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Original article

Impact of chronic use of cibenzoline on left ventricular pressure gradient and left ventricular remodeling in patients with hypertrophic obstructive cardiomyopathy

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ABSTRACT

Background: Cibenzoline, a class Ia antiarrhythmic drug, is useful for reducing the left ventricular pressure gradient (LVPG) in patients with hypertrophic obstructive cardiomyopathy (HOCM). However, chronic effects of cibenzoline on LVPG and left ventricular (LV) remodeling are unknown.
Methods: Forty-one patients with HOCM participated in this study. Echocardiographic, electrocardiographic, and brain natriuretic peptide (BNP) data collected before and after cibenzoline treatment were compared. From the relation between LVPG and plasma concentration of cibenzoline, an efficacious plasma concentration of cibenzoline was estimated.
Results: The mean follow-up period was 74.2 ± 47.1 months. The LVPG decreased from 104.8 ± 62.6 mmHg to 27.6 ± 30.5 mmHg ($p < 0.0001$). The LV end-diastolic dimension increased from 42.8 ± 5.8 mm to 46.2 ± 5.4 mm ($p < 0.0001$), but neither LV end-systolic dimension nor LV fractional shortening changed significantly. The left atrial dimension decreased from 40.0 ± 4.7 mm to 36.2 ± 5.1 mm ($p < 0.0001$). The E-wave velocity/A-wave velocity ratio increased, early diastolic annular velocity (Ea) increased, and E/Ea ratio decreased. The interventricular septal wall thickness, LV posterior wall thickness, the Sokolow-Lyon index, and the depth of negative T wave decreased. The heart rate-corrected QT interval was shortened. Plasma BNP level decreased from 418.8 ± 423.7 pg/ml to 213.7 ± 154.1 pg/ml ($p < 0.02$). The safe and efficacious plasma concentration of cibenzoline was between 300 ng/mL and 1500 ng/mL.
Conclusions: Long-term treatment with cibenzoline attenuated LVPG, improved LV diastolic dysfunction, and induced LV hypertrophy regression in patients with HOCM without causing serious complications.
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Introduction

Sudden cardiac death and congestive heart failure are the most serious complications of hypertrophic cardiomyopathy (HCM). Beta-blockers and calcium antagonists are reported to be of little use in preventing these complications, especially regarding the transition from typical HCM to end-stage heart failure [1]. To prevent the serious complications of HCM, 2 essential cardiac disorders, left ventricular (LV) hypertrophy and LV diastolic dysfunction, must be corrected. In addition, patients with hypertrophic obstructive cardiomyopathy (HOCM) should be carefully monitored for abnormal LV pressure gradient (LVPG) characteristics, and clinicians should take action as necessary to correct this problem.

In 1982, Pollick reported for the first time that disopyramide, a class Ia antiarrhythmic drug, was useful for the attenuation of LVPG [2]. The potent negative inotropic effect of disopyramide is believed to reduce LVPG [3]. Another class Ia antiarrhythmic drug, cibenzoline, has also been found useful for reducing LVPG [4,5]. Unlike disopyramide, cibenzoline has little anticholinergic activity [6], which makes it suitable for long-term use. In addition, it has been shown that cibenzoline improves LV diastolic dysfunction in patients with both HOCM and hypertrophic nonobstructive

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cardiomyopathy (HNCM) [7]. A prolonged QT interval is a major electrocardiographic characteristic of patients with HCM. Disopyramide and cibenzoline are among the drugs that may induce such prolongation, increasing the risk of torsade de pointes.

Reports on the long-term effects of prolonged medical treatment on LV function and LV remodeling are rare. To examine whether cibenzoline remains effective during prolonged use, in this study, we assessed the changes in LVPG, LV functions, and LV hypertrophy in patients with HOCM. We also measured QT interval changes to determine the optimal safe long-term cibenzoline dose.

Methods

Study patients

This study was approved by the Human Investigations Committee of Ehime University Hospital (No. 14–25 in 2002) and Uwajima City Hospital (No. 24 in 2003). All 41 patients with HOCM who were treated with cibenzoline for more than 12 months participated in this study after providing informed consent. All patients had LVPG exceeding 30 mmHg without provocation. Of 41 patients with HOCM (21 women and 20 men), 24 had subaortic obstruction, and 17 had mid-ventricular obstruction. Patients who had atrial fibrillation [8], a history of heart failure, and plasma creatinine levels greater than 1.2 mg/dl were excluded from this study. Before cibenzoline treatment, 35 patients were already receiving beta-blockers and 28 patients were receiving calcium antagonists. The doses of beta-blockers and calcium antagonists remained unchanged during the study. Body surface area (BSA) was calculated in all patients.

