Pharmacological Conversion of Atrial Fibrillation in the Patients of Graves' Disease

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Background: Hyperthyroidism is one of the common causes of atrial fibrillation (AF), and AF is associated with increased morbidity and mortality due to thromboembolism. The sinus rhythm maintenance rate of hyperthyroidism-induced AF patients after conversion to sinus rhythm is excellent. The present study was undertaken to assess the efficacy and safety of bepridil, a multichannel blocker, in patients with hyperthyroidism-induced persistent AF.

Methods and Results: Sixty-two patients with hyperthyroidism-induced persistent AF were treated with bepridil. Oral bepridil therapy resulted in conversion to sinus rhythm in 32 (51.6%) of the 62 patients. There were no significant differences in clinical characteristics between the responders and non-responders. At the observation period of an average of 23.9 months, the sinus rhythm maintenance rate was found to be 81.3%. Adverse effects consisted of abnormal QTc prolongation in 3 patients and sinus bradycardia in 10 patients. There was one death in which a causal association with bepridil could not be ruled out.

Conclusions: Bepridil is as beneficial treatment to convert AF for the patients with hyperthyroidism-induced persistent AF as it is for the patients with AF due to other causes. However, bepridil should be used with caution to avoid serious side effects.

Key words: hyperthyroidism, Graves' disease, atrial fibrillation (AF), bepridil, cardioversion

INTRODUCTION

Atrial fibrillation (AF) is one of the common complications among the patients of hyperthyroidism, especially Graves' disease. The prevalence of AF in hyperthyroidism is reported from 2% to 20% [1–3]. In two thirds of those patients, AF spontaneously converts to sinus rhythm when their hyperthyroidism is controlled to normal thyroid function, while the other one third requires cardioversion [4].

According to many randomized controlled trials for the treatment of AF, rate control is more important than rhythm control to reduce the mortality rate of AF patients [5–7], irrespective of the etiology of their AF, although patients with AF have higher morbidity rate, mainly as a result of thromboembolism, than patients in sinus rhythm [8]. In general, the rhythm control might be more beneficial for the patients with AF, however, it is recommended the rate control for the patients with hyperthyroidism-induced AF because the hyperthyroidism is a controllable condition [9]. It is because that the sinus rhythm maintenance rate after cardioversion of hyperthyroidism-induced persistent AF is much higher than after cardioversion of AF caused by any other condition [10], including hypertension, cardiac valvular disease, and heart failure [1–4, 11], and the high long-term sinus rhythm maintenance rate after conversion of hyperthyroidism-induced persistent AF.

Disopyramide has been shown to restore hyperthyroidism-induced AF to sinus rhythm, however, the conversion rate was reported only 15% [2]. Bepridil hydrochloride is a diarylaminopropylamine derivative and a multichannel calcium blocker [12, 13], and it was initially introduced as an antianginal drug. Bepridil was later reported to exert antiarrhythmic effects that included restoration of AF to sinus rhythm [14], and it antiarrhythmic effects were found to be attributable to a lidocaine-like fast kinetic block of the inward sodium current, blockade of several outward potassium currents, and inhibition of sodium-calcium exchange [12].

Since there have been no reports of studies in which bepridil was used to treat hyperthyroidism-induced persistent AF, we reviewed the records of patients who had been treated with low dose bepridil therapy in order to assess its efficacy and safety for this condition.

METHODS

Patients

Sixty-two patients who present with AF in Graves' disease were treated with bepridil (100–200 mg/day)

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Table 1 Clinical characteristics of the patients (n = 62)

Characteristic	*Value*
Age (years)	
Mean ± SD	49.2 ± 11.6
Gender	
Female	29
Male	33
Duration of thyrotoxicosis (months)	
Median	17.1
Range	2.0–115.2
Duration of AF (months)	
Median	25.1
Range	3.6–80.7
Maximum serum FT3 level (pmol/L)	
Mean ± SD	28.0 ± 12.1
Maximum serum FT4 level (pmol/L)	
Mean ± SD	78.3 ± 34.3
Therapy for thyrotoxicosis (no. of patient)	
ATD only	37 (59.7%)
RI	22 (35.5%)
Surg	3 (4.8%)

