A Case of the Toxicity of Pilsicainide Hydrochloride With Comparison of the Serial Serum Pilsicainide Levels and Electrocardiographic Findings

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SUMMARY

We treated an 88-year-old man with aortic valvular stenosis/insufficiency and paroxysmal atrial fibrillation, who developed ventricular tachycardia due to pilsicainide toxicity.

He was treated at the outpatient clinic of his local hospital, and was administered pilsicainide (100 mg/day) for atrial fibrillation. The electrocardiographic findings on admission to our hospital indicated wide QRS with frequent episodes of ventricular tachycardia. We diagnosed him as having pilsicainide toxicity because of a low cardiac output and renal dysfunction. His creatinine level was 2.4 mg/dL and the serum pilsicainide level was 2.42 µg/mL on admission. Fluid infusion and continuous hemodiafiltration were performed to achieve an early reduction in the serum pilsicainide level. His serum pilsicainide concentration was significantly decreased by these treatments, and the prolongation of the QTc and ventricular tachycardia improved in parallel to the decrease in the serum pilsicainide level. The changes in the serum pilsicainide level showed a significant positive correlation with the changes in the electrocardiographic findings (PQ, QRS, ST intervals, and QTc).

Pilsicainide should be administered with great care to elderly patients, especially patients with cardiac dysfunction and renal dysfunction. Estimation of the serum level may be possible from the electrocardiographic findings if the pilsicainide toxicity occurs.

Key words: Pilsicainide hydrochloride, Toxicity, Ventricular tachycardia, Serial serum pilsicainide levels, Serial electrocardiographic changes

In recent years, various antiarrhythmic drugs have been developed and used clinically. In particular, administration of class Ic antiarrhythmic agents has increased because of their high efficacy, although attention has also been focused on the induction of arrhythmias by these drugs.1-3) We report here a case with pil-
sicainide hydrochloride toxicity in which it was possible to clarify the correlation between the serial serum pilsicainide levels and serial electrocardiographic findings.

**CASE REPORT**

In August 2001, an 88-year-old man was referred to our hospital due to dyspnea. At the time, he was receiving antihypertensive therapy at the outpatient clinic of his local hospital. He was diagnosed as having congestive heart failure due to aortic valve stenosis and insufficiency. After his symptoms resolved with drug therapy, he was followed-up without surgical valve replacement because of his advanced age. In January 2002, he was hospitalized again because of congestive heart failure. Because paroxysmal atrial fibrillation occurred after admission, pilsicainide was administered at a dose of 100 mg/day in consideration of his high serum creatinine level (1.8 mg/dL), and consequently, his cardiac rhythm recovered to sinus rhythm. His electrocardiogram showed complete right bundle branch block with right axis deviation and ST segment depression in leads II, III, aVF, and V4 through V6 (Figure 1). He was then followed at his local hospital again. At night on August 27, 2003, he was referred to our hospital from a local hospital.

![Electrocardiographic findings after recovering to sinus rhythm by administration of pilsicainide 100 mg/day in January, 2002.](image)

**Figure 1.** Electrocardiographic findings after recovering to sinus rhythm by administration of pilsicainide 100 mg/day in January, 2002.
hospital due to loss of appetite, dizziness, and loss of consciousness. The electrocardiographic findings revealed sinus rhythm with prolongation of the PQ and QRS. The PQ, QRS, and QTc values were increased to 0.36 seconds, 0.28 seconds, and 0.79 seconds, respectively, while Brugada syndrome-like ST-segment elevation was noted in leads V₁ through V₃ (Figure 2A). Electrocardiography revealed a wide QRS and frequent episodes of ventricular tachycardia. This arrhythmia was diagnosed as polymorphic ventricular tachycardia (Figure 2B). He was diagnosed as having a toxic arrhythmia due to an overdose of pilsicainide hydrochloride because his creatinine and BUN levels were 2.4 mg/dL and 47.0 mg/dL, respectively. Indeed, his serum pilsicainide level showed a significant increase to 2.42 µg/mL.

After admission to our intensive care unit, frequent and intermittent ventricular tachycardia continued. He was administered lidocaine hydrochloride infusion without cardioversion because his blood circulation and consciousness level were stable.

Figure 2. ECG findings on admission with pilsicainide toxicity in August 27, 2003.
A: The electrocardiographic findings revealed sinus rhythm with prolongation of the PQ and QRS. The PQ, QRS, and QTc values were increased to 0.36 seconds, 0.28 seconds, and 0.79 seconds, respectively, while Brugada syndrome-like ST-segment elevation was noted in leads V₁ through V₃.
B: Electrocardiography revealed a wide QRS and frequent episodes of ventricular tachycardia. This arrhythmia was diagnosed as polymorphic ventricular tachycardia.
According to a report on the clearance of pilsicainide, the mean clearance of this drug by hemodialysis was 32% in patients receiving oral therapy at a dose of 25 mg. Therefore, pilsicainide therapy was withdrawn and we infused the fluid and performed continuous hemodiafiltration (CHDF) to achieve an early reduction in the serum pilsicainide level beginning at midnight on August 28. The hemodialysis conditions were as follows: blood flow rate: 100 mL/min, filtration fluid flow rate: 700 mL/hr, dialysate flow rate: 400 mL/hr, infusion fluid flow rate: 300 mL/hr, removal of water: none, and duration of hemodialysis: 36 hours. After 24 hours of CHDF, 15.3 and 132.3 mg of pilsicainide had been removed in the filtrate and excreted in the urine, respectively, and the amount removed in the filtrate accounted for about 12% of the urinary excretion (Figure 3).

