Efficacy and Safety of Bepridil for Patients with Persistent Atrial Fibrillation after Failed Electrical Cardioversion

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Introduction: Bepridil is effective for atrial fibrillation (AF), but it can induce torsades de pointes. Thus we examined the efficacy and safety of bepridil when started at 100 mg/day for AF after failed electrical cardioversion (EC).

Methods and Results: We studied 28 consecutive patients (58 ± 12 years old) with failed EC. After administration of bepridil, we examined the time to restore the sinus rhythm, the duration of the maintained sinus rhythm. Our patients were divided into the two groups and various clinical factors were compared, including medication and echocardiographic and electrocardiographic parameters: the SR group who maintained sinus rhythm during follow-up period and the AF group who still had AF. Sixteen patients (57%) could maintain sinus rhythm (SR group). Adverse arrhythmic events were not observed. There were no significant differences in any clinical factors between the two groups before and after bepridil.

Conclusions: Bepridil was effective and safe for persistent AF with failed EC. (J Arrhythmia 2011; 27: 131–136)

Key words: Atrial fibrillation, Cardioversion, Antiarrhythmic agent, Bepridil

Introduction

Atrial fibrillation (AF) is the most frequent arrhythmia observed in medical practice,1–3) and the prevalence of AF increases with age. Superiority of rhythm control to rate control for treatment of AF is not established,4–6) however in certain patients including younger patients and patients with severe symptoms, there is an actual need to maintain sinus rhythm.7,8) However, if we select the rhythm control-therapy for AF including antiarrhythmic agents and/or electrical cardioversion (EC), it is frequently difficult to restore sinus rhythm and maintain sinus rhythm for the long term. Bepridil is an antiarrhythmic agent that inhibits several ion channels including the sodium channel, potassium channel and calcium channel.9–12) Recently, it has been reported that bepridil could restore the sinus rhythm in patients with persistent atrial fibrillation.13,14) However, even in doses of 200 mg/day, bepridil prolongs the QT interval and induces torsades de pointes, which can develop into severe ventricular tachycardia, by
inhibiting some potassium channels. In this study, we examined the efficacy and safety of bepridil, especially 100 mg/day-bepridil for AF after failed EC, and we evaluated the differences in various clinical factors including medication and echocardiographic and electrocardiographic parameters between patients who maintained sinus rhythm and those who remained in AF or relapsed into AF from sinus rhythm.

Methods

Study patients

Between June 2005 and July 2007, we attempted EC in a relatively young set of 44 patients (age < 65 years old) with non-valvular persistent AF (> 2 months). Among the 44 patients, 16 patients could recover sinus rhythm by EC and be maintained using antiarrhythmic agents other than bepridil. In this study, we investigated the remaining 28 patients (22 male; mean age: 58 ± 12 years old) with persistent AF who failed to restore sinus rhythm after EC and took bepridil at 100 mg/day. The duration of AF was determined by electrocardiogram and from the patient reports. Patients with valvular AF, congestive heart failure, left ventricular dysfunction (ejection fraction < 45%), or who had an implanted pacing device were excluded from this study. All patients underwent echocardiography, 24-hour Holter ECG and blood examination. Anticoagulation therapy using warfarin was performed in all patients between an international normalized ratio of 2.0 and 3.0 for at least 3 weeks before EC. After admission, all patients underwent transesophageal echocardiography to check for a thrombus in the left atrium. The protocol of the EC was as follows; shock was delivered with external paddles positioned in the anterior-apex position connected to an external electrical cardioverter for biphasic external cardioversion. A first shock was delivered at an energy of 200 joules. If the first shock attempt failed to convert to sinus rhythm, a second shock was delivered at 300 joules. The next shock was delivered at 360 joules. If cardioversion was unsuccessful at 360 joules, intravenous antiarrhythmic agents, either disopyramide or pilsicainide, were added and a final cardioversion was attempted at 360 joules. We divided the study patients into the following two groups and compared the various factors including QT and QTc: SR group who restored sinus rhythm and maintained sinus rhythm by taking bepridil and AF group who relapsed into AF after once restored sinus rhythm or had never restored sinus rhythm by taking bepridil.

