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【 CASE REPORT 】

Pilsicainide Intoxication with Neuropsychiatric Symptoms Treated with Continuous Hemodiafiltration

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Abstract:

A 72-year-old lady with atrial fibrillation and chronic renal failure was hospitalized due to bradycardic shock with electrocardiographic QRS prolongation. She had experienced limb shaking two days before hospitalization, and additionally developed hallucinations one day before admission. Pilsicainide intoxication was diagnosed from a review of her medications and electrocardiographic findings. Consequently, continuous hemodiafiltration was performed resulting in a resolution of the hallucinations and the QRS prolongation.

This is a rare case of psychiatric symptoms caused by pilsicainide intoxication. It is important to know the mode of excretion of a drug and to adjust its dose, so that such drug-related incidents can be avoided.

Key words: pilsicainide, psychiatric symptoms, continuous hemodiafiltration

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Introduction

Pilsicainide, a pure sodium channel blocker with slow recovery kinetics, is an antiarrhythmic drug that was developed in Japan (1, 2). Because it is largely excreted in the urine, it is important to adjust the dose according to the patient's renal function (3). We herein report a rare case of pilsicainide intoxication with neuropsychiatric symptoms.

Case Report

A 72-year-old lady with known atrial fibrillation, gastritis, hypercholesterolemia, renal osteodystrophy and chronic renal failure on hemodialysis (HD) was an inpatient in a psychiatric hospital due to depression. Seven days before admission to our hospital, she was administered pilsicainide, a class 1c drug which is mainly excreted in the urine, at a dose of 150 mg/day. This was administered as an alternative to propafenone for atrial fibrillation because propafenone had not been available at the hospital. Other than the prior drug, the patient was taking lansoprazole 10 mg once daily, ezetimibe 10 mg once daily, calcium carbonate 500 mg three times daily, alfacalcidol 0.25 μg once daily, and sevelamer hydrochloride 750 mg three times daily, respectively. The patient had not received any anti-depressant medication because she experienced reactive depression due to financial anxiety which improved only after conducting family discussions and undergoing psychiatric counseling.

Four days prior to admission, she fell and fractured a rib which was stabilized with banding. On the next day, she was discharged from the psychiatric hospital because her depression was deemed to have stabilized. Two days before admission, she experienced shaking limbs and difficulty walking, and she visited the emergency department of another hospital. Her blood pressure was 115/69 mmHg and heart rate was 74/min. She was discharged back to her home due to an absence of any laboratory test abnormalities, but she was then re-hospitalized at the psychiatric facility because of auditory and visual hallucinations. Her blood pressure was 141/68 mmHg and heart rate was 65/min at the time of admission to the psychiatric facility. On the following day, she was transferred to our hospital because of difficulty accessing her renal shunt.

On a physical examination at admission, the following findings were observed: Body mass index was 17.6. She was

