artery blood flow increased without any side effect on the action potential [9, 10].

The effect of beta-blockers on the endothelial function shows a different value [11], where nonselected beta-blockers of generation I have a negative effect on endothelial function [12]; however, generation III beta-blockers (as nebivolol, carvedilol) have an additional vasodilator action and their positive effect on endothelial function was proven [13, 14]. Considering the selected b-blockers of generation II, good efficacy was noted on long-term application but in high doses, they led to blocking the alpha-adrenoreceptors [15]. In addition, it was not unusual that during a short treatment course, in patients with stable angina and normal endothelial function, the additional vasodilatation action of Ivabradine occurred more during exertion, while in patients with endothelial dysfunction this advantage was less significant compared with Bisoprolol. Relating to this, the known effects of Bisoprolol and Ivabradine on endothelial function may be important in development of methods of differentiated pharmacotherapy.

Conclusions

Ivabradine and Bisoprolol after two weeks of treatment according the results of treadmill test have similar possibilities of increasing time of ST-segment depression onset and angina attacks in patients with stable angina of II and III functional class. In addition treatment with Bisoprolol accompanied with lower values of double score at rest ($P<0.005$) and at peak of exercise ($P<0.01$), whereas Ivabradine significantly greater increased chronotropic reserve ($P<0.05$).

Two-week treatment with ivabradine, compared with bisoprolol, accompanied by an increase of endothelium-dependent vasodilation ($P<0.05$), and the coefficient of brachial artery sensitivity to the tension slope ($P<0.005$). At the same time in patients with angina with normal endothelium-dependent vasodilation of brachial artery ($\Delta D \geq 10\%$) the effect of ivabradine, estimated by rate of increase of the duration of exercise on the treadmill ≥1 min, was observed more frequently than in the treatment with bisoprolol ($P<0.05$).

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