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Original Article

Assessment of drug-induced proarrhythmias due to pilsicainide in patients with atrial tachyarrhythmias

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ABSTRACT

Background: Pilsicainide, a pure Na^+ channel blocker, is a popular antiarrhythmic drug for the management of atrial tachyarrhythmias (AT), in Japan. However, serious drug-induced proarrhythmias (DIPs) may unexpectedly occur. We assessed the clinical background of AT patients presenting with DIPs caused by pilsicainide.

Methods: This study retrospectively enrolled 874 consecutive patients (543 men, 63.6 ± 15.3 years old, and 57.9 ± 16.5 kg of body weight), who were orally administered pilsicainide for AT management. We evaluated the relationship between DIPs and serum pilsicainide concentration, renal dysfunction (estimate glomerular filtration rate, eGFR), and electrocardiogram (ECG) parameters.

Results: Among the patients, 154 (17.6%) had renal dysfunction (eGFR < 50 mL/min), including 12 (1.4%) on hemodialysis. DIPs were present in 10 patients (1.1%): all had renal dysfunction, and one was on hemodialysis. The eGFR in DIP patients was significantly lower than that in the non-DIP patients (32.2 ± 15.1 *vs.* 68.4 ± 22.1 mL/min, $p < 0.001$). Among the clinical factors measured, only renal dysfunction (eGFR < 50 mL/min) was significantly associated with DIPs (OR 44.6; 95% CI 5.61–335.0, $p < 0.001$). Interestingly, among the ECG parameters, the corrected QT (QTc) intervals in DIP patients were longer than those in non-DIP patients (555.8 ± 37.6 *vs.* 430.7 ± 32.6 ms, $p < 0.001$). As pilsicainide concentration increased, both QRS and QTc intervals prolonged. The latter were improved by discontinuing pilsicainide administration, and additional treatments.

Conclusions: DIPs caused by pilsicainide administration were strongly associated with renal dysfunction. Hence, confirmation of renal function would be necessary prior to and/or during the pilsicainide administration.

1. Introduction

Pilsicainide has a pure Na^+ channel blocking action with slow recovery pharmacokinetics and, according to the Vaughan Williams classification, is considered an IC antiarrhythmic drug. In Japan, pilsicainide is a popular antiarrhythmic drug for the management of atrial tachyarrhythmias (AT), and in particular atrial fibrillation (AF) [1,2]. Pilsicainide is recognized as safe and easy-to-use. However, serious drug-induced proarrhythmias (DIPs) may unexpectedly occur [3,4]. There are only a few well-organized reports describing the association between DIPs and pilsicainide administration [3,4].

We assessed the complication rate of DIPs caused by pilsicainide, and the relationship between DIPs and the drug serum concentration, renal dysfunction, including the estimated glomerular filtration rate (eGFR), and 12-lead electrocardiogram (ECG) parameters, such as the QRS and corrected QT (QTc) intervals after pilsicainide administration.

2. Materials and methods

2.1. Study population

This is a retrospective study. Initially, 905 consecutive patients were enrolled who were orally administered pilsicainide for the management of ATs such as AF, supraventricular tachycardia (SVT), and frequent atrial premature contractions (APCs), between

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Table 1
Patients' characteristics.

Male (%)	543 (62.1)
Age (years)	63.6 ± 15.3
Height (cm)	157.7 ± 27.2
Weight (kg)	57.9 ± 16.5
BMI (kg/m^2)	22.7 ± 3.8
Pilsicainide toxicity (%)	10 (1.1)
Serum Cr (mg/dL)	0.95 ± 0.86 (0.83)
eGFR (mL/min)	68.0 ± 22.3
eGFR < 50 (%)	154 (17.6)
Hemodialysis (%)	12 (1.4)
HT (%)	393 (45.0)
DM (%)	132 (15.1)
DL (%)	196 (22.4)
IHD (%)	112 (12.8)
Stroke (%)	73 (8.4)
CHF (%)	165 (18.9)
Pilsicainide mean dose (mg/day)	89.4 ± 44.7
Pill in the pocket (%)	310 (35.5)
Concomitant drugs	
β-blocker (%)	170 (19.5)
CCB (%)	171 (19.6)
ARB (%)	275 (31.5)
ACE-I (%)	46 (5.3)
Diuretics (%)	124 (14.2)
Other AADs (%)	113 (12.9)

BMI, body mass index; DM, diabetes mellitus; Cr, creatinine; CKD, chronic kidney disease; CHF, chronic heart failure; IHD, ischemic heart disease, HT, hypertension; DL, dyslipidemia lipidemia; CCB, calcium channel blocker; ARBs, angiotensin receptor blockers; ACE-I, angiotensin-converting enzyme inhibitor; AAD, antiarrhythmic drug. Data are expressed as the mean ± SD, median, or numbers (%).

