Clinical Evaluation of Adverse Effects During Bepridil Administration for Atrial Fibrillation and Flutter

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Background  Bepridil hydrochloride (Bpd) has attracted attention as an effective drug for atrial fibrillation (AF) and atrial flutter (AFL). However, serious adverse effects, including torsade de pointes (Tdp), have been reported. 

Methods and Results  Adverse effects of Bpd requiring discontinuation of treatment were evaluated. Bpd was administered to 459 patients (361 males, 63±12 years old) comprising 378 AF and 81 AFL cases. Mean left ventricular ejection fraction and atrial dimension (LAD) were 66±11% and 40±6 mm, respectively. Adverse effects were observed in 19 patients (4%) during an average follow-up of 20 months. There was marked QT prolongation greater than 0.55 s in 13 patients, bradycardia less than 40 beats/min in 6 patients, dizziness and general fatigue in 1 patient each. In 4 of 13 patients with QT prolongation, Tdp occurred. The major triggering factors of Tdp were hypokalemia and sudden decrease in heart rate. There were no differences in the clinical backgrounds of the patients with and without Tdp other than LAD and age, which were larger and older in the patients with Tdp.

Conclusion  Careful observation of serum potassium concentration and the ECG should always be done during Bpd administration, particularly in elderly patients.  (Circ J 2006; 70: 662–666)

Key Words: Adverse effects; Atrial fibrillation; Atrial flutter; Bepridil hydrochloride; Torsade de pointes
QRS width, QT interval, QTc, and atrioventricular conduction were evaluated from the ECG recordings, and serum potassium concentration, liver and renal function were also investigated by blood examination. We tried to keep the serum potassium concentration >4.0 mmol/L. The QT interval was taken as the longest QT in the 12-lead ECG, and averaged by 10 beats.

Statistical Analysis

The results are presented as the mean ± SD. Differences between the ECG changes were compared using an unpaired t-test and the significance was set at p<0.05.

Results

Adverse effects were observed in 19 patients (4%) during the follow-up period of 0.5–72 months (average 20 months). There was dizziness and general fatigue in 1 patient each, bradycardia <40 beats/min without QT prolongation >0.55 s in 4 patients, and marked QT prolongation >0.55 s in 13 patients (Table 1).

In the 2 patients with dizziness and general fatigue, these symptoms disappeared following discontinuation of Bpd. In 2 of the 4 patients with bradycardia, the arrhythmia was improved by decreasing the dose from 150 to 100 mg and from 100 mg to 50 mg daily, respectively. However, in the remaining 2 patients, Bpd was discontinued because of recurrence of AF/AFL after decreasing the dosage. No changes were observed in QRS width in any of the patients before and after administration of Bpd. However, both QT and QTc were prolonged significantly from 0.40±0.04 to 0.44±0.05 s (p<0.01) and from 0.44±0.03 to 0.45±0.04 (p<0.05), respectively. Deterioration of atrioventricular conduction, apart from first-degree atrioventricular block, did not occur.

In 13 patients with marked QT prolongation, the QT interval (QTc) was significantly prolonged from 0.42±0.03 (0.46±0.03) to 0.60±0.05 (0.54±0.05) following Bpd administration (Table 2). In 4 of these 13 patients, Tdp occurred in the 2nd, 9th, 18th and 181st week, respectively, following Bpd administration. In all patients with Tdp, the LVEF was >50%, and none had obvious left ventricular hypertrophy, liver or renal dysfunction before Bpd administration. In all patients with Tdp, the serum potassium concentration was >4.2 mmol/L before Tdp, and decreased to <3.8 mmol/L just prior to Tdp onset. Marked QT prolongation did not occur before Tdp (Table 1). In the other patients without Tdp, the serum potassium concentration remained >4.0 mmol/L. In cases 1, 2 and 4, a sudden decrease in heart rate was caused by latent sick sinus syndrome and in each case a pacemaker was implanted. In case 3, AF was converted to SR, with a sudden decrease in heart rate from 100 to approximately 40 beats/min with marked QT prolongation in the 2nd week following Bpd administration. The bradycardia recovered gradually after discontinuation of Bpd. In case 1, deterioration of renal function because of dehydration, and in case 4, high fever and congestive heart failure from infectious endocarditis was also the likely triggers of Tdp. In this study, a concomitant drug, digoxin, was administered to 192 patients and in 8 patients with marked QT prolongation, digoxin may have contributed to QT prolongation. However, its serum concentration was in the acceptable range of 0.8–1.4 ng/dl and marked QT prolongation did not occur in the other 184 patients.

