A Case of Sick Sinus Syndrome that Developed Torsades de Pointes, Pacing Failure and Sensing Failure During Administration of Bepridil

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SUMMARY
A 65-year-old Japanese woman was admitted to hospital because of palpitations and faintness. She was diagnosed as having sick sinus syndrome and a permanent pacemaker was therefore implanted. Administration of bepridil (200 mg daily) was started for prevention of atrial flutter and fibrillation after PM implantation. On the twenty