The time course of the serum pilsicainide levels showed a significant positive correlation with the changes in the QTc (r = 0.943) and QRS interval (r = 0.925), and the clearance of pilsicainide from the blood was more than 50 percent in the 24 hours after the initiation of CHDF (Figure 4). As shown in Figure 5, the serum pilsicainide levels also displayed a positive correlation with the ST interval.

![Figure 3](image-url)

**Figure 3.** Serial changes in pilsicainide elimination in the filtrate and urinary excretion.

The amount of pilsicainide eliminated in the filtrate and excreted in the urine during the initial 24 hours was 15.3 mg and 132.3 mg, respectively.

Equipment for CHDF: APF-06S (PAN membrane: ASAHI Medical Inc)
Dialysate and replacement fluid: Sublood-B (Fuso Pharmaceutical Industries Ltd.)
Blood: 100 mL/min. Filtrate: 700 mL/hr.
Dialysate: 400 mL/hr. Replacement fluid: 300 mL/hr.
with the STc (ST interval/√RR; r = 0.885), and with the PQ interval (r = 0.973) (Figure 6). Briefly, as the serum pilsicainide levels decreased, the PQ, QRS, and ST intervals decreased, and the extents of the decreases were dependent on the serum pilsicainide levels.
Figure 6. Correlation between serum pilsicainide levels and PQ time in serial ECG findings.

Figure 7. ECG findings at remission of pilsicainide toxicity.
As a result, the arrhythmia resolved about 3 hours after treatment and we stopped the lidocaine hydrochloride infusion. Ventricular arrhythmia did not occur after discontinuation of the lidocaine hydrochloride infusion, and the serum pilsicainide level returned to the therapeutic range after 32 hours. The electrocardiographic findings at the time of final improvement showed that the PQ interval, QRS interval, and QTc were 0.24 seconds, 0.18 seconds, and 0.52 seconds, respectively (Figure 7).

**DISCUSSION**

Pilsicainide is an antiarrhythmic drug that was developed in Japan. It is a class Ic antiarrhythmic agent according to the Vaughan-Williams classification, and is largely excreted in the urine. Therefore, the appropriate dose should be determined with great care in patients with renal dysfunction. Shimizu, *et al* have reported that the initial dose of pilsicainide should be set at 50 mg, and if the effect is insufficient, it may be increased to 100 mg in patients with a creatinine clearance of 30-50 mL/min and a serum creatinine level of 1.0-1.7 mg/dL, while pilsicainide therapy should be started at a dose of 25 mg/day in patients on hemodialysis. In our patient, we believe that the serum pilsicainide levels increased markedly due to overdosage combined with a low cardiac output and decreased renal blood flow due to aortic valve stenosis/insufficiency, old age, and increasing renal dysfunction. The higher serum pilsicainide levels induced ventricular tachycardia as a result of the QTc and QRS prolongation.

There have been no previous reports on the use of continuous hemodiafiltration in patients with pilsicainide intoxication and there are no studies in which the time course of the serum pilsicainide level was compared with the electrocardiographic changes. Since pilsicainide is originally a sodium channel blocker, it can affect the QRS interval, but may have little influence on the ST interval. It is worthy of note that the PQ interval, ST interval, and QTc were all increased in our patient when the serum pilsicainide levels became abnormally high.

It is also interesting that Brugada syndrome-like ST-segment elevation was noted in the right precordial leads at the time when the serum pilsicainide level became abnormally high and ventricular extrasystoles were frequent. Brugada syndrome has attracted attention as a cause of sudden death, and it has been suggested that the occurrence of lethal arrhythmia may possibly be predicted by characteristic electrocardiographic findings of right bundle branch block and the ST-segment elevation in the right precordial leads, which may develop after intravenous injection of sodium channel blockers. In fact, pilsicainide has recently been useful as an adjunct to the diagnosis of Brugada syndrome. Fujiki, *et al* reported that the ST-segment elevation was increased by oral administration...
of pilsicainide in patients with asymptomatic Brugada syndrome.9) Chinushi, et al reported that the ST-segment elevation in the right precordial leads was increased after pilsicainide was administered intravenously at a dose of 25 mg in patients with Brugada syndrome and a history of ventricular fibrillation although the mechanism of ST-segment elevation in this syndrome has not been elucidated fully.10,11)

This case was not considered to be Brugada syndrome, taking into consideration the etiology of the ventricular tachycardia with ST segment elevation like Brugada syndrome which was induced by higher pilsicainide levels. However, the mechanism of the ventricular tachycardia in our case suggests the possibility of a similar electrophysiological mechanism to that of ventricular tachycardia with Brugada syndrome.

REFERENCES