Abbreviations: ATD, antithyroid drug; RI, radioiodine therapy;
Surg, subtotal thyroidectomy.
Duration of AF was calculated as the interval between the time AF was diagnosed andbepridil was started.

to induce conversion to sinus rhythm between September 2004 and December 2009 at Ito Hospital that specializes in the management of thyroid disease. We excluded patients who were in heart failure or had severe cardiac valvular regurgitation at the time bepridil therapy was started, and patients who were still in a subclinical hyperthyroid state (normal free triiodothyronine (FT3) and free thyroxin (FT4) levels, but low thyroid-stimulating hormone (TSH) levels) or had been in a euthyroid state for less than two months. The underlying cause of the hyperthyroidism was Graves' disease, and none of the patients had an autonomously functioning thyroid nodule or toxic multinodular goiter. All patients gave their informed consent including the benefits of reverting to sinus rhythm, the excellent sinus rhythm maintenance rate of hyperthyroidism-induced AF patients after conversion to sinus rhythm, and the adverse effects of Bepridil such as life-threatening arrhythmias.

Protocol

Oral bepridil therapy was started after the patient had been in euthyroid for at least two months, because spontaneous reversion to sinus rhythm is still expected in the early euthyroid period. All patients had been evaluated by means of thyroid function tests, an ECG, a chest X-ray, and a trans-thoracic echocardiogram. All patients were fully anticoagulated with warfarin, and their prothrombin time (INR: international normalization ratio) was maintained within the effective range (1.5–3.0) and were also treated with digoxin (0.125–0.25 mg/day). Their QTc interval and ST-T changes on the ECG, their serum electrolyte levels and thyroid function were checked before Bepridil was started at 100–200 mg/day and in every visit (2–4 week intervals) during treatment. Based on the results of previous studies showing that bepridil does not restore sinus rhythm rapidly and that restoration of sinus rhythm sometimes takes as long as 3 months [15], the patients were classified into responders and non-responders at the end of 3 months of treatment. After pharmacological conversion to sinus rhythm, the additional treatment for maintaining sinus rhythm was left to the attending physicians.

Statistical Analysis

The statistical analysis was performed with the JMP 8.0.2 software package (SPSS Inc., Chicago, IL). The means and standard deviation of continuous data were calculated and analyzed by a two-way analysis of variance. Continuous variables with a non-normal distribution were expressed as median values. If the linearity assumption was violated, the Spearman rank correlation test was used. The Mann-Whitney test or paired t-test was used for the comparisons, and P values < 0.01 were considered significant.

RESULTS

Table 1 summarizes the clinical characteristics of hyperthyroidism-induced AF patients. The hyperthyroidism had been managed by an individualized treatment regimen that conformed to widely accepted guidelines [16]. All 62 patients were treated with antithyroid drugs (methimazole or propylthiouracil). Twenty-two patients of 62 were with a combination of radioiodine (^{131}I) therapy and 3 patients of them were underwent subtotal thyroidectomy (Table 1) following administration of antithyroid drugs. The mean age of 62 patients were 49.2 ± 11.6 years old.

Table 2 Comparison between responders and non-responders to bepridil (n = 62)

Characteristic	*Bepridil*		*p-value*
	Responders (n = 32)	*Non-responders (n = 30)*	
Age (years)			
Mean ± SD	49.9 ± 12.5	48.4 ± 10.7	NS
Gender			
Female	14	15	NS
Male	18	15	
Duration of thyrotoxicosis (months)			
Median	11.6	21.3	NS
Range	3.2–78.1	2.0–115.2	
Duration of AF (months)			
Median	17.5	26.6	NS
Range	3.6–80.7	7.4–64.0	
Maximum serum FT3 level (pmol/L)			
Mean ± SD	27.4 ± 12.2	29.0 ± 12.2	NS
Maximum serum FT4 level (pmol/L)			
Mean ± SD	78.6 ± 35.5	78.0 ± 33.7	NS
Echocardiographic parameters			
LVEF (%) Mean ± SD	64.9 ± 8.2	62.8 ± 8.8	NS
LAD (mm) Mean ± SD	40.6 ± 6.2	39.9 ± 5.3	NS
Heart rate (bpm)			
Before Mean ± SD	80.8 ± 20.6	72.7 ± 18.5	NS
After bepridil Mean ± SD	59.7 ± 10.8	64.2 ± 14.4	0.0319
QTc interval (ms)			
Before Mean ± SD	397.4 ± 25.5*	392.8 ± 20.8*	NS
After bepridil Mean ± SD	434.5 ± 51.4*	414.7 ± 27.1*	NS
ΔQTc (ms)			
Median	39.0	29.0	0.168
Range	- 58–153	- 44–76.0	
Duration of follow up (months)			
Median	26.9	34.5	NS
Range	3.7–55.9	0.6–74.8	NS