The ethics committee at Osaka Rosai Hospital approved this study, and written informed consent was obtained from all patients before echocardiographic examinations.

Administration of bepridil

After cessation of all oral antiarrhythmic agents, bepridil was given at an initial dose of 100 mg/day for 3 months, with titration to 150–200 mg/day if 100 mg/day-bepridil failed to restore sinus rhythm. Bepridil was continued for at least 12 months even if the sinus rhythm was not recovered. Bepridil was discontinued if severe side effects including torsades de pointes occurred.

Electrocardiographic parameters

Serial electrocardiograms were recorded at each visit (once a month) to determine whether the patient had converted to a sinus rhythm or remained with AF, and we documented all instances when the patients complained of palpitation. The 12-lead electrocardiogram was recorded at a paper speed of 25 mm/s and a gain of 10 mm/mV. The following electrocardiographic parameters were measured just before and 12 months after administration of bepridil: QRS duration, RR interval, QT interval and QTc interval. The QT interval was manually measured from the lead with the longest interval, using hand-held calipers to the nearest 10 ms from the beginning of the QRS complex to the end of the T-wave. The end of the T-wave was defined as the intersection between the tangent to the down-sloping T wave and PR baseline. The heart rate-corrected QT interval (QTc) was determined by dividing the QT interval by the square root of the preceding RR interval that showed the smallest difference between the average values of RR intervals. If the electrocardiogram of the patients showed AF, we used the averaged value of ten continuous beats according to the above-mentioned electrocardiographic parameters. In each patient, the serial electrocardiographic parameters were measured at the same lead. We defined each parameter just before bepridil as pre each parameter (e.g. pre QT), defined each parameter 12 months after bepridil as post parameter (e.g. post QT), and defined difference in each parameter over 12 months as a Δ value for each parameter (e.g. ΔQT = post QT – pre QT). In the presence of persistent AF, each electrocardiographic parameter was calculated as the average value of ten serial ten cardiac cycles. We compared the above-mentioned electrocardiographic parameters between the SR group and the AF group.
Statistical analysis

Data are presented as means ± SD for continuous variables. Continuous variables were compared using Student’s t-test, and categorical variables were compared using Fisher’s exact test. A two-sided P-value of < 0.05 was considered statistically significant. Analysis was performed using Statview 5.0 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Among the 28 patients, 19 patients (68%) recovered sinus rhythm once. The average time taken to restore sinus rhythm was 2.0 ± 2.3 months (range; 0.3–10 months). The average duration for maintaining the sinus rhythm period was 17 ± 10 months (range; 1–40 months). Sixteen patients (57%) maintained sinus rhythm during the follow-up period. Therefore, the SR group consisted of these 16 patients. In the SR group, 14 patients (88%) received 100 mg/day-bepridil, one patient received 150 mg and the other received 200 mg (average dosage: 109 ± 27 mg). The AF group consisted of the remaining 3 patients, who relapsed to AF, and the 9 patients who had never restored to sinus rhythm. All patients in the AF group received 200 mg/day-bepridil. Clinical and echocardiographic findings of each group before starting bepridil are shown in Table 1. A representative case of the SR group is shown in a Figure 1. Various electrocardiographic parameters between SR and AF groups are shown in Table 2. There were no significant differences in all the electrocardiographic parameters between the two groups (Table 2).

During the follow-up period, two adverse events associated with bepridil occurred. One was sinus bradycardia (33 bpm). The patient had taken 100 mg/day-bepridil for 3 months, but sinus rhythm was not restored. Then, when the dosage was increased to 150 mg/day, sinus bradycardia appeared 1 month later. The other event was a remarkable prolongation of QTc (571 msec). Discontinuation of bepridil prevented these patients from suffering subsequent arrhythmic events. Ventricular arrhythmias, such as torsades de pointes or sudden cardiac death, did not occur in the study patients.

