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SHORT COMMUNICATION

Incidence and outcomes of bepridil-induced interstitial pneumonia

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KEYWORDS
Bepridil;
Drug-induced interstitial pneumonia;
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Summary
Background: The incidence of bepridil-induced pulmonary toxicity, such as interstitial pneumonia, is still unknown. The aim of the present study was to evaluate the incidence of bepridil-induced pulmonary toxicity.
Methods and results: A total of 253 patients treated with bepridil between January 2009 and January 2011 were retrospectively evaluated. Eight out of the 222 evaluable patients (male/female: 5/3, age range: 64–97 years, average age: 80.5 years, median age: 81.0 years) showed bepridil-induced pulmonary toxicity.
Conclusions: The incidence of bepridil-induced pulmonary toxicity was 3.60% in our study population.

Introduction

Bepridil inhibits the Na^+, K^+ and Ca^{2+} channels in cardiomyocytes, and exerts antiarrhythmic effects by reducing the maximum depolarization rate of the atrial muscles, atrioventricular node, ventricular muscles, etc. Bepridil has been used for the treatment of atrial fibrillation, ventricular tachyarrhythmia and angina pectoris. There have

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been several reported cases of bepridil-induced pulmonary toxicity [1–3]; however, the incidence of bepridil-induced pulmonary toxicity is still unknown. The aim of the present study was to evaluate the incidence of bepridil-induced pulmonary toxicity.

Methods

Patients

Two hundred fifty-three patients treated with bepridil between January 2009 and January 2011 at Saiseikai Yamaguchi General Hospital were retrospectively evaluated.

Methods

The diagnosis of bepridil-induced pulmonary toxicity was made according to the following criteria originally developed for the clinical diagnosis of amiodarone-induced pulmonary toxicity [4]. Any two of the following findings: (1) new or worsening symptoms; (2) new abnormalities or worsening of chest roentogenograms; (3) a decline of at least 15% in the diffusing capacity for carbon monoxide or the total lung capacity, with the exclusion of other diagnostic possibilities (especially occult congestive heart failure), together with a reasonable constellation of symptoms or findings consistent with the diagnosis. The incidence of bepridil-induced pulmonary toxicity in the 222 evaluable patients who had been treated with bepridil for at least one year and who underwent chest X-rays and/or chest computed tomography scans pre- and post-bepridil treatment were analyzed with the clinical data by three specialized respirologists. The outcomes and treatment of the patients with bepridil-induced pulmonary toxicity were also evaluated.

Table 1 Clinical characteristics of the study patients.

n	222
Male/Female	157/65
Age, years	73.9 ± 11.0
Heart disease	
Atrial fibrillation	140
Ischemic heart disease	119
Ventricular tachycardia	40
Valvular heart disease	23
Chronic heart failure	158
Cardiomyopathy	4
Comorbidities	
Hypertension	173
Diabetes mellitus	74
Concomitant drugs	
ACEI/ARB	111
Calcium-channel blocker	77
α,β-blocker	116
Diuretic	65
Aldosterone antagonist	35
Digoxin	14
Statin	53
Uricosuric agent	31
Antiplatelet agent	175
Radiographic findings	
Interstitial pneumonia	0

Results

The average (median) age of the 222 evaluated patients was 73.9 (76) years old, and the ratio of males/females was 157/65 (Table 1). Eight cases (male/female: 5/3, age range: 64–97 years, average age: 80.5 years, median age: 81.0 years) showed bepridil-induced pulmonary toxicity, making the incidence 3.60% in our population. All eight patients demonstrated no remarkable abnormal chest X-ray findings before the start of bepridil administration. The latency to developing pulmonary toxicity after starting bepridil treatment ranged from 14 days to 10 months (average: 152 days, median: 195 days). All eight cases discontinued bepridil administration, and six out of these eight patients received corticosteroids (starting dose of prednisolone: 20–500 mg/day) in addition to the cessation of bepridil. All eight cases showed improvement of the pulmonary toxicity after the cessation of bepridil. In addition, the drug lymphocyte stimulation test (DLST) was performed in three out of the eight patients, and all three of these patients showed negative results.

Discussion

This is the first study reporting the incidence of bepridil-induced pulmonary toxicity, and the incidence was 3.60% (eight out of 222 cases) in our patient population. Six prior cases of bepridil-induced pulmonary toxicity had been reported in the English literature [2], and one case of acute interstitial pneumonia had also been reported as a side effect in a randomized study of amiodarone and bepridil out of the 20 patients in the bepridil-arm [5]. The diagnosis of drug-induced pulmonary toxicities, including those due to bepridil, is associated with uncertainties, largely because of the restrictions regarding the re-challenge of patients, and the diagnostic criteria we use are generally non-specific. Therefore, the incidence in the present study can only be considered a loose approximation at best.

We next compared the cases in the present study with the other six reported cases of bepridil-induced interstitial pneumonia (Table 2). All of the previously reported cases were elderly males, had received doses ranging from 150 mg to 400 mg, had generally received treatment for two weeks to two months prior to the development of symptoms, but had developed symptoms up to 226 days after beginning the treatment. Similar to the previous cases, most of our patients were over 80 years old. In contrast, our patients included three females out of the eight total cases, and this is the first report of a female with bepridil-induced pulmonary toxicity. Three patients showed symptoms within two weeks after starting bepridil administration in our present study, but five patients demonstrated symptoms more than six months after starting the treatment, and a longer duration of time to the development of the pulmonary toxicity of bepridil was suggested in our study than was reported previously.