Abbreviations: LVEF, left ventricular ejection fraction; LAD, left atrial diameter.
*$p < 0.0001$ by the paired *t*-test, before vs. after bepridil.

1) Conversion Rate

AF converted to sinus rhythm in response to treatment with bepridil alone in 32 (responders) of the 62 patients with persistent AF, and thus the bepridil cardioversion rate was 51.6%. The median interval between the start of bepridil therapy and sinus rhythm restoration was 28 days (range 15.5–50.8). Of the 30 non-responders at 3 months after the start of bepridil, 5 were treated with a disopyramide/cibenzolinein combination plus bepridil for an additional month, and sinus rhythm was restored in 3 of them.

2) Comparison between the Clinical Characteristics of the Responders and Non-responders

Table 2 shows the clinical characteristics of the responders and non-responders to treatment with bepridil alone. The difference in age between the two groups was not significant, and the proportions of each sex in the two groups were similar. There were no significant differences in duration of hyperthyroidism, duration of AF, or maximum serum FT3 and FT4 levels between the responders and non-responders. There were no significant differences in LVEF (left ventricular ejection fraction), LV (left ventricle) size, or LAD (left atrium diameter) between the responders and non-responders, and there were no significant differences between the two groups in the presence or severity of mitral, aortic, or tricuspid regurgitation based on the echocardiography findings.

The QTc intervals of the two groups before the start of bepridil were comparable. The comparison between the QTc intervals before and after the completion of bepridil therapy showed that the QTc intervals had become significantly longer in both groups.

The average heart rates in the two groups before the start of bepridil therapy were comparable, but at the completion of bepridil therapy the average heart rate in the responder group had decreased significantly in comparison with the non-responder group.

