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Case Report

Normal dose of pilsicainide showed marked negative inotropic effects in a patient who had no underlying heart disease



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ABSTRACT

We report the case of an otherwise healthy 64-year-old female who developed cardiopulmonary arrest after the administration of pilsicainide for treatment of paroxysmal atrial fibrillation. She had had an episode of paroxysmal atrial fibrillation, but no liver dysfunction, renal dysfunction, or echocardiographic abnormality before her admission. On the day of admission and the following day, 50 mg of pilsicainide was administered intravenously over 10 min (total 100 mg). Shortly after the second injection, she developed marked bradycardia and hypotension and eventually fell into a state of pulseless electrical activity. Immediate cardiopulmonary resuscitation was started. Although application of a temporary pacemaker restored her heart rate, echocardiography revealed no left ventricular contraction. We started percutaneous cardiopulmonary support (PCPS) and intra-aortic balloon pumping (IABP). Her cardiac contraction gradually recovered and returned to completely normality 3 days after the onset. The patient was discharged in an ambulatory condition.

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1. Introduction

Pilsicainide is one of the most common antiarrhythmic agents for the treatment of paroxysmal atrial fibrillation (pAF). It has a pure sodium channel-blocking action with a slow recovery time constant [1–3], and exerts its antiarrhythmic action by suppressing the maximum depolarization rate of the cell membrane action potential, resulting in a decrease in the impulse conduction rate. Since pilsicainide is considered relatively safe and potent for rhythm conversion and maintenance of sinus rhythm in patients with pAF [4], it has been widely used in Japan and is recognized as the first-line drug for pAF in the Japanese Circulation Society Guidelines for Drug Treatment of Arrhythmias (2009). Here we report a very rare case where pilsicainide induced marked negative inotropic and chronotropic effects, despite the absence of any detectable underlying heart disease.

2. Case report

A 64-year-old woman was transferred to our hospital by ambulance with strong palpitations. She was 150 cm in height and weighed 55 kg. She was fully conscious and there were no abnormal neurological findings. Blood pressure was 131/93 mmHg and her pulse was irregular, with a mean rate of 140 bpm (Fig. 1A). Percutaneous oxygen saturation (SpO₂) under room air was 96%. She had a history of pAF, which had been treated at another hospital. On that occasion, 100 mg of pilsicainide was administered orally and she suffered cardiac arrest. As the patient did not remember this event on her current admission, we started our treatment without having this information.

The supervising physician administered 0.5 mg of propranolol and 50 mg of pilsicainide intravenously for about 8 min around midnight, but the AF persisted until the next morning. Her blood test showed no liver or renal dysfunction and her echocardiography study showed normal cardiac function (Table 1). At 9:00 am the next morning, we added 0.25 mg of intravenous digoxin, and another 50 mg of pilsicainide dissolved in 100 ml of normal saline was administered from 12:08 pm over 10 min (Fig. 2A). Mild bradycardia developed during administration (Fig. 2B). Just after the completion of the injection, at 12:22 pm, she fell into a state of