Study protocol

Before the oral administration of cibenzoline, baseline echocardiographic and electrocardiographic parameters were measured. To estimate the effect of long-term cibenzoline on LV parameters, we performed blood sampling to measure the plasma concentration of cibenzoline between April 2010 and March 2013. Blood sampling was performed 2 h after oral administration, when the maximal plasma concentration was expected [9]. Electrocardiographic and echocardiographic studies were performed immediately after blood sampling. In addition, brain natriuretic peptide (BNP) was measured before and after the administration of cibenzoline in 19 patients.

We selected LVPG as a surrogate marker for cibenzoline's effectiveness. Patients were divided into 2 groups based on their LVPG response to cibenzoline. In group A, LVPG at the chronic treatment stage was <50% of the initial LVPG, whereas in group B, LVPG was >50%. In group B, an additional 100 mg dose of cibenzoline was administered in the morning, and cibenzoline plasma concentration and LVPG measurements were repeated approximately 1 month later.

Dose of cibenzoline

Since the effect of cibenzoline is short acting, it was administered 3 times per day: after breakfast, at approximately 14:00 h, and at approximately 21:00 h. Since cibenzoline decreases plasma sugar level [10], cibenzoline was administered twice daily to patients with fasting plasma sugar levels <70 mg/dL. The mean dose of cibenzoline at the start of the study was 293 ± 26 mg/day.

M-mode and Doppler echocardiography

Echocardiographic studies were performed with a SEQUIA-512 (ACUSON Inc., Mountain View, CA, USA) or ProSound II SSD-6500SV (Hitachi-Aloka Inc., Tokyo, Japan) ultrasound system. According to the American Society of Echocardiography's criteria [11], LV dimensions at end-diastole and end-systole, interventricular septal wall thickness, and LV posterior wall thickness were measured. Fractional shortening was calculated, and left atrial dimension was measured. The LVPG was measured from continuous-wave Doppler recordings of the LV outflow and mid-ventricular tract [4,5]. Peak E-wave and peak A-wave velocities and their ratio were measured. In 30 patients, the early diastolic annular velocity (Ea) was measured by tissue Doppler, and E/Ea was calculated [12].

Electrocardiography

Heart rate was determined from electrocardiogram. To estimate the grade of LV hypertrophy, the Sokolow-Lyon index (SV1 + RV5) [13] and maximal depth of negative T wave were measured on a 12-lead electrocardiogram. The QT interval was measured, and heart rate-corrected QT interval (QTc) was calculated according to Bazett's formula [14]: $QTc = QT/\sqrt{RR}$.

Statistical analysis

All values are expressed as mean ± standard deviation. Data obtained before and after administration of cibenzoline were compared using Student's *t*-test for paired samples. A value of $p < 0.05$ was considered statistically significant.

Results

Follow-up periods

The mean patient age at the start of this study was 67 ± 12 years. The mean follow-up period was 74.2 ± 47.1 months (range: 14–228 months). The mean BSA value was 1.64 ± 0.18. The hemodynamic results are summarized in Table 1.

Effect of cibenzoline on LVPG and plasma concentration

Fig. 1A illustrates all patients' LVPG changes. In most patients, LVPG markedly decreased (group A), except for 6 individuals who showed a poor response (group B). As shown in Fig. 1B, the plasma concentration of cibenzoline was significantly higher in group A than in group B. The plasma concentration in group B increased from 304.4 ± 238.8 ng/mL to 920.0 ± 828.5 ng/mL following the administration of an additional 100 mg of cibenzoline. This resulted in a significant reduction in LVPG values as shown in Fig. 1C. Fig. 2 shows the echocardiographic changes resulting from cibenzoline therapy in a patient with this study's highest LVPG, decreasing from about 300 mmHg to 30 mmHg, together with an improved transmitral Doppler flow pattern.

Change in plasma level of BNP

Plasma level of BNP decreased from 418.8 ± 423.7 pg/ml to 213.7 ± 154.1 pg/ml ($p < 0.02$) after the treatment with cibenzoline.

Effect of cibenzoline on LV dimensions and fractional shortening

As shown in Fig. 3A, LV end-diastolic dimension significantly increased after cibenzoline administration, whereas the LV end-systolic dimension and fractional shortening remained unchanged (Table 1). These changes showed no differences between patients with subaortic obstruction and mid-ventricular obstruction (Table 1).

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