The plasma N-terminal pro B-type natriuretic

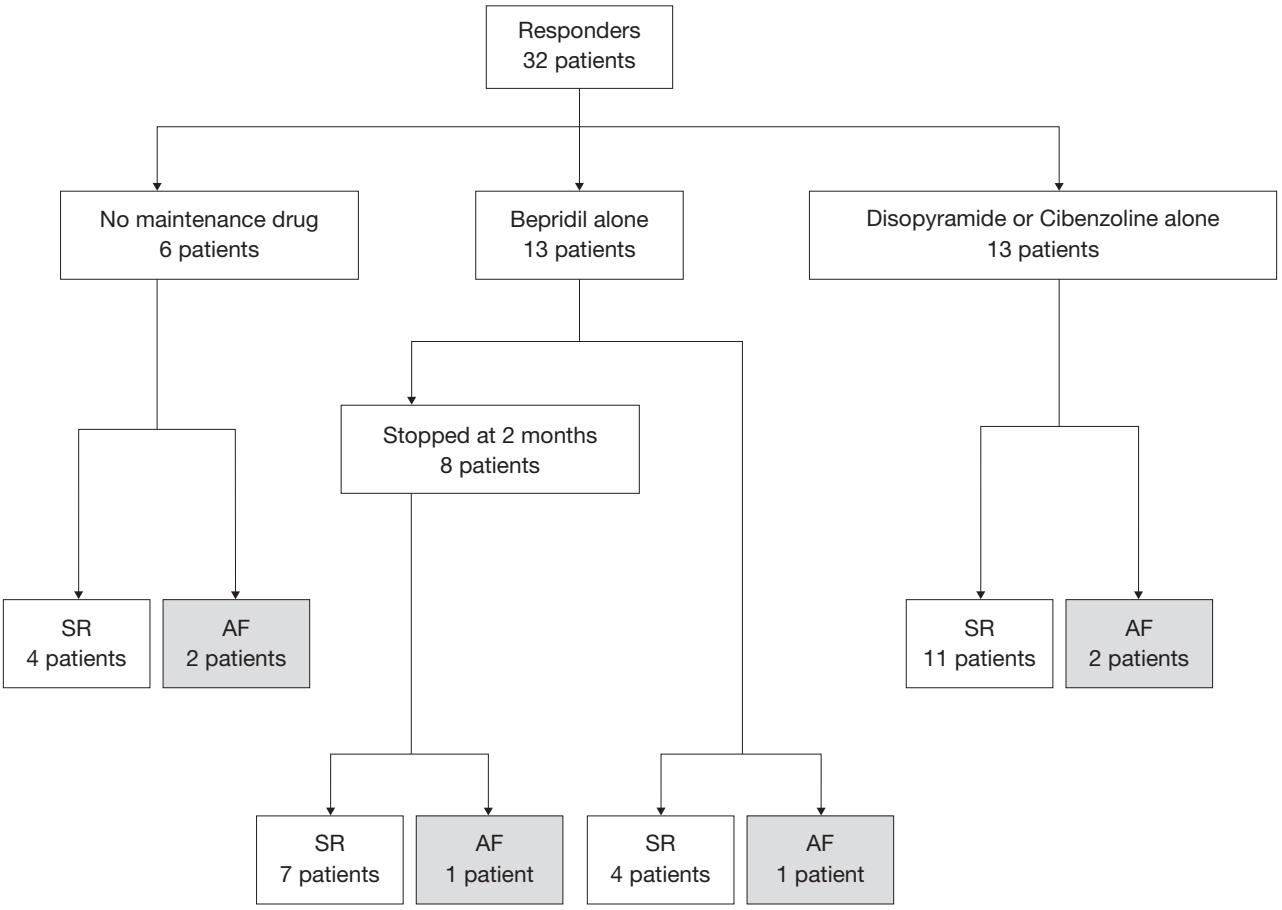

Fig. 1 Sinus rhythm maintenance therapies and outcome
Abbreviations: SR, sinus rhythm; AF, atrial fibrillation.

peptide (NT-proBNP) levels of the two groups did not differ significantly before the start of bepridil therapy. However, the NT-proBNP level decreased after restoration of sinus rhythm in the responder group (from a median concentration of 449 pg/ml [range 250.4–679.2] to 52 pg/ml [38–114]). In contrast, the NT-proBNP level remained high (441.9 ± 232.0 pg/ml) at the completion of bepridil therapy in the non-responder group.

3) Maintenance of Sinus Rhythm

The maintenance therapies used to prevent recurrence of the AF varied (Fig. 1). In 6 patients bepridil was discontinued soon after sinus rhythm was restored. Thirteen patients were continued on bepridil alone, either at the same or a lower dose, even after sinus rhythm had been restored. In 8 of these 13 patients, bepridil was stopped two months after conversion to sinus rhythm, and the other 5 patients were taking bepridil at the time of the most recent follow-up examination. The 13 other responders were treated with disopyramide (200–300 mg/day) or cibenzoline (200 mg/day) alone as the maintenance drug instead of bepridil. Eleven out of these 13 patients who were treated with disopyramide or cibenzoline remained in sinus rhythm, but AF recurred in the other 2 patients.

Sinus rhythm was maintained during the average follow-up period of 21.9 ± 12.8 months in 26 (81.3%) of the 32 responders, including in the 13 patients who were not being treated with any maintenance drug at the time of the most recent examination. The rates of sinus rhythm maintenance in the responder group according to the Kaplan-Meier method are shown in Fig. 2, and the rate was 93.5% at one year, 89.3% at 2 years, 72.2% at 3 years, and 61.8% at 4 years.