Circulation Journal Vol.70, June 2006
There were no significant differences between the 13 patients with marked QT prolongation and the remaining 446 patients without QT prolongation in their clinical backgrounds, including age, sex, LVEF, LAD, underlying diseases and dose of Bpd. However, LAD and age differed between the 4 patients with Tdp and the 9 patients without Tdp (45±2 vs 38±4 mm, p<0.01, and 71±8 vs 60±8 years old, p<0.05), and Tdp did not occur in patients without obvious underlying heart disease. In the 4 patients with Tdp, a sudden decrease in heart rate with concomitant serum potassium concentration <4.0 mmol/L was a prominent feature.

**Case Reports (Table 1, Fig 1)**

**Case 1** The patient was a 78 years old male who had undergone aortic valvular replacement and whose left ventricular function was within normal limits (patient no. 1). Bpd concomitant with digoxin was effective for paroxysmal AFL (Fig 1a, Middle strip). At the 18th week following administration of Bpd, he complained of faintness and the ECG revealed Tdp with marked QT (QTc) prolongation of 0.65 s (0.57) (Figs 1a, Right strip, b). There was also deterioration of renal function because of dehydration (serum urea nitrogen, creatinine and digoxin levels rose from 23 to 47 mg/dl, 0.82 to 1.43 mg/dl, 1.2 to 1.4 ng/dl, respectively). Concomitant renal dysfunction, hypokalemia (3.4 mmol/L), and a sudden decrease in heart rate caused by latent sick sinus syndrome were the likely triggering factors for Tdp. He had a pacemaker implanted and the AFL was successfully suppressed with Bpd 100 mg daily.

**Case 2** The patient was a 64-year old female with moderate mitral valvular stenosis and normal left ventricular function (patient no. 4). Bpd 150 mg daily, together with digoxin, was administered for paroxysmal AFL refractory to disopyramide and aprindine. Bpd was further increased to 200 mg daily for recurrent AFL, and SR was successfully maintained (Fig 1c, Middle strip). Forty months later, she was admitted to hospital with high fever, anorexia and diarrhea. The ECG revealed Tdp with marked QT (QTc) prolongation of 0.65 s (0.57) (Fig 1c, Right strip) and premature ventricular beats which degenerated into Tdp. She was diagnosed as having infectious endocarditis with latent sick sinus syndrome, and temporary ventricular pacing at a rate of 100 beats/min was performed. One month following admission, mitral valvular replacement and permanent pacemaker implantation was done. Thereafter, AFL was successfully suppressed with Bpd 100 mg daily. In this case, congestive heart failure and bradycardia concomitant with hypokalemia (3.7 mmol/L) were the most likely triggering factors for Tdp.

**Table 2 Clinical Background of Patients With/Without QT Prolongation and Tdp**

<table>
<thead>
<tr>
<th>QT prolongation</th>
<th>Tdp</th>
</tr>
</thead>
<tbody>
<tr>
<td>(–) (n=446)</td>
<td>(+) (n=13)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62±12</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>351/95</td>
</tr>
<tr>
<td>Bpd dose (mg/day)</td>
<td>164±37</td>
</tr>
<tr>
<td>EF (%)</td>
<td>65±11</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>40±6</td>
</tr>
<tr>
<td>QT (Bpd–) (s)</td>
<td>0.40±0.04</td>
</tr>
<tr>
<td>QT (Bpd+) (s)</td>
<td>0.42±0.04*</td>
</tr>
</tbody>
</table>

***p<0.01, **p<0.05.

Abbreviations as in Table 1.

**Discussion**

The 2 main findings of this study are: (1) adverse effects of Bpd occurred in 19 of 459 AF/AFL patients (4%) during an average 20 months of follow-up; and (2) in 4 of the 19 patients (0.9% of 459 patients), Tdp was triggered by a sudden decrease in heart rate and concomitant hypokalemia. Significant clinical differences were not predicted between patients with and without Tdp, except higher age and larger LAD. Careful observation of serum potassium concentration, heart rate and QT interval should always be performed during Bpd administration, particularly in elderly patients.

