EFFECT OF SELECTIVE BETA-BLOCKADE WITH BISOPROLOL IN THE TREATMENT OF RECENT-ONSET ATRIAL FIBRILLATION

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ABSTRACT
The incidence of atrial fibrillation has been rapidly increasing in recent years. The increased tonus of the sympathetic nervous system is related to the development of atrial fibrillation.

OBJECTIVE: To study the effect of bisoprolol, a highly selective beta-blocker, on patients with recent-onset atrial fibrillation (< 48 hours) for regularization of the rhythm using propafenone.

PATIENTS AND METHODS: The study includes 164 patients (81 women, 83 men, age 59.09 ± 10.81) with successfully restored sinus rhythm in recent-onset atrial fibrillation. The patients received either propafenone (group A, n = 82) or a combination of propafenone and bisoprolol (group B, n = 82). The studied patients were randomly allocated to the groups. Propafenone was administered intravenously as a 2 mg/kg bolus followed by infusion of 0.0078 mg/kg/min for 120 min and orally in dosage of 300 mg three times every 8 hours if arrhythmia persisted. Bisoprolol was administered in a single dose at the very beginning of propafenone treatment and only in patients from group B at a dose of 5 or 10 mg. Regularization of the rhythm was assessed at the 3rd, 6th, 12th and 24th hour.

RESULTS: In the initial stages of regularization the combined therapy restored the sinus rhythm in a greater number of patients in comparison with the monotherapy (at the 6th hour 67.07% in group B versus 48.78% in group A, P < 0.05; at the 12th hour it was 87.80% versus 75.60%, respectively, P < 0.05).

CONCLUSION: Early regularization of rhythm in patients with recent-onset atrial fibrillation reduces the likelihood of recurrent episodes of arrhythmia. This makes the application of selective beta-blockade clinically significant.

Key words: recent-onset atrial fibrillation, bisoprolol, sinus rhythm

INTRODUCTION
Atrial fibrillation (AF) is the most common arrhythmia in clinical practice – it has been estimated that it affects about 1% of the entire population. Some seven million people are known to have the condition in Europe. Atrial fibrillation is 1.5 times more common in men than in women.

Propafenone is a drug of first choice for treatment of recent-onset atrial fibrillation (arrhythmia duration < 48 hours) in patients without structural heart diseases. In a combination therapy with beta-blockers it has been used to reduce the arrhythmogenic effect of propafenone.

The role of the autonomic nervous system in the genesis of AF has long been established. Research shows that an increased tonus of the sympathetic division initiates and stabilizes AF. This is the ground for the assumption that blocking the receptor-mediated sympathetic effects on the atria could have implications for the restoration of the sinus rhythm.

OBJECTIVE
To investigate the role of beta 1-adrenoceptor blockade with bisoprolol in the treatment of recent-onset atrial fibrillation with propafenone.

MATERIALS AND METHODS
PATIENTS
The study was conducted in the Intensive Care Cardiologic Unit of St. Marina University Hospital in Varna between 01.2006 and 06.2011. The study recruited 164 patients (81 women, 83 men, age 59.09 ± 10.81) with recent-onset atrial fibrillation (arrhythmia duration of < 48 hours before hospitalization) who have had a successful drug-induced rhythm
regularization. The onset of the rhythm disorder was determined from the medical history of the patients. Electrocardiography made immediately after hospitalization, was used to confirm the diagnosis. Patients were randomly assigned to two groups: group A (n = 82, 42 men, 40 women, age 57.49 ± 11.92) received propafenone in a monotherapy and group B (n = 82, 41 men, 41 women, age 60.70 ± 9.37) received propafenone and bisoprolol in combination. The patients were followed up for 24 hours since beyond this time limit propafenone treatment (administered either per os or intravenously) shows no advantage over the use of placebo. If arrhythmia persisted after 24 hours, participation of patients in the study was discontinued.

The age range for participants in the study was 19-75 years preferred by many leading authors that study AF and means to treat it with drugs, including F. Bellandi, L. Bianconi, and G. Boriani.

Patients were excluded from the study if they had a history of ischemic heart disease, heart failure, congenital and acquired valvular defects, left ventricular hypertrophy with wall thickness > 14 mm, II-III grade of atrioventricular block or bifascicular block, obstructive pulmonary disease, severe hepatic and renal failure. The criteria are similar to those used in most studies for the treatment of paroxysmal atrial fibrillation with propafenone.

The design of the study does not require approval by the ethics committee, as the medications used are part of the European recommendations for the treatment of AF. The study is not intended to test new drugs, but to consider new aspects of their effects.

