The Resurfacing of Bepridil Hydrochloride on the World Stage as an Antiarrhythmic Drug for Atrial Fibrillation

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Bepridil hydrochloride is a multiple ion channel blocker with relatively strong suppressive effects for various K\(^+\) channels. Recent clinical studies mainly done in Japan have revealed the efficacy of the agent for the management of atrial fibrillation (AF). The pharmacological conversion effect for persistent AF seems particularly promising. The agent also has robust effects in maintaining sinus rhythm after pharmacological or electrical conversion, as well as suppressing recurrent attacks of paroxysmal AF. Though torsades de pointes may develop due to QT prolongation, an appropriate dosage and careful follow-up can prevent this serious complication. Now that the antiarrhythmic efficacy of bepridil for AF is recognized in Japan, the agent is poised to resurface on the world stage as a treatment for AF.

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Key words: bepridil, persistent atrial fibrillation, torsades de pointes

Introduction

Bepridil hydrochloride is an anti-anginal drug classified as a calcium channel blocker.\(^1\) The agent blocks multiple ion channels, including sodium and potassium channels.\(^3,4\) Its potassium-channel-blocking action is relatively strong, and Class III antiarrhythmic effects akin to those of amiodarone are expected for various arrhythmias. Yet soon after the introduction of bepridil, the K\(^+\) channel blocking action of the agent and relatively large doses required (even for Western patients) reportedly led to a high incidence of QT prolongation following torsades de pointes (TdP).\(^5\) As a consequence, the agent was withdrawn from the commercial market in the West almost 20 years ago. Meanwhile, bepridil was approved as an antiarrhythmic drug in Japan. Over the last decades, Japanese arrhythmologists have accumulated therapeutic experience with the agent mostly for the treatment of atrial fibrillation (AF), with good data on dosing.\(^6\)–\(^9\) Though only a few clinical studies have been conducted so far, bepridil has resurfaced as an effective drug for AF. In this review we describe the clinical efficacy and safety of bepridil with a focus on the treatment of AF.

Efficacy for persistent and paroxysmal AF

Persistent AF is usually defined as a fibrillation of the atrium which lasts for more than 7 days and...
requires electrical or pharmacological conversion to sinus rhythm. Spontaneous conversion to sinus rhythm is very difficult for persistent AF. To cure the condition, cardiologists schedule pharmacological or intentional electrical cardioversion under appropriate anticoagulation therapy. In administering pharmacological conversion, the efficacy of class Ia and Ic drugs declines when the AF lasts for long periods. Worse still, persistent atrial flutter and adverse effects may develop in patients treated with these drugs. Class III drugs may be effective from the standpoint of cardioversion, but the results are not always favorable. Kochiadakis, et al compared the conversion to sinus rhythm between amiodarone and propafenone in patients with chronic AF (lasting for more than 3 weeks). Conversion was achieved in 16 of 34 (47%) patients treated by amiodarone versus 13 of 32 (40.6%) patients treated by propafenone. These findings were inconclusive, however, as the patient populations were too small. In the SAFE-T study, 665 patients with persistent AF were randomly assigned to 3 groups treated respectively with amiodarone (267), sotalol (261), and placebo (137). After administration for 28 days, spontaneous conversion was obtained in 27.1% of patients in the amiodarone group, 24.2% of patients in the sotalol group, and 0.8% of patients treated with placebo. These results indicated that even the class III drugs were incapable of achieving conversion to sinus rhythm in more than 30% of patients with long-lasting AF. Are there any drugs capable of conferring higher conversion effects? It may be that bepridil, an agent used mainly in Japan, does just that. Our group has already reported the preliminary results with sinus rhythm conversion and maintenance effects of bepridil for persistent AF. Though this was a non-randomized retrospective study, it provides the only published data on the efficacy of bepridil for a relatively large population of patients with persistent AF.

