A Case of Sinus Pause due to the Proarrhythmia of Pilsicainide

Tetsuro Toeda, MD, Ritsuko Susa, MD, Takashi Saigawa, MD, Takashi Abe, MD, Yoshifumi Yamaguchi, MD, Katsuya Fuse, MD, and Hiroshi Murooka, MD

SUMMARY
A 74-year-old man received oral administration of pilsicainide, a pure sodium channel blocker with slow recovery kinetics, to convert paroxysmal atrial fibrillation to sinus rhythm and developed loss of consciousness two days later. The ECG monitoring revealed sinus pause with markedly prolonged PQ interval and QRS width. Two days after the drug was discontinued, the duration of the QRS complex was normalized. This drug is rapidly absorbed from the gastrointestinal tract, most of which is excreted from the kidney. The plasma concentration of pilsicainide, although not measured, must have been very high, since his renal function was impaired. When pilsicainide is prescribed in patients with coronary artery disease or renal dysfunction, close attention must be paid to avoid life-threatening arrhythmias due to high plasma concentrations of the drug. This is an interesting case because the proarrhythmia of the drug was not tachyarrhythmia, such as ventricular tachycardia or torsades de pointes, but sinus pause. (Jpn Heart J 2000; 41: 405-410)

Key words: Pilsicainide, Sinus pause, Proarrhythmia

Pilsicainide, a pure sodium channel blocker with slow recovery kinetics, is known to be effective in converting recent-onset atrial fibrillation to sinus rhythm.1) This drug has been shown to increase PQ interval and QRS width, and the percentage prolongation of the PQ interval was well correlated with the plasma levels.2) Adverse effects associated class IC or III antiarrhythmic drugs have been reported.3-5) High plasma concentrations of these drugs have been known to induce life-threatening tachyarrhythmias such as ventricular tachycardia, torsades de pointes and ventricular fibrillation. It has been reported that pilsicainide intoxication induced incessant ventricular tachycardia6) and idioventricular rhythm.7) On the other hand, bradyarrhythmias such as sinus pause and atrioventricular block have been also reported as a manifestation of proarrhythmia. We report here a case of sinus pause who received pilsicainide to...
TOEDA, ET AL

convert paroxysmal atrial fibrillation to sinus rhythm and developed loss of consciousness two days later.

CASE REPORT

On November 4, 1999, a 74-year-old man was admitted to hospital because of loss of consciousness.

Nine years ago he had anginal pain and underwent diagnostic cardiac catheterization. Coronary angiography showed 99% stenosis in the right coronary artery and 90% stenosis in the left anterior descending artery. At that time, he received an internal mammary artery graft to the left anterior descending artery and saphenous vein grafts to the right coronary artery. Three years after coronary artery bypass grafting (CABG) he underwent follow-up catheterization because the electrocardiogram showed poor R wave progression in leads V1 to V3. The two grafts were patent and the left ventricular ejection fraction was 60%. He has taken warfarin, digoxin, furosemide and spironolactone for 9 years after CABG.

On November 2, 1999, he visited our hospital because he began to feel palpitations and shortness of breath beginning three days earlier. The electrocardiogram, which showed sinus rhythm six months previously revealed atrial fibrillation. Pilsicainide, 50 mg three times daily given orally, was prescribed to convert atrial fibrillation to sinus rhythm. Two days later, he suddenly lost consciousness and was brought to the emergency room. He appeared acutely ill, cyanotic and dead on arrival. The pulse was irregular and too subtle to count. His blood pressure was less than 50 mm Hg and his respiration was shallow and unstable. The ECG monitoring disclosed sinus pause and ventricular escape beats with a heart rate of less than 40/min (Figure 1). Cardiopulmonary resuscitation was immediately started. Cardiac massage and mechanical ventilation were performed and dopamine (15 µg/kg/min), dobutamine (15 µg/kg/min) and atropine sulfate (1.0 mg) were intravenously administered. One hour after cardiopulmonary resuscitation the blood pressure increased to more than 100 mm Hg and his body became warm without any cyanosis. The electrocardiogram once again showed atrial fibrillation with a wide QRS complex of 0.12 sec duration (Figure 2A). Laboratory examination revealed a white blood cell count of 9,200/mm³, C-reactive protein of 0.3 mg/dl, BUN of 28.4 mg/dl and creatinine of 1.36 mg/dl indicative of mild renal dysfunction. Serum enzymes and electrolytes were within normal range. Arterial blood gas analysis after cardiopulmonary resuscitation showed pH 7.571, PO₂ 204 mm Hg, PCO₂ 19.2 mm Hg, bicarbonate 18.1 mEq/l and
base excess −2.4 mEq/l. On the next day mechanical ventilation was removed and he recovered from the unconsciousness without any paralysis or mental disorientation. Pilsicainide was discontinued on admission. Two
days later, the electrocardiogram demonstrated persistent atrial flutter-fibrillation with a normal QRS interval of 0.08 sec (Figure 2B). The Holter monitoring recorded one month after discharge still showed atrial flutter-fibrillation with a maximum R-R interval of 1.64 sec.