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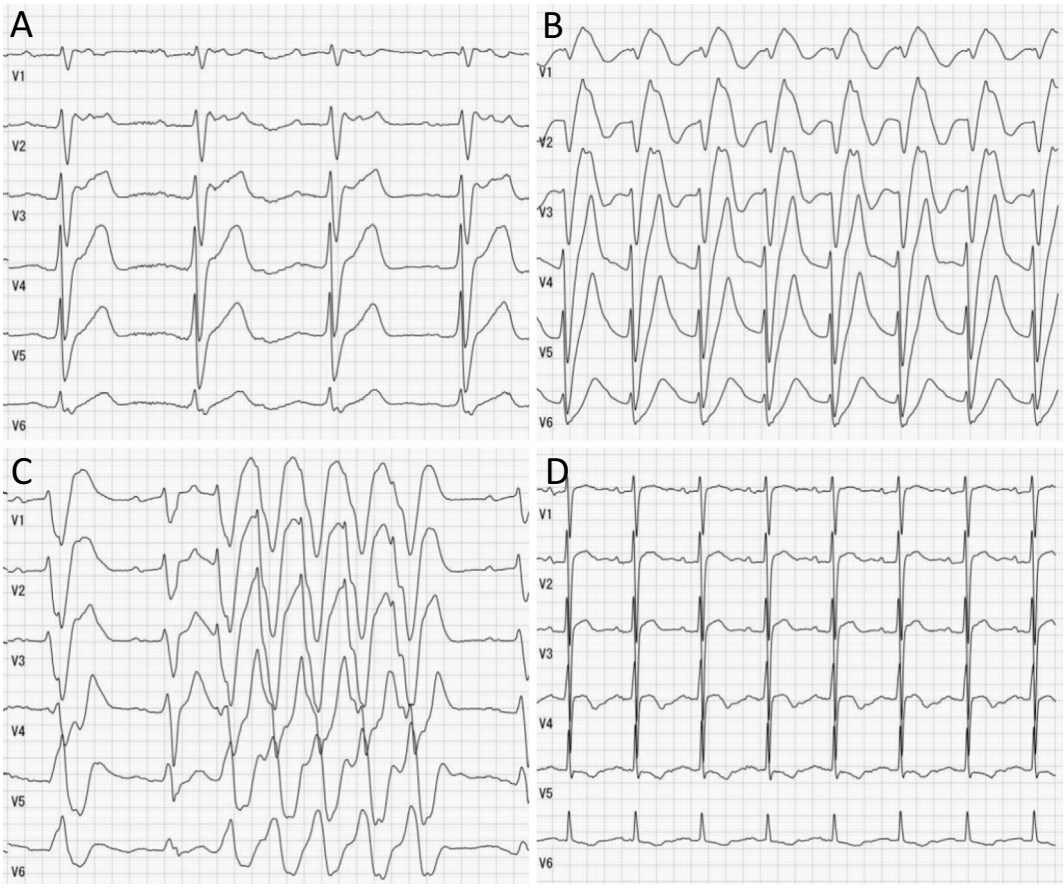

Figure 1. Electrocardiographic findings. (A) Electrocardiogram with a wide QRS complex of 160 ms duration recorded before starting dialysis. (B) Electrocardiogram recorded 8 hours after starting dialysis. (C) Electrocardiogram with a non-sustained ventricular tachycardia recorded 10 hours after starting dialysis. (D) Electrocardiogram recorded 40 hours after starting dialysis.

conscious but somewhat disoriented. Her speech was confused. Her blood pressure was 69/40 mmHg, heart rate was 38/min, respiratory rate was 23/min and body temperature was 37.5°C, respectively. Auscultation revealed an ejection systolic murmur. Her breaths sounds were clear, and her abdomen was soft and non-distended with normal bowel sounds. Her hands were tremulous. Her arteriovenous fistula sound was inaudible by auscultation.

A chest radiograph revealed cardiomegaly without congestion. An electrocardiogram revealed sinus rhythm with prolongation of the PR (560 ms), QRS (238 ms), and QTc (633 ms) values, respectively (Fig. 1A). Echocardiography on admission showed no local asynergy. Head computed tomography showed no obvious abnormal findings. Head magnetic resonance imaging could not be performed because the patient was unable to remain still in the machine and her hemodynamics were deemed to be too unstable to undertake the study. Routine laboratory tests revealed a serum sodium level of 139 mEq/L, a potassium level of 4.9 mEq/L, and a glucose level of 89 mg/dL. Arterial blood gas analysis showed pH 7.379, pO_2 66 mmHg, partial pressure oxygen (pCO_2) 31 mmHg, and HCO_3^- 17.8 mmol/L, respectively. From the above results, pilsicainide intoxication was strongly suspected.

After admission to our intensive care unit, a temporary pacemaker was inserted but it failed to pace adequately. Pilsicainide was discontinued, and continuous hemodialysis (CHD) was performed.

The patient's hallucinations persisted after hospitalization. Although her heart rate and blood pressure improved, the wide QRS continued for eight hours after commencing dialysis (Fig. 1B). After 10 hours of CHD, non-sustained ventricular tachycardia occurred frequently (Fig. 1C), and the treatment was thus changed to continuous hemodiafiltration (CHDF). After a total of 40 hours of CHDF, the hallucinations resolved and the QRS width returned to baseline (Fig. 1D).