Bepridil was administered to 170 patients with persistent AF (83 males). The average age was 58 years and the mean duration of AF was 3.3 months. Underlying heart disease, including hypertension and ischemic heart disease, was observed in 70 patients. The mean left ventricular ejection fraction (EF) was 64% and left atrial dimension (LAD) was 40 mm. Bepridil was administered starting from 100 mg daily and increased up to a maximum of 200 mg. Concomitant anti-coagulation therapy and rate control drugs such as digitalis, β-blockers, or calcium antagonists were used when necessary. Sinus rhythm was restored in 98 of 170 patients (58%), with a mean conversion time of 2.2 months (Figure 1). Most of these 98 patients experienced sinus rhythm conversion within 3 months, and 86 (78%) have maintained sinus rhythm for an average follow-up of 20 months. Thirty-four of 72 patients who failed to achieve pharmacological conversion to sinus rhythm underwent DC cardioversion. DC cardioversion restored sinus rhythm in 21 patients, and sinus rhythm was maintained in 18 (86%) of these patients over an average follow-up of 20 months.

A few earlier studies have investigated persistent AF using bepridil. Perelman et al compared the effects of amiodarone and bepridil in 14 patients with chronic AF. The conversion rate to sinus rhythm was 4 of 10 patients (40%) with amiodarone and 9 of 14 patients (64%) with bepridil. In a study with a fairly small population, Fujiki et al observed that bepridil alone or in combination with aprindine restored sinus rhythm in 69% of 32 patients with persistent AF. Imai et al reported that a combination of bepridil and class Ic antiarrhythmic drugs was effective for conversion to sinus rhythm. In 32 cases of persistent AF refractory to class I antiarrhythmic drugs, 9 patients were restored to sinus rhythm by bepridil alone. When the other 23 without conversion to sinus rhythm were treated with a combination...
of bepridil and class Ic drugs, sinus rhythm was restored in 22 (96%) patients. Though these studies investigated bepridil in combination with class I drugs, and only in small patient populations, they suggest that bepridil is effective to some degree in converting persistent AF to sinus rhythm.

Bepridil requires a somewhat longer interval for conversion, as it acts slowly in bringing about a steady serum concentration. In our study, the mean interval to conversion was 2.2 months. One of the mechanisms of late conversion is the reverse-remodeling effect brought by T-type Ca$^{2+}$ blocking action. The effect of T-type Ca$^{2+}$ channel blocking in preventing the mid to late phase of atrial remodeling has been explained. Morphological changes were observed in the fibrillatory waves of the patients in whom bepridil restored sinus rhythm: the fibrillation waves were initially fine and of low amplitude, and thereafter they gradually became larger and more organized until just before the sinus rhythm was restored. Fujiki et al compared the interval of the fibrillation cycle length (FCL) using spectral analyses before and after bepridil. They noted a greater increase of FCL in responders, and the fibrillation waves coarsened somewhat before termination. In one of our earlier studies, the fibrillatory wave morphology changed from small and fine to coarse and large before sinus restoration.7)

**Recommended approach for persistent AF**

Based on these clinical experiences, we recommend the following approach for persistent AF (Figure 2). If patient has long-lasting AF (< 1 year), commence bepridil under appropriate anticoagulation therapy. Add rate control drugs and upstream therapy, including angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, and statins, if necessary. If sinus conversion is obtained within 3 months, continue the bepridil therapy. If sinus conversion is not obtained, schedule DC cardioversion as the next step. This approach can be expected to bring about sinus conversion in more than 50% of patients with persistent AF.

Clinical data on the long-term efficacy of sinus rhythm maintenance by bepridil is scanty. In a study by Imai et al on 32 cases of persistent AF, bepridil alone restored sinus rhythm in 9 patients and maintained it in 8.9) In patients administered bepridil in combination with class Ic drugs, sinus rhythm was maintained in all of the restored patients (96%) over an average follow-up of 14 months. In our study with 98 patients in whom sinus rhythm had been pharmacologically restored by bepridil, sinus rhythm was maintained in 86 (78%) of the patients over an average follow-up of 20 months.13) In a prospective, multi-center trial reported by Roy et al, AF recurred after a mean follow-up of 16 months in 71 of 201 (35%) patients treated with amiodarone and 127 of 201 patients (63%) treated with sotalol or propafenone. In SAFE-T, a comparison of sinus rhythm maintenance in patients treated with amiodarone, sotalol, or placebo over a much longer period, amiodarone maintained sinus rhythm in 50% of the patients who received it over a follow-up of almost 30 months.12) Amiodarone is superior to sotalol and placebo, but not always effective in preventing recurrence over in the long term. In this regard, bepridil seems to have a comparable effect to amiodarone for maintaining sinus rhythm. Further investigation will be required to clarify this issue.

