Clinical Efficacy of Bepridil for Class I Antiarrhythmic Drug-Induced Atrial Flutter in Patients with Paroxysmal Atrial Fibrillation

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Background: Class I antiarrhythmic drugs can promote the organization of atrial fibrillation (AF) and sometimes converts AF into atrial flutter (AFL) concomitant with difficulty of rate control. We studied the usefulness of Bepridil, which exhibits a class III-like effect, for class I drug-induced AFL in patients with paroxysmal AF.

Methods: The study population consisted of 17 consecutive patients (15 men, mean age 65 ± 8 years) with AFL converted from paroxysmal AF following oral treatment of class IA or IC antiarrhythmic agents including pilsicainide (n = 8), cibenzoline (n = 5), flecainide (n = 2), aprindine (n = 1), and propafenone with cibenzoline (n = 1). After the occurrence of AFL, class I drug was replaced by bepridil with a dose of 100–200 mg per day in all patients.

Results: After the treatment with bepridil, 15 (88%) out of the 17 patients restored sinus rhythm after 1 to 68 days (average of 21 days). In 12 (80%) of the 15 patients, sinus rhythm was maintained for an average of 23.6 months (range of 1 to 62 months) follow-up period. Although torsade de pointes was not recognized, a marked QT prolongation (0.60 sec) was observed in one patient during the administration of bepridil at a daily dose of 200 mg. In this patient, QT interval was normalized (0.45 sec) after reduction of bepridil to 150 mg daily.

Conclusion: Bepridil treatment may be safe and effective for class I drug-induced AFL in patients with paroxysmal AF to restore and maintain sinus rhythm as an alternative therapy for catheter ablation. However, the QT interval must be carefully monitored during this medication.

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Key words: Bepridil, Class I antiarrhythmic drug, Atrial flutter, Atrial fibrillation

Introduction

Class IA or IC antiarrhythmic agents are frequently used as a first-line therapy in the management of patients with atrial fibrillation (AF). However, these agents may result in the induction of atrial flutter (AFL), especially if class IC drugs are used (so-called IC flutter).1) The incidence of class I drug-induced AFL in the treatment of AF has been reported as 3.5 to 24%.2–4) Although catheter

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Ablation for class I drug-related AFL in patients with AF has been established as a hybrid therapy, continuous medication is needed for prevention of AF in most of the patients. In addition, not all patients are good candidates for catheter ablation and they may not agree to undergo the therapy, especially if they are elderly. Bepridil, which has a class III-like effect, has been reported to be effective for the treatment of AF and AFL. Therefore, we studied the clinical efficacy of Bepridil for AFL after treatment with class I antiarrhythmic agents in patients with paroxysmal AF.

Methods

The study population consisted of 17 consecutive patients (15 men, mean age of 65 ± 8 years; range, 49 to 76 years) with "common type" AFL converted following oral treatment with class I antiarrhythmic agents for paroxysmal AF. Common type AFL was defined as a predominantly negative, sawtooth-like atrial activation pattern in the inferior leads, with positive atrial deflections in lead V1 and negative deflections in lead V6. The history of paroxysmal AF ranged from 1 to 144 months (average, 45.2 months). Eleven patients had underlying cardiovascular disease: 7 patients suffered from hypertension, 2 from post-myocardial infarction, one from aortic stenosis, and another from mitral stenosis. All patients had their left ventricular function evaluated using echocardiography before the bepridil administration. The mean left ventricular ejection fraction was 68 ± 8% and left atrial diameter (LAD) was 40.3 ± 6.1 mm. The antiarrhythmic agents causing AFL were pilsicainide (n = 8), cibenzoline (n = 5), flecainide (n = 2), aprindine (n = 1), and propafenon with cibenzoline (n = 1). After the occurrence of AFL, class I drugs were discontinued in all patients and bepridil was started with a dose of 100–150 mg per day. If sinus rhythm was not restored and QT interval was not prolonged more than 0.50 sec, the bepridil dose was increased to 150–200 mg daily after one or 2 weeks. If sinus rhythm was restored, the treatment was maintained unless adverse complications occurred. For rate control, digoxin, beta-blocker, and calcium antagonists such as verapamil or diltiazem were used concomitantly if required. In all patients, anticoagulation therapy with warfarin was concurrently started to prevent thromboembolic complications.

Statistical analysis

Continuous variables are presented as the mean ± SD and were compared by paired t test. Categorical variables were compared by Fisher’s exact test. A p value <0.05 was considered statistically significant.