In patients with AF or AFL refractory to catheter ablation, or who are reluctant to undergo this procedure, the remaining therapeutic modality is pharmacological therapy. In rhythm control therapy, amiodarone has shown relatively favorable efficacy, but it sometimes has serious extracardiac adverse effects such as lung fibrosis.1-4 Bpd was recently reported as effective for AF and AFL.5,9-12 It has also multi-ion channel blocking effects similar to amiodarone, but fewer extra-cardiac adverse effects.5-12 However, Tdp, which is one of the most serious adverse effects, has been reported, especially in elderly patients and patients with hypokalemia, a history of ventricular fibrillation, or preexisting QTc prolongation over 0.47.7 In that report by Manouvrier et al, Bpd was administered in relatively high doses, which also contributed to the development of Tdp. In our study, Tdp occurred despite the maximum dose being 200 mg, which is lower than that used in the other reports, so other triggering factors may contribute to the occurrence of Tdp. We could not detect any differences in the clinical background of the patients with and without Tdp except for greater age and larger LAD. In the 4 patients with Tdp the common causes or triggers of Tdp were a sudden decrease in heart rate and hypokalemia. In addition, the deterioration in renal function in case 1, and the high fever and congestive heart failure in case 2 could have also triggered Tdp. Therefore, physicians must pay attention to the patient’s general condition, the ECG changes, particularly a decrease in the heart rate to less than 50 beats/min and QT prolongation greater than 0.50 s, hypokalemia, and deterioration of liver or renal function. As Bpd has a relatively long half-life (80 h following 20 days administration at a dose of 200 mg daily), adjusting the dose of Bpd according to the patient’s age, body weight, liver or renal function is necessary. We usually limit the maximum dose of Bpd to 200 mg daily, and decrease or discontinue it and/or concomitant drugs, such as digitalis or verapamil, as soon as possible in patients with bradycardia or QT prolongation. Furthermore, we
Fig 1. Time course of ECG changes in 2 representative cases with torsade de pointes (Tdp). The left strips in (a) and (c) reveal the ECG before bepridil (Bpd) administration in cases 1 and 2 (patients 1 and 4), respectively, and the middle strips are the ECG following Bpd administration. The right strips show the ECG just before Tdp. The numbers on each strip reveal the QT interval (s). (a) The left strip shows atrial flutter (AFL) with 4:1 atrioventricular conduction. At the 4th week of Bpd administration, sinus rhythm was maintained with QT prolongation from 0.44 to 0.48 s (Middle strip). At the 18th week following administration of Bpd, the ECG revealed marked QT prolongation of 0.56 s (Right strip). (b) Tdp in case 1. (c) The left strip shows AFL with 2:1 atrioventricular conduction. At the 4th week of Bpd administration, sinus rhythm was maintained with QT prolongation from 0.32 to 0.44 s (Middle strip). Although, further QT prolongation was not detected until the 44th month, at the 45th month AFL recurred with marked QT prolongation of 0.65 s (Right strip). The second ventricular beat in the right strip is a premature ventricular contraction. (d) Tdp in case 2 (patient 4).
advise patients to discontinue Bpd temporarily if they have serious vomiting, diarrhea, or anorexia, and we recommend they come to the hospital if they experience dizziness, faintness or syncope.

**Study Limitations**

First, there were several patients with QT prolongation between 0.50 and 0.54 s. Although Tdp did not occur in these patients, they were potentially at high risk for Tdp, especially in the case of bradycardia or hypokalemia. Therefore, adverse effects should be investigated in a larger number of patients over a longer follow-up period. Second, although monitoring the serum drug concentration of Bpd is useful in preventing its adverse effects, it is not available commercially and thus we did not measure it.

**Conclusion**

Adverse effects after Bpd administration were observed in 19 of 459 AF/AFL patients (4%), including 4 patients with Tdp (0.9%), during an average follow-up of 20 months. Significant clinical differences were not predicted between patients with and without Tdp except higher age and larger LAD, and prediction of Tdp is sometimes difficult. However, the main triggers of Tdp were bradycardia and hypokalemia, and therefore careful attention should always be given to these factors and QT prolongation during Bpd administration, particularly in elderly patients.

**References**