4) Adverse Effects of Treatment

The QTc interval increased to more than 500 msec in 3 patients (from 419, 405, and 437 msec to 547, 558, and 587 msec, respectively) when sinus rhythm was restored. No signs of tachyarrhythmias or bradycardia were detected in these three patients. None of the patients' serum potassium level decreased below 3.5 mEq/dl. Ten patients exhibited sinus bradycardia (heart rate below 50 bpm) when sinus rhythm was restored, but 9 of them were asymptomatic. The other patient, a 35-year-old male, experienced dizziness and had a heart rate of 38 bpm when sinus rhythm was restored. Since he was being treated with atenolol (a β-blocker) and digoxin for tachycardia during the AF, bepridil and atenolol were stopped immediately when he complained of dizziness. His heart rate then became normal, and the dizziness resolved. A 50-year-old female patient was found dead at home on day 16 of bepridil (200 mg) therapy. The patient had grade 2 mitral regurgitation and grade 1 tricuspid regurgitation but a normal LV ejection fraction. Her LV size was 51 mm, and her left atrial size was 41 mm. The patient's PT (INR) had been maintained within the therapeutic range, and the QTc interval prior to the start of bepridil therapy (369 msec) was within the normal range. The QTc interval after the start of bepridil therapy was

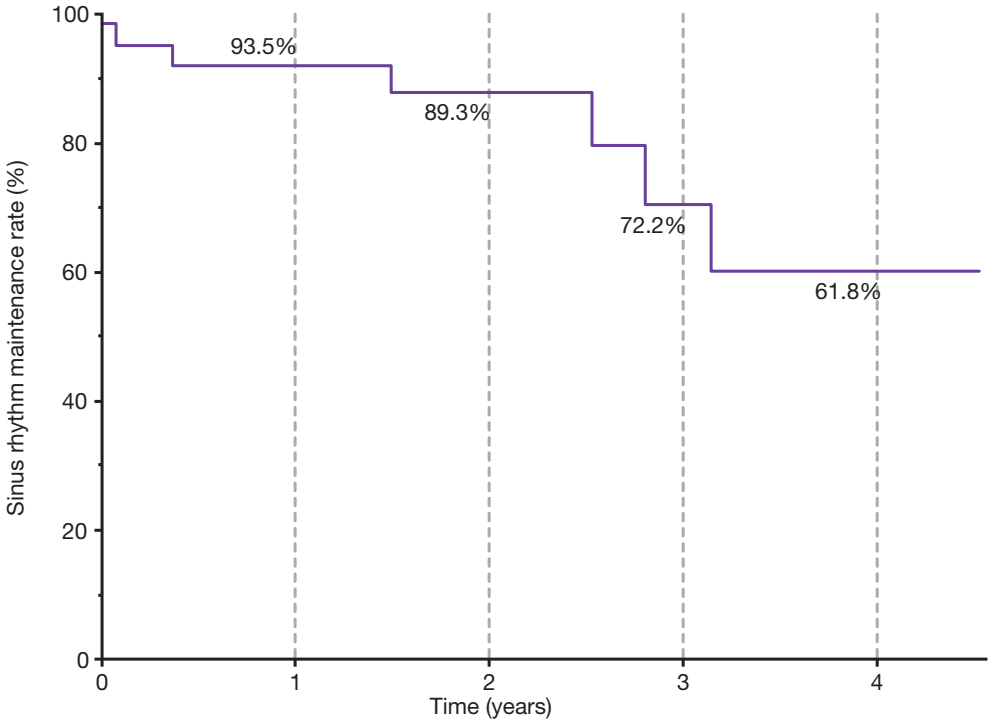

Fig. 2 Kaplan-Meier plot of sinus maintenance in the responders to bepridil (n = 32)

unknown, because she died before the first follow-up date. Although an autopsy was not performed and the cause of death is unknown, a bepridil-related event cannot be ruled out.

None of the patients experienced any other adverse effects, such as gastrointestinal discomfort or liver or kidney damage. No thromboembolic or bleeding events were observed during the study.

DISCUSSION

Bepridil was first developed as an antianginal drug, but after it was reported to have antiarrhythmic effects that included restoration of AF to sinus rhythm [17], bepridil attracted attention as a means of pharmacotherapy for AF [15, 18–21].