Figure 1 Time duration to restore sinus rhythm after bepridil treatment in each patient.
Results

After treatment with bepridil, 15 (88%) out of 17 patients restored sinus rhythm after 1 to 68 days (average of 21 days) (Figure 1). Although paroxysmal AF occurred in 3 patients, sinus rhythm was maintained in 12 (80%) of 15 patients for an average of 23.6 months (range of 1 to 62 months) follow-up period. The maintenance dose of bepridil was 100 mg/day in 1 patient, 150 mg/day in 8 patients, and 200 mg/day in 3 patients. One patient underwent pulmonary vein isolation by catheter ablation for recurrence of paroxysmal AF. The efficacy of bepridil for converting to sinus rhythm did not differ between patients with and without underlying heart disease (73% vs. 67%). Although the rate of conversion to sinus rhythm was slightly higher in patients with LAD < 40 mm than in patients with LAD ≥ 40 mm, the difference was not significant (78% vs. 63%). Heart rate decreased significantly after bepridil treatment from 71 ± 14.2 beats/min to 58.0 ± 11.2 beats/min (p < 0.05). QT and QTc intervals during sinus rhythm were significantly prolonged after bepridil treatment from 0.39 ± 0.03 sec to 0.46 ± 0.04 sec (p < 0.01) and from 0.42 ± 0.03 to 0.44 ± 0.03 (p < 0.05), respectively (Table 1, 2). Although torsade de pointes was not recognized, marked QT prolongation (0.60 sec) was observed in 1 patient during the administration of bepridil of 200 mg daily. In this patient, QT interval was normalized (0.45 sec) after reduction of bepridil to 150 mg daily and AF did not recur.

Discussion

The present study demonstrated a favorable result with bepridil for treatment of AFL following administration of class I antiarrhythmic drugs for paroxysmal AF. Bepridil treatment may be simple and effective, and seems to be an alternative therapy for catheter ablation in patients with class IA or IC antiarrhythmic drug-induced AFL. However, patients should be monitored to watch for QT prolongation during the treatment.11)
Mechanism of termination of class I anti-arrhythmic drug-induced AFL and maintenance of sinus rhythm by bepridil

Depression of conduction velocity of atrial tissue by a class I drug, especially a class IC agent, may facilitate reentry by slowing and organization of intraatrial conduction.3,5) This prevents the simultaneous occurrence of the multiple reentrant circuits necessary for perpetuation of AF and results in a single atrial reentrant circuit manifested as AFL.3) Class I antiarrhythmic agents also can slow isthmus conduction and limit transverse conduction across the crista terminalis, which leads to perpetuation of isthmus-dependent AFL.4) In addition, the class IA or IC drugs may induce some serious conditions in patients with AFL. The obvious danger is the development of a fast ventricular rate, because the relative slow atrial rate caused by the class IA or IC agent with or without an anticholinergic effect may be followed by 1:1 atrioventricular conduction.5) This can lead a cardiac catastrophe in patients with AF. In order to terminate the AFL, prolongation of the refractory period within the tachycardia circuit is more important than slowing the conduction velocity.13) Bepridil has multiple ion-channel blocking effects: sodium, potassium, and calcium channels.9,14) Bepridil especially blocks the multiple components of the potassium currents including I_{Kr}, I_{kv},15) I_{K-er},16) I_{K-Ach},17) and I_{K-ATP}.18) The precise mechanism of efficacy for AFL in the treatment of bepridil is unknown. These potassium channel blocking actions may prolong the action potential duration, which leads to prolongation of the atrial refractory period, following termination of the AFL and maintenance of sinus rhythm. Bepridil also has a T-type calcium channel blocking effect, which can prevent electrical atrial remodeling for a long time compared with L-type calcium channel blockers.19) Recently, bepridil has been reported to suppress the shortening of atrial effective refractory period in a canine rapid atrial stimulation model.20) This reverse electrical remodeling effect may contribute to maintenance of sinus rhythm.

Efficacy of medical treatment for class I anti-arrhythmic drug-induced AFL

Recently, the efficacy of combination therapy with class I drugs and bepridil has been reported in patients with class I drug-induced AFL. Suzuki et al.21) has reported that 15 of the 16 patients (94%) with class I drug-induced AFL were restored to sinus rhythm 35 ± 5 days after additional administration of bepridil while class IC drugs were continued. In addition, 12 patients (75%) maintained sinus rhythm during the follow-up period of 21 ± 5 months without any serious complications. However, the combination therapy between class IC drugs and bepridil may increase the possibility of proarrhythmias. Our therapeutic strategy with bepridil after cessation of the class I agent is simple and is as effective as the previously reported combination therapy with class IC and bepridil; 88% of the patients restored sinus rhythm after an average of 21 days and sinus rhythm was maintained in 80% of the patients for an average of 23.6 months, and may lower the possibility of adverse effects. Bepridil has been reported to be effective for maintenance of sinus rhythm in patients with paroxysmal and persistent AF.8,9) Therefore, we propose bepridil as a first-line drug for class I antiarrhythmic drug-induced AFL. But an additional class I drug may be necessary in some patients.

Study limitations

First, our study included only a small number of patients and had no controls. We may have overestimated the efficacy of conversion to sinus rhythm by bepridil. In some patients, especially in patients with conversion to sinus rhythm within a week, class I drug-induced AFL may restore sinus rhythm only by cessation of the class I drug. We could not deny this possibility because we had no controls. A larger number of patients and controls are necessary to verify our results. Second, although sinus rhythm was maintained in most of the patients, paroxysmal AF may occur with some patients without any obvious symptoms. Anti-coagulant therapy with warfarin must be continued in all of our study patients even though sinus rhythm is maintained.

Conclusions

Bepridil treatment may be safe and effective for class I drug-induced AFL in patients with paroxysmal AF to restore and maintain sinus rhythm as an alternative therapy for catheter ablation. However, we should carefully monitor the QT interval during the bepridil treatment.

References
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