Recent basic studies seem to add evidence in support of the efficacies of bepridil. Bepridil blocks not only slow components of the multiple K$^+$ currents, but also the ultra rapid (I_{K-u}) K$^+$

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**Figure 2** Therapeutic protocol for persistent AF.
current. $I_{Kr}$ is only seen in the atrium, and the efficacy of bepridil for AF might be explained by this effect. Bepridil may prevent the recurrence of paroxysmal AF via a conformed effect in inhibiting the human Kv1.5 channel current related to $I_{Kr}$.19) When Yoshida et al compared the efficacy of class Ic drugs and bepridil for preventing paroxysmal AF, they found that the efficacy of bepridil for paroxysmal AF was attributable to a class III antiarrhythmic action with relatively short f-f intervals (small excitable-gap).20) Bepridil appears not only to reverse the effects for mid- to long-term remodeling, but also to suppress short-term remodeling, in the atrium.

**Adverse effects of bepridil**

Despite the efficacy of bepridil for AF, previous reports warned that the relatively strong potassium channel blocking effects often render TdP due to QT prolongation. Perelman et al concluded that, in light of the high rate of ventricular arrhythmias such as TdP, the risks of bepridil outweigh the benefits.5) We note, however, that the dose of bepridil ranged from 200 mg to 600 mg in their study. This relatively high dose of bepridil surely increased the incidence of serious ventricular arrhythmias in their subjects. Coumel summarized the French experience on the safety of bepridil by gathering data on the incidence of TdP. TdP incidence increased in a subgroup of elderly women with hypokalemia induced by diuretics.21) According to post-marketing surveillance from 1981 to 1989, a total of 108 episodes of TdP were observed. Significantly, however, most of the patients who developed TdP had been receiving relatively high doses of bepridil (318 ± 40 mg/day). In the Japanese experience, Yasuda et al reported a 0.9% (4 of 459 patients) incidence of TdP in a relatively large population of elderly patients with AF or atrial flutter (AFL), hypokalemia, bradycardia, and prolonged QT intervals.22) These patients received an average bepridil dose of 150 ± 41 mg/day. The risk of TdP should always be considered during administration of bepridil even under careful observation, and even at doses of less than 200 mg/day. Thus, we have proposed that the maximum dose of bepridil should be 200 mg/day.

Pulmonary fibrosis is reported as a rare but serious complication during bepridil administration. Vasilomanolakis et al reported an autopsy finding of death by bepridil-induced pulmonary fibrosis in one case. Autopsy specimens of lung tissue indicated strong fibrotic interstitial changes. They concluded that these changes were an adverse complication of bepridil.23) Sekita et al reported a similar case that could be saved by steroid pulse therapy.24) Though the precise mechanism of pulmonary fibrosis is still unknown, similar case reports are sporadically seen.25,26) We experienced two patients who developed pulmonary fibrosis after bepridil administration, out of the over 1,000 patients we treated. Though its cause remains elusive, this complication should be always kept in mind.

**Indication for patients with LV dysfunction**

Because of its class III effect, bepridil can also be applied in patients with left ventricular (LV) dysfunction. Bepridil basically acts as a calcium channel blocker and weak sodium channel blocker. This explains why its cardio-suppressive effect is relatively small and controversial. According to a study on the hemodynamic effects of intravenous bepridil in patients with depressed LV function with ejection fractions (EFs) of 0.45 or less, Josephson et al found bepridil to exert significant negative effects in the patients with depressed LV function.27) De Marco et al, on the other hand, reported no deleterious effect of oral bepridil on cardiac performance in patients with reduced LV function.28) In fact, there is no available clinical data as to whether oral bepridil can be used in patients with depressed LV function.