It was later found that the serum concentration of pilsicainide at admission was 4.85 μg/mL, which was significantly higher than the therapeutic range between 0.16-0.24 μg/mL. Because it takes time to measure the serum concentration of pilsicainide, treatment was commenced based on the history, electrocardiographic findings and neuropsychiatric symptoms as indirect indicators.

The clinical course is summarized in Fig. 2.

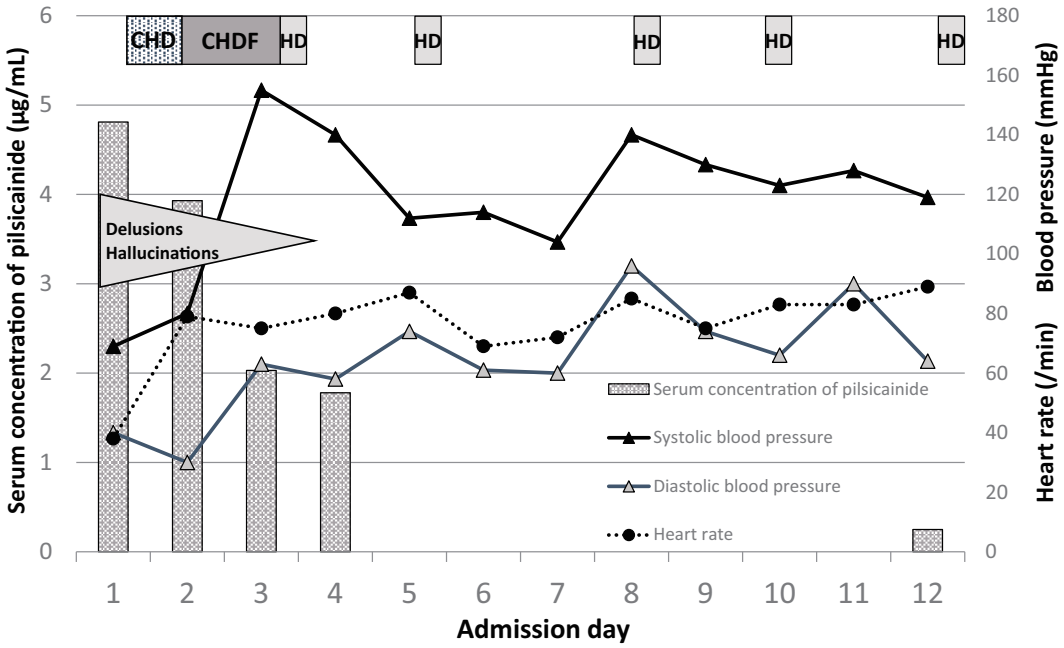

Figure 2. **Clinical course of this patient. Left Y axis is the serum concentration of pilsicainide (μg/mL) and right Y axis is blood pressure (mmHg) and heart rate (/min). HD: hemodialysis, CHD: continuous hemofiltration, CHDF: continuous hemodiafiltration**

Discussion

Pilsicainide is a class Ic antiarrhythmic agent according to the Vaughan-Williams classification (4). Because it is largely excreted in the urine, the $T_{1/2}$ is prolonged in patients with renal failure (3). It is important to adjust the dosage according to the renal function. The usual dose of pilsicainide is 100-150 mg per day, but for dialysis patients, it is recommended to reduce the dose to 25-50 mg after dialysis (5). In our case, the patient had been prescribed the regular dose of 150 mg of pilsicainide and, as a result, she developed toxic symptoms.