DRUGS AND METHOD OF ADMINISTRATION

All participants in the study (both group A and group B) were started on propafenone while monitored and only after the diagnosis was confirmed by the history of the patients disease and an ECG study, physical examination and if there were no contraindications for the therapy. Propafenone is an antiarrhythmic drug of IC class introduced into clinical practice in Europe in 1977. As by Vaughan Williams’ classification (1970) it is a drug that blocks fast sodium channels in phase 0 of the action potential, and inhibits the calcium (I\text{Ca}), and the rapid potassium transport (I\text{K}) in the repolarisation of atrial cardiomyocytes. In the study the drug was administered according to the dosage regimen typically prescribed for it: 2 mg/kg bolus i.v., followed by infusion at a dose of 0.0078 mg/kg/min for 120 min. If the rhythm disorder persisted treatment with propafenone was continued with 300 mg p.o. received three times a day at intervals of 8 hours.

The bisoprolol used in the study is a highly selective beta-blocker with 120 times higher selectivity for beta 1-receptors against beta-2 receptors. It has a rapid, almost complete gastrointestinal absorption, high bioavailability (90%) and low interindividual variability. In this study it was administered at a single dose only in patients from group B immediately after starting treatment with propafenone. The routine drug dosage of 5 mg or 10 mg p.o. was used.

STATISTICS

Restoration of sinus rhythm was assessed at the 3rd, 6th, 12th and 24th hour. Statistical analysis was performed using SPSS for Windows v. 16.0. Descriptive statistics was used to calculate the indicators share, cumulative percentages, means and standard deviations. Evaluation of the hypotheses was done using the Student’s t-criterion for comparison of mean variables and indicators for relative share; Differences were considered significant at p < 0.05.

RESULTS

Table 1 shows that both groups of patients (group A and group B) were matched (P > 0.05) by number, age, sex structure and size of left atrium.

Table 2 presents the results of the therapy. Mono-therapy until the 3rd hour of treatment causes regularization of rhythm in 26.83% of the patients, and the combination therapy - in 36.58% of the patients (P > 0.05). At the 6th hour the combination therapy restored sinus rhythm in 67.07% versus 48.78% for patients on monotherapy (P < 0.05). At the 12th hour in the combined therapy group conversion of the rhythm occurred in 87.80% while in the monotherapy group - in 75.60% of the patients (P < 0.05). At the 24th hour the percentages in both groups become equal (100%) which follows from the study design.

In the course of drug regularization transient episodes of bradyarrhythmia (minimum heart rate 43 beats/min) were observed in three patients on monotherapy and four patients on combined therapy (minimum heart rate 48 beats/min). There were no cases of acute left ventricular failure.

DISCUSSION

The beta 1-selective blockers inhibit receptor-mediated effect of the sympathetic nervous system on atrial action potential of cardiomyocytes. Calcium influx (I\text{Ca}) and potassium repolarisation flows car-


Table 1. Distribution of patients in group A and group B by number, age, sex structure and size of left atrium

<table>
<thead>
<tr>
<th></th>
<th>Group A (monotherapy)</th>
<th>Group B (combined therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients in group</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Age</td>
<td>57.49 ± 11.92</td>
<td>60.70 ± 9.37</td>
</tr>
<tr>
<td>Male/Female</td>
<td>42 / 40</td>
<td>41 / 41</td>
</tr>
<tr>
<td>Anterior-posterior size of left atrium</td>
<td>37.20 ± 4.81</td>
<td>37.74 ± 5.01</td>
</tr>
</tbody>
</table>

Data are presented as Mean ± SD; P > 0.05.

Table 2. Patients with restored sinus rhythm at the 3rd, 6th, 12th and 24th hour after initiation of monotherapy and combination therapy

| Method of cardioversion | Time of regularization within 3 hours up until the 6th hour at the 12th hour at the 24th hour |
|-------------------------|--------------------------------------------------|---------------------------------|----------------------------|
| Group A (n = 82)        | 22 (26.83%)                                      | 40 (48.78%)                     | 62 (75.60%) | 82 (100%) |
| Propafenone (monotherapy) |                                           |                                |               |            |
| Group B (n = 82)        | 30 (36.58%)                                      | 55 (67.07%)                     | 72 (87.80%) | 82 (100%) |
| Propafenone + bisoprolol (combined therapy) |                                           |                                |               |            |

Data are presented as absolute values and cumulative rates.

ried by ultra-fast (I_{kur}) and slow (I_{ks}) channels are under strict adrenergic control. Their sympathetic stimulation mediated by beta1-receptors, leads to shortening of the effective refractory period (ERP) and the action potential duration (APD) of atrial myocytes. Changes in electrophysiological properties of cardiomyocytes can be the cause of the emergence and retention of re-entry circuits of atrial fibrillation. Thus, the sympathetic nervous system is directly related to the pathogenesis of the disease and its drug assisted blockade could be involved in disruption of the mechanisms of atrial fibrillation.