We studied the safety and efficacy of bepridil in patients with LV dysfunction retrospectively. In 481 patients with paroxysmal AF and persistent AF treated with bepridil, we compared 22 patients with EF < 40% (group L) and 459 patients with EF > 40% (group N) (Table). In group L, bepridil was started at a dose of 50 mg/day, and increased to a maximum of 200 mg/day when necessary. The average EF was 32% in group L and 66% in group N. In persistent AF, the sinus conversion effect was 50% in group L and 57% in group N. The sinus rhythm maintenance effect during the 20-month follow-up was 57% in group L and 62% in group N. In paroxysmal AF, group L and group N had no-recurrence rates of 80% and 74%, respectively. Thus, the conversion and maintenance effect of sinus rhythm did not significantly differ between these two groups. ECG parameters with QT interval, QTc, and QRS width showed no significant changes from before to after the bepridil administration. Interestingly enough, adverse effects were seen in 19 patients in group N versus no patients in group L. This result could be explained by our very selective and careful use of bepridil for this population of patients with LV dysfunction. Again, the initial doses were small and the subsequent dosing was
maintained at less than 200 mg/day. The patients were examined in frequent follow-ups with ECG recording, electrolyte check, and clinical examinations. On the basis of our finding from this study, we think it is feasible to use bepridil in patients with deteriorated LV function, as long as we do so with caution.

**Implications for the safe use of bepridil**

Through our clinical experience, we have determined several points to bear in mind regarding the use of bepridil as an antiarrhythmic drug: 1) the maximum dose should be kept within 200 mg/day. Physicians should be especially cautious when administering the drug to 2) elderly and female patients, and patients with 3) hypokalemia, 4) bradycardia, 5) prolonged QT interval before administration, and 6) LV dysfunction. We also recommend weekly monitoring of the QT interval, heart rate on ECG, and electrolytes during the first month after starting the bepridil administration. Other precipitating factors, which influence the QT interval, should also be watched.

**Conclusion**

Bepridil shows favorable efficacy in obtaining AF conversion and sinus maintenance for patients with persistent AF. It also appears to be useful for preventing attacks in patients with paroxysmal AF. Though TdP due to bepridil-induced QT prolongation is a concern, bepridil may be applied even in patients with impaired LV function. Now that the antiarrhythmic efficacy of bepridil for AF is recognized in Japan, the agent is poised to resurface on the world stage as a treatment for AF.

**References**

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**Table** Safety and efficacy of bepridil for AF between normal and impaired LV function

<table>
<thead>
<tr>
<th>Group</th>
<th>N (n = 459)</th>
<th>L (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>62 ± 12</td>
<td>65 ± 11</td>
</tr>
<tr>
<td>EF (%)</td>
<td>66 ± 8</td>
<td>32 ± 7</td>
</tr>
<tr>
<td>LAD (mm)*</td>
<td>39 ± 6</td>
<td>46 ± 7</td>
</tr>
<tr>
<td>Dose (mg/day)</td>
<td>165 ± 37</td>
<td>159 ± 40</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>152 (33%)</td>
<td>10 (46%)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>117 (26%)</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>n = 198</td>
<td>n = 17</td>
</tr>
<tr>
<td>Conversion rate</td>
<td>113 (57%)</td>
<td>9 (53%)</td>
</tr>
<tr>
<td>SR maintenance rate</td>
<td>89 (79%)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Mean F/U (months)</td>
<td>20.1</td>
<td>20</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>n = 261</td>
<td>n = 5</td>
</tr>
<tr>
<td>No recurrence</td>
<td>192 (74%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Mean F/U (months)</td>
<td>20.7</td>
<td>14.9</td>
</tr>
<tr>
<td>ECG parameters in Group L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QT</td>
<td>0.40 ± 0.05</td>
<td>0.42 ± 0.56</td>
</tr>
<tr>
<td>QTc</td>
<td>0.44 ± 0.05</td>
<td>0.45 ± 0.04</td>
</tr>
<tr>
<td>QRS</td>
<td>0.10 ± 0.01</td>
<td>0.10 ± 0.01</td>
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<tr>
<td>Adverse complications</td>
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<td></td>
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<tr>
<td>Bradycardia</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
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<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>QT &gt; 0.55</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Tdp (+)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Tdp (−)</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

EF: ejection fraction, LAD: left atrial dimension, ACE-I: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker, SR: sinus rhythm, F/U: follow-up, Tdp: torsade de pointes * p < 0.01


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