It has been reported that pilsicainide intoxication induces arrhythmias such as ventricular fibrillation (6), ventricular tachycardia (7-9), sinus arrest (10) and atrioventricular block (11). Conversely, reports of psychiatric symptoms are rare. There have been a few reports describing excitatory delirium, visual hallucinations, and delusions caused by excessive intake of pilsicainide (12, 13). The reports of psychiatric symptoms caused by pilsicainide are summarized in the Table. Although there have been reports of the drug causing unconsciousness due to hypotensive shock (7, 10, 14, 15), these cases had psychiatric symptoms without persistent hypotension. Although the mechanism by which pilsicainide causes psychiatric symptoms is unknown, it is very important to have a detailed medication history to guide the physician.

Treatment of pilsicainide intoxication is symptomatic such as cardiac pacing and drug elimination. In this case, a temporary pacemaker was inserted but it failed to pace adequately. Pilsicainide should also be recognized as causing pacing failure (15, 16). In non-dialysis patients, maintaining blood pressure with fluid replacement and vasopressor drugs has been reported to be effective (11, 13, 16). Moreover, sodium bicarbonate infusion is one of the treatments to consider, because it interferes with the binding of group Ic antiarrhythmic drugs to sodium channels (17, 18). In this case, sodium bicarbonate was present in the CHD dialysate to aid in the treatment of drug toxicity. However, it is often recommended that sodium bicarbonate be given as bolus infusions. In this case, it was considered unsafe to do so because of the concern of inducing fluid overload.

The effectiveness of CHDF for pilsicainide poisoning remains controversial. Pilsicainide is a small molecule with a molecular weight of 272.3, a large volume of distribution of 1.46 and a relatively high protein binding rate (3). Protein binding rate in patients with renal failure has been reported to be 37% (3). In four hours of HD, the removal rate is reported to be 37%, which is lower than that of small molecules such as urea nitrogen and creatinine (19). This is considered to be due to the high distribution volume and protein binding rate. It has been reported that the removal rates of pilsicainide at four hours of HF, 18 hours of CHF and 3.2 liters of plasma exchange are 25%, 25% and 45%, respectively (9, 12). It is difficult to compare which therapy has the best removal rate because conditions such as blood flow and fluid volume are different.

Since this was a dialysis patient with hypotension, CHDF was selected. In this case, the removal rate with 14 hours of CHF was 18.3%. The removal rate at three hours of CHF and at 21 hours of CHDF was 48% in total. The removal rate was calculated using the following formula (19): [1-(original drug serum concentration / starting weight) / (final

Table. The Reports of Psychiatric Symptoms Caused by Pilsicainide.

	Age Sex	Serum creatinine level (mg/dL)	Time point	Symptoms	Blood Pressure (mmHg)	ECG Findings	Pilsicainide dosage	Maximum serum concentration (μg/mL)	Treatment
Case 1	56 F	9.03 (on HD)	On admission	Numbness of fingers, dizziness	170/74	First degree AV block, prolongation of the QRS	150 mg/ day	2.88 (after 4h HD)	HD,Plasma exchange
			The day after admission	Hallucinations, delusions	Not described	Not described			
Case 2	48 M	1.24	On admission	Excitatory delirium	133/96	Not described	4,500 mg at once	7.04	Antibacterial drug, Antiviral drug
			140 min after admission	Hypotension	Not described	Wide QRS tachycardia			
Our case	76 F	11.6 (on HD)	Emergency department of another hospital	Shaking limbs, difficulty walking	115/69	Unknown	150 mg/ day	4.81	Pacing, CHDF
			On admission to psychiatric facility	Hallucinations, delusions	141/68	Unknown			
			On admission to our hospital	Difficulty accessing her renal shunt	69/40	Wide QRS bradycardia			

HD: hemodialysis, AV block: atrioventricular block, CHDF: continuous hemodiafiltration

drug serum concentration / ending weight)] ×100. Although CHF and CHDF drug removal rates could not be calculated individually, it is considered that continuous hemodiafiltration is a useful treatment for pilsicainide poisoning in the presence of hypotension.

When prescribing new medications, it is important to know the mode of excretion of the drug and to adjust the dose and/or interval e.g. renal dosing, so that drug-related incidents can be avoided.

The authors state that they have no Conflict of Interest (COI).

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