Table 1 Differences in patient characteristics between SR and AF groups

<table>
<thead>
<tr>
<th></th>
<th>SR group (n = 16)</th>
<th>AF group (n = 12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>61.7 ± 11.3</td>
<td>54.4 ± 11.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>11/5</td>
<td>11/1</td>
<td>0.20</td>
</tr>
<tr>
<td>BSA(m2)</td>
<td>1.78 ± 0.25</td>
<td>1.89 ± 0.20</td>
<td>0.24</td>
</tr>
<tr>
<td>Duration of AF (months)</td>
<td>20.5 ± 33.2 (2-84)</td>
<td>17.2 ± 22.2 (3-70)</td>
<td>0.77</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>131.5 ± 14.4</td>
<td>132.0 ± 17.6</td>
<td>0.94</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.8 ± 12.2</td>
<td>78.7 ± 11.6</td>
<td>0.99</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>90.4 ± 13.9</td>
<td>89.1 ± 15.9</td>
<td>0.83</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>7 (44)</td>
<td>6 (50)</td>
<td>0.99</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td>2 (13)</td>
<td>1 (8)</td>
<td>0.99</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β blocker (n, %)</td>
<td>7 (44)</td>
<td>4 (33)</td>
<td>0.70</td>
</tr>
<tr>
<td>Ca antagonist (n, %)</td>
<td>2 (13)</td>
<td>2 (17)</td>
<td>0.99</td>
</tr>
<tr>
<td>Digoxin (n, %)</td>
<td>1 (6)</td>
<td>3 (25)</td>
<td>0.29</td>
</tr>
<tr>
<td>None/class Ia/class Ic (n, %)</td>
<td>8 (50)/2(13)/6 (37)</td>
<td>3 (25)/5(42)/4 (33)</td>
<td>0.35</td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dd (mm)</td>
<td>49.9 ± 6.9</td>
<td>51.7 ± 4.5</td>
<td>0.46</td>
</tr>
<tr>
<td>EF (%)</td>
<td>66.1 ± 10.6</td>
<td>61.8 ± 6.0</td>
<td>0.22</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>47.3 ± 6.8 (41-57)</td>
<td>48.0 ± 8.1 (38-60)</td>
<td>0.81</td>
</tr>
<tr>
<td>Mitral valve regurgitation (0, 1, 2, 3)</td>
<td>1.0 ± 0.6</td>
<td>1.0 ± 0.9</td>
<td>0.99</td>
</tr>
<tr>
<td>Tricuspid valve regurgitation (0, 1, 2, 3)</td>
<td>1.0 ± 0.7</td>
<td>1.4 ± 1.0</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Values are expressed as means ± standard deviation. Values of duration of AF (atrial fibrillation) and LA (left atrial diameter) are also shown as minimum to maximum value.

SR: sinus recovery, BSA: body surface area, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, Dd: Left ventricular end-diastolic diameter, EF: Left ventricular ejection fraction, LA: Left atrial diameter.
Discussion

The present study demonstrated that 19 of 28 patients (68%) with persistent AF lasting ≥2 months who failed to restore sinus rhythm after EC recovered sinus rhythm after taking 100 mg/day-bepridil, 16 (57%) maintained a sinus rhythm during the follow-up period. Serious adverse events including sudden death or torsades de pointes did not occur. The average left atrial (LA) diameter in the study patients was 49 ± 7 mm, and it was considered that structural remodeling of LA occurred in these patients. Nevertheless, bepridil, especially 100 mg/day-bepridil, was effective in restoring and maintaining the sinus rhythm in approximately half of the patients.