Bisoprolol is a highly selective beta-blocker. Maximum plasma concentration is reached as early as at 3 hours after administration and remains stable in the following hours. Experimental studies have found that bisoprolol extends ERP of the atria and has a potential antiarrhythmic effect in the treatment of AF. It is possible to co-administer bisoprolol with propafenone, which due to its high efficiency, is a drug of first choice for treatment of atrial fibrillation. Based in these findings we can use bisoprolol as the drug for a selective beta-blockade in propafenone treatment.

Summary analysis of the results shows that there are significant differences in the regularization effects of propafenone monotherapy and combined therapy with propafenone and bisoprolol. As early as 3 hours of treatment, combination therapy causes regularization of rhythm in a larger percentage of patients, although the difference failed to reach statistical significance (36.58% to 26.83%, P > 0.05). Such an early positive effect can be explained by the bisoprolol pharmacokinetics. At the 6th hour the tendency becomes significant (67.07% versus 48.78%, P < 0.05) and is confirmed at the 12th hour (87.80% versus 75.60%, P < 0.05).

It is evident that addition of bisoprolol to propafenone therapy causes earlier conversion of the rhythm in a larger proportion of patients compared with propafenone alone. This fact could have important clinical significance for the prognosis of recent-onset atrial fibrillation. It is known that prolonged episodes of AF reduce the likelihood of recovery and sustained maintainance of sinus rhythm. Daoud et al. first demonstrated that even a brief episode of atrial fibrillation of about 7 minutes leads to changes of atrial electrical activ-
ity which persist after restoration of sinus rhythm and increase the possibility of recurrence of the rhythm disorder.23

Rapid atrial activation during atrial fibrillation shortens the action potential and the refractory period of atrial cardiomyocytes, reduces the length of re-entry wave λ and causes electrical heterogeneity.24 These changes turn into arrhythmia substrate and facilitate its persistence. This makes the arrhythmia itself a major provoking moment for its persistence. Therefore, the earlier termination of AF by the use of selective beta-blockade would not only improve treatment outcomes, but also the prognosis regarding recurrences of arrhythmia.

CONCLUSIONS
Adding a selective beta-blocker to standard treatment regimen with propafenone leads to earlier conversion of the rhythm in the majority of patients. Early restoration of sinus rhythm prevents progressive electrical remodelling of the atria, reduces the frequency and duration of subsequent episodes of arrhythmia making selective beta-blockade clinically significant in patients with recent-onset atrial fibrillation.

REFERENCES
Effect of Selective Beta-Blockade with Bisoprolol in the Treatment of Recent-Onset Atrial Fibrillation


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ЭФФЕКТ СЕЛЕКТИВНОЙ БЕТА-БЛОКАДЫ ПРЕПАРАТОМ BISOPROLOL ПРИ ЛЕЧЕНИИ ПРИСТУПНОГО ПРЕДСЕРДНОГО МЕРЦАНИЯ

М. Негрева, А. Пенев

РЕЗЮМЕ

ВВЕДЕНИЕ: Частота предсердного мерцания быстро нарастает за последние годы. Повышенный тонус симпатической нервной системы имеет отношение к его развитию.

Цель: Изучить влияние высокоселективного бета-блокера bisoprolol на пациентов с приступным предсердным мерцанием (давность аритмии < 48 ч.) при регуляции ритма с помощью пропафеноне.

ПАЦИЕНТЫ И МЕТОДЫ: Группу составляют 164 пациента (81 женщина, 83 мужчина, возраст 59.09 ± 10.81) с успешно восстановленным синусовым ритмом при приступном предсердном мерцании. Пациенты лечены с помощью препарата пропафеноне (группа А, n = 82) или с помощью комбинированной терапии пропафеноне и bisoprolol (группа Б, n = 82). Больные распределены по группам на случайном принципе. Лечение препаратом пропафеноне проведено по схеме i.v. 2 мг/кг болус, вслед за чем проведена инфузия 0.0078 мг/кг за 120 мин. и р.о. пропафеноне 300 мг три раза через 8 ч. при сохраняющейся аритмии. Bisoprolol применен однократно только в самом начале лечения пациентов группы Б препаратом пропафеноне в дозе 5 или 10 мг. Регулирование ритма оценено на 3-ий, 6-ой, 12-ой и 24-ый час.

РЕЗУЛЬТАТЫ: В ранние часы регулирования комбинированная терапия по отношению к монотерапии восстанавливает синусовый ритм при более большем проценте пациентов (до 6-ого часа - группа Б - 67.07%; группа А - 48.78%; р < 0.05; до 12-ого часа соответственно 87.80% и 75.60%; р < 0.05).

ЗАКЛЮЧЕНИЕ: Раннее регулирование ритма пациентов с приступным предсердным мерцанием уменьшает вероятность повторных эпизодов аритмии. Этот факт делает применение селективной бета-блокады клинически значимой.