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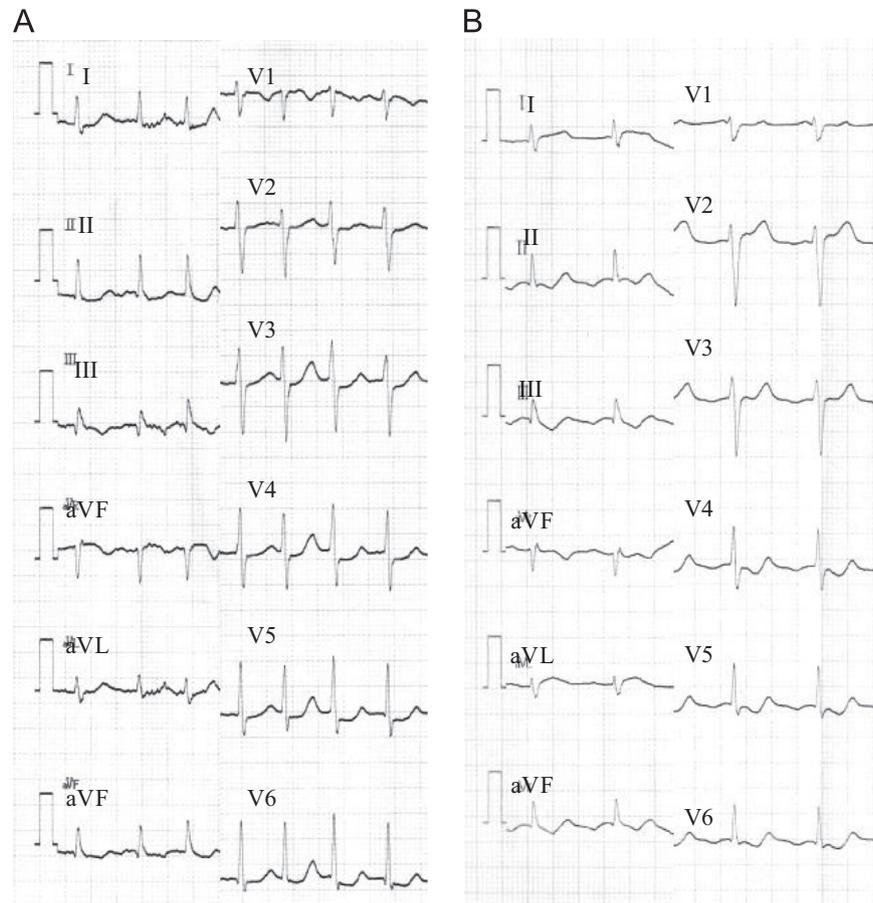


Fig. 1. 12-lead ECG around the administration of pilsicainide. (A) 12-lead ECG before the first administration of pilsicainide. (B) 12-lead ECG after the second administration of pilsicainide.

Table 1
Results of ultrasound cardiography.

	1 day		2 days	3 days	4 days
	Before administration	After administration			
LVDD (mm)	41	44	49	36	41
LVDs (mm)	24	43	42	24	23
EF (%)	74	3.6	31	64	76

LVDD, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; and EF, ejection fraction.

pulseless electrical activity (Fig. 2C). We immediately started cardiopulmonary resuscitation. As the patient's circulatory status did not improve after the intravenous administration of 1 mg of epinephrine (Fig. 1B), we inserted a temporary pacemaker at 13:25 pm. The stimulation threshold of the temporary pacemaker was below 0.3 V. As profound hypotension remained even with these efforts, while no actual cardiac contraction was observed on the echocardiogram (left ventricular ejection fraction 3.6%, Table 1), we decided to use percutaneous cardio-pulmonary support (PCPS) and intra-aortic balloon pumping (IABP), which were able to stabilize her hemodynamic condition. The blood concentration of pilsicainide at this point, approximately 3 h after administration, was within the safe and effective range (0.39 $\mu\text{g}/\text{dl}$). The left ventricular ejection fraction recovered to 31% by the second day, and as it was almost normalized on the third day

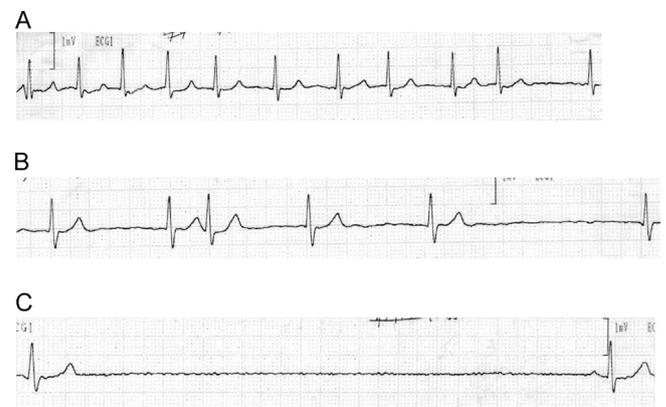


Fig. 2. ECG monitoring around the second administration of pilsicainide. (A) ECG monitoring before the administration; atrial fibrillation with rapid ventricular response. (B) ECG monitoring during the administration; atrial fibrillation with slow ventricular response. (C) ECG monitoring after the administration; long sinus arrest.