Effect on converting sinus rhythm

Bepridil inhibits multiple ion channels, including sodium, potassium (IKr, IKs, IKAch, IKur) and...
calcium channels. In particular, bepridil prolongs the action potential duration of the atrium by blocking various potassium channels, and is expected to restore and maintain the sinus rhythm in patients with persistent AF. These effects are similar to amiodarone, which is a class III anti-arrhythmic agent.19,20 Yoshida et al.21 reported that the main effectiveness of bepridil on preventing paroxysmal AF was due to a class III antiarrhythmic action. Recent reports have shown that bepridil converted AF to sinus rhythm more frequently and maintained sinus rhythm for longer, without extra-cardiac complications, compared to amiodarone. Fujiki et al.13 reported that the overall success rate for conversion with bepridil alone or in combination with aprindine was 69% in their study patients. Nakazato et al.14 reported that the rate of maintenance of sinus rhythm with combination of bepridil and EC was 81% during the follow-up period. Although our study patients had previously failed EC and had a larger LA compared with the previous study14 and we did not use other antiarrhythmic agents, which have been considered as negative factors on maintaining sinus rhythm, the success rate of conversion with bepridil in the present study was 68%, and the rate of maintenance of sinus rhythm with bepridil was 57%. The efficacy of bepridil in our study was similar to that achieved with amiodarone.22 Moreover, the dosage of bepridil in the present study was lower than that of 200 mg/day commonly used in clinical practice.13,23 Therefore, bepridil, especially when administered at a dosage of 100 mg/day, is clinically useful for maintaining sinus rhythm.

Bepridil and adverse complications

Bepridil is very useful for AF patients, while some previous studies have reported that bepridil provoked life-threatening complications, such as torsades de pointes, which can be caused by QT prolongation. Parellman et al. reported that bepridil was related to the development of ventricular arrhythmia and they concluded that bepridil was unsuitable for the treatment of AF.15 However, the dosage in their study was 200–600 mg/day, which is higher relative to our study. On the other hand, Fujiki et al.13 reported that bepridil at a dose of 200 mg/day and serum K ≥ 3.8 mEq/L could prevent proarrhythmic effects. They also demonstrated the usefulness and safety of bepridil. However, Yasuda et al.23 demonstrated that bepridil at doses less than 200 mg/day prolonged the QT and induced torsades de points. Nevertheless, in their study consisting of 459 patients, adverse effects were observed in only 19 patients (9%), including 13 patients with prominent QT prolongation and torsades de points in 4 patients. Moreover, the majority of their study patients received 200 mg/day-bepridil while 50% of our study patients received 100 mg/day-bepridil. Indeed, in SR group of our study patients, approximately 90% of the patients received 100 mg bepridil. Therefore, the absence of torsades de points events in our study support the safety of 100 mg/day-bepridil in patients with an enlarged left atrium and at older age, both of which are risk factors for torsades de points.23 In our study, two adverse events associated with bepridil occurred; one was sinus bradycardia and the other a remarkable prolongation of the QTc. The dosage of bepridil in these two cases was 150 and 200 mg/day, respectively. There were no severe adverse arrhythmic events, including torsades de points, in our study.

Study limitations

In this study, there were some limitations. First, there was no placebo control, so we could not determine the rate of sinus recovery without drugs (natural sinus recovery). However, a previous study24 showed that a placebo did not induce sinus recovery in similar patients. Our patients consisted of patients with persistent AF who failed EC, so natural sinus recovery is very unlikely in these patients. Therefore, we did not use placebo control in our study. Second, the definition of AF recurrence depended on the 12 lead-electrocardiogram on each visit and palpitation as the symptom. Certainly this was a limitation as to our method. However, we evaluated the electrocardiogram and asked all patients to report their symptoms every month in and we tried to find AF recurrence as much as possible to minimize this limitation. Finally, in this study, the AF group included both the patients who relapsed into AF and those who had never restored to sinus rhythm. Essentially, the former and latter patients should be evaluated separately, however the former group consisted of only 3 patients. Therefore, in this study, we evaluated both groups together as the AF group in which bepridil was not effective.

Conclusion

Bepridil, especially at a dose of 100 mg/day, is effective and safe for converting to and maintaining sinus rhythm in patients with persistent atrial fibrillation who failed to restore sinus rhythm after EC.
References