**DISCUSSION**

Pilsicainide is a class IC drug, available in Japan, that is particularly effective for terminating paroxysmal atrial fibrillation. In the Pilsicainide Suppression Trial on Atrial Fibrillation (PSTAF) clinical study, a single oral dose of pilsicainide produced conversion of atrial fibrillation to sinus rhythm within 90 minutes in 45% of 40 patients compared with 8.6% of 35 patients in the placebo group. In this study one patient receiving pilsicainide developed atrial flutter with 2:1 atrioventricular conduction but without hemodynamic deterioration, and another patient with WPW syndrome developed a sinus pause of 8.0 seconds after termination of atrial fibrillation. This drug strongly blocks cardiac sodium channels with slow recovery kinetics and markedly depresses conduction in all regions of the heart. Therefore, PQ interval, QRS width, sinoatrial conduction, and AH and HV intervals were significantly prolonged after oral administration of this drug. We speculate that in this patient sinus pause is not sinus arrest but SA block, since pilsicainide is a potent sodium channel blocker and suppresses the transmission of the sinus impulse to the atrium. However, transient failure of impulse formation at the SA node, that is sinus arrest, might take place, because an in vitro study has demonstrated that pilsicainide depresses the membrane calcium current only at higher concentrations.

Pilsicainide is rapidly absorbed from the gastrointestinal tract, most of which is excreted from the kidney. Takabatake, et al. reported the half-life of elimination was 3.4 hours in normal subjects, but was prolonged to 23.7 hours in severe renal failure. The plasma concentration of pilsicainide, although actually not measured, must have been very high in this patient since his renal function was mildly impaired. The PQ interval and the QRS width were markedly prolonged on admission and the QRS width was normalized two days later. Ino, et al. demonstrated that the percentage prolongation of the PQ interval was well correlated with the plasma levels. Because of individual variation in sensitivity to the drug, the dose should be adjusted cautiously in patients with renal dysfunction by monitoring the drug concentration and the electrocardiogram.

An increase in the rate of sudden death in patients taking a class IC
drug, such as flecainide or encainide, has been reported in the Cardiac Arrhythmia Suppression Trial (CAST) study.\(^3\text{-}^5\) It is speculated that this result might be a proarrhythmic effect due to the interaction of ischemia and class IC antiarrhythmic drugs. The present patient had coronary artery disease and underwent CABG surgery. Therefore, it is possible that he suffered from ischemic events while taking pilsicainide. Sadanaga, et al.\(^{10}\) reported that the combination of ischemia and pilsicainide led to a much greater prolongation of the QRS duration and might be one possible mechanism for the induction of proarrhythmias in the CAST study. Since he was elderly and had coronary artery disease, he might have had sick sinus syndrome and developed sinus pause resulting in loss of consciousness. However, until now he has never experienced any symptoms, such as dizziness, palpitations or syncope, caused by sick sinus syndrome. Although the mechanism responsible for sinus pause is not clear, it may be related to an increase in ischemia-produced atrial conduction delay due to pilsicainide.

Orally administered pilsicainide, which is absorbed rapidly and excreted almost exclusively from the kidney, is a very effective drug for terminating atrial fibrillation. When pilsicainide is prescribed to convert atrial fibrillation to sinus rhythm in patients with coronary artery disease or renal dysfunction, close attention must be paid to avoid life-threatening arrhythmias due to high plasma concentrations of the drug.

**REFERENCES**