Earlier studies of treatment with a high dose (600 mg/day) in the United States and Europe showed that it was effective, but because it induced QT prolongation and life-threatening arrhythmias, including torsades de pointes, the risks outweighed the benefits [22]. However, several recent Japanese clinical studies found that low-dose bepridil (100–200 mg/day) is effective in converting AF to sinus rhythm without any serious arrhythmogenic adverse effects [15, 19, 23], and the Japanese Circulation Society has listed bepridil as an effective drug in its new guidelines for the pharmacotherapy of AF [9].

[9]Pharmacotherapy of AF has an advantage over electrical cardioversion and the catheter ablation method, because it can be used on an outpatient basis. This advantage is the reason why we started to use bepridil to treat patients with hyperthyroidism-induced persistent AF. The conversion rate with bepridil in this study (51.6%) was much higher than the conversion rate of 16% (17/106 patients) with disopyramide in a previous study conducted on patients with the same clinical background of post-thyrotoxicosis persistent AF [2], thereby indicating that bepridil is more effective for converting AF to sinus rhythm.

It is well known that as the duration of AF grows longer, the spontaneous conversion rate declines and the recurrence rate after conversion rises. However, bepridil converted AF to sinus rhythm very effectively even in patients with longstanding AF, especially in patients whose AF was secondary to thyroid dysfunction. The fact that the duration of AF in the responder group and non-responder group in the present study did not differ significantly may mean that the efficacy of bepridil is great enough to overcome the influence of the duration of AF. Thyroid function and cardiac conditions did not differ significantly between the two groups, suggesting that they were not factors that interfered with the efficacy of bepridil.

Various sinus rhythm maintenance regimens were used by the attending physicians in this study, mainly because no antiarrhythmic drugs have been shown to be adequately effective as a maintenance drug. Despite the variety of treatments, including no maintenance drug, the overall AF recurrence rate in the present study was very low (18.7%) compared to the AF recurrence rate in the J-BAF study (75.0–91.7%) [15]. This high sinus rhythm maintenance rate (81.3%) in comparison with the maintenance rates after treatment of AF due to other causes indicates that rhythm control is the optimal choice of treatment for hyperthyroidism-induced persistent AF [9].

B-type natriuretic peptide (BNP) and NT-proBNP are released by the myocardium in response to increased wall tension, and their plasma levels are good markers of heart failure [24, 25]. Plasma BNP and NT-proBNP levels have also been shown to be mildly elevated in patients with AF who do not have signs of heart failure, and in thyrotoxicosis patients [26]. The NT-proBNP level before the start of bepridil therapy

was moderately high in both responders and non-responders. This NT-proBNP level is slightly higher than the levels reported in patients with AF alone and in patients with hyperthyroidm alone. Thus, the combination of AF and hyperthyroidm may have synergistically caused the higher elevation in our population, and the reduction in plasma NT-proBNP levels to within their normal range after the return to sinus rhythm suggests that atrial function became normal and that the influence of the post-hyperthyroidism state on NT-proBNP levels eventually disappeared over time.

Prolonged QTc intervals were observed after bepridil treatment in both groups. Although the differences in delta QTc (post QTc – pre QTc) between the responder group and non-responder group was not statistically significant, the delta QTc values tended to be higher in the responder group than in the non-responder group. The percentage of patients who developed sinus bradycardia was higher in the responder group, suggesting that the concentration of bepridil in the myocardium of the responder group might have been higher than in the non-responder group and that an effective concentration of bepridil in the myocardium might be necessary to restore AF to sinus rhythm.

Patients whose sinus rhythm is maintained have the benefit of being free from thromboembolism and no longer requiring anticoagulation therapy, which entails the risk of bleeding. However, because of the high risk of arrhythmias, bepridil therapy requires cautious administration, starting at a low dose, and periodic ECG examinations.

CONCLUSIONS

This study showed that bepridil converted hyperthyroidism-induced persistent AF to sinus rhythm as much as it does after a long duration of AF due to other causes, and the sinus rhythm maintenance rate was very high. Bepridil is very benificial medicine for the patient of hyperthyroidism-induced AF, however, it should be used with caution, and frequent or continuous ECG monitoring is necessary, to avoid serious side effects.

DISCLOSURE STATEMENT

The authors declare that they had no conflicts of interest in regard to this study.

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