(64%), PCPS and IABP were terminated. On the fourth day, the patient was well enough to be extubated (Table 1).

MRI, including delayed enhancement, revealed no cardiac abnormalities on the tenth day, and cardiac catheterization on the fourteenth day showed no significant coronary lesions. Sinus node function and atrioventricular conduction were also within normal limits on electrophysiological testing. In addition, no significant finding was noted in her myocardial biopsy specimen and no variant was found in the cardiac sodium channel genes, SCN5A and KCNH2. Rehabilitation was carried out for 2 months,

and she was discharged in ambulatory condition. AF did not recur during this period of admission. The prescribed drug at the time of discharge was only warfarin, and we recommended that pulmonary vein isolation should be performed when the next attack of AF occurred.

3. Discussion

We report the case of a patient with pAF who had no specific medical history, but showed catastrophic negative inotropic and chronotropic effects in response to pilsicainide. Although the negative inotropic effect of pilsicainide is believed to be relatively weak, there are some reports of a significant increase in pulmonary artery wedge pressure after its administration [5,6]. It has also been reported that the administration of large doses (3–6 mg/kg) of pilsicainide to anesthetized dogs lowered blood pressure and heart rate in a dose-dependent manner [7]. The concentration of serum pilsicainide in these dogs was far higher than in our case. Cardiac suppression has been observed in patients who attempted suicide who took massive doses of pilsicainide and atenolol. In such cases, however, the separate effect of pilsicainide was unclear [8]. In another suicide attempt, where approximately 2000 mg of pilsicainide was taken, severe pump failure occurred [9]. Though the patient's hemodynamic state in that case was supported by a combination of IABP and PCPS, as in our patient, the hemodynamic progression appears to have been milder, taking into account that a far larger dose of pilsicainide was administered.

It is recommended that pilsicainide be administered over 10 min, with 1.0 mg/kg being the maximum daily dosage allowed. However, a single oral dose of pilsicainide has been shown to be effective, feasible and safe, and the single dose is always from 100 to 150 mg [4,10]. Both the time to maximum drug concentration (Tmax) and the half-life of pilsicainide are approximately 3 h. Though the half-life of pilsicainide is prolonged in cases of renal dysfunction, since it is a renally excreted drug [11], renal dysfunction was not observed in our patient. In fact, given that the blood concentration of pilsicainide 3 h after re-administration in our case was 0.39 µg/ml, we do not consider that the pilsicainide concentration was sufficiently high to induce the serious cardiac suppression [12]. In addition, we could not detect any sodium channel abnormalities. An effect of digoxin was considered as one of the possible causes of bradycardia. However, because the heart rate dropped within a short time after pilsicainide administration, while about 3 h had passed since digoxin had been injected, digoxin may not have played an important role in the bradycardia. Some negative inotropic effects of propranolol might have been involved, as the pilsicainide was administered about 12 h after the injection of propranolol. However, since the half-life of

propranolol is 2.3 h, we consider that the role of the injected propranolol would have been limited if any.

Thus, there is no clear answer at the present time as to why this amount of pilsicainide caused such a fatal inhibitory effect on our patient's seemingly normal heart. However, we should recognize that this type of totally unexplained serious adverse effect can happen totally unexpectedly, even in patients who have apparently normal cardiac function.

Disclosures

This study involved no financial support or off-label or investigational drug use. The patient gave informed consent for the publication of the clinical data and her anonymity has been preserved.

Conflict of interest

None.

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