January 2005 and December 2014, at our institute. Thirty-one (3.4%) patients whose eGFR was not assessed were excluded; thus, 874 patients were finally enrolled into the study. Their characteristics are outlined in Table 1.

2.2. Ethical considerations and Institutional Review Board approval

The study protocol was approved by the Institutional Review Board (IRB) of the Toho University Medical Center Omori Hospital (approval number: 27-13), on May 13, 2015. All patients signed an informed consent form for the study protocol.

2.3. Administration of pilsicainide

Pilsicainide was used continuously or temporarily for the management of tachyarrhythmias. The administration of pilsicainide commonly started at 75–150 mg/day, and the dosage was determined by the age, weight, or clinical characteristics of the patients. In patients who used pilsicainide temporarily, the dosage begun at 25–100 mg/day. The patients underwent follow-up reviews every 1–3 months, and the presence of symptoms, physical examinations, 12-lead ECGs, and blood tests were assessed. However, patients who received pilsicainide temporarily did not undergo follow-up reviews, and were examined only once, or a few times, after the drug administration.

2.4. Definition of DIP

According to the definition of DIP due to pilsicainide, the patients had to meet the following criteria: (1) proarrhythmias, such as life-threatening arrhythmias (bradycardia or ventricular tachycardia/fibrillation), were caused by the drug; (2) ECG abnormalities were not caused by other etiologies; and (3) discontinuing the drug and having treatment improved ECG abnormalities. Regarding pilsicainide levels, although the effective concentration is known, the precise toxic threshold is generally unclear. The serum concentration of pilsicainide was determined using high performance liquid chromatography (HPLC).

2.5. Assessment of ECG parameters

The 12-lead ECGs were recorded by electrocardiography (Nihon Kohden, Tokyo, Japan). The QRS, JT, and QT interval (from the onset of the QRS complex to the end of the T wave) were measured automatically. However, we visually assessed whether the parameters measured were correct. The QTc interval adjusted the QT interval correctly by using the Bazett's formula: $QTc = QT/(RR)^{1/2}$, where QTc is the corrected QT interval, QT is the measured QT interval, and RR is the measured RR interval.

2.6. Statistical analysis

All continuous data were expressed as mean ± standard deviation, medians (quartile: 25–75%), or numbers (expressed as percentage, %). Comparisons between groups were analyzed using univariate (unpaired Student's *t*-test and Fisher's exact test) and multivariate analyses using a logistic regression model. A p value of < 0.05 was considered statistically significant. All statistical analyses were performed using the R commander software, version 1.24 [5].

3. Results

3.1. Baseline characteristics

The patients' mean age was 63.6 ± 15.3 years, 543 (62.1%) were male, and the body mass index (BMI) was 22.7 ± 3.8 kg/m^2. AF occurred in 677 patients (77.5%), SVT in 87 (10.0%), frequent APCs in 56 (6.4%), undetermined arrhythmias with palpitations in 10 (1.1%), and other forms of arrhythmia in the remaining 44 patients. The mean pilsicainide dose administered was 89.4 ± 44.7 mg/day, and 310 patients (35.5%) received pilsicainide temporarily. The mean eGFR was 68.0 ± 22.3 mL/min; 154 patients (17.6%) had an eGFR of < 50 mL/min, and 12 (1.4%) were on hemodialysis. DIPs were detected in 10 patients (1.1%). These baseline characteristics are listed in Table 1.

Out of 874 patients administered with pilsicainide, the drug serum concentration was assessed only in 202 (23.1%). Fig. 1 shows the distribution of pilsicainide serum concentration according to the dose administered.

3.2. Risk factors of DIP

In DIP patients, the eGFR was significantly lower than that in non-DIP patients (32.2 ± 15.1 *vs.* 68.4 ± 22.1 mL/min, $p < 0.001$, Table 2). Although clinical factors, such as age, renal dysfunction (eGFR < 50 mL/min), use of angiotensin receptor blockers (ARBs), and diuretics had a significant association with DIPs, a multivariate analysis showed that only renal dysfunction (eGFR < 50 mL/min) was significantly associated with DIPs (OR 44.6; 95% CI 5.61–335.0, $p < 0.001$, Tables 2 and 3).

3.3. Characteristics and follow-up of DIP patients

Among the 874 patients, DIPs were observed in 10 (1.1%). All DIP patients had AF, and they all displayed renal dysfunction. The pilsicainide serum concentrations were high with only one exception. The serum potassium level was between 3.1 and 7.2 mM. The 10 DIP patients' characteristics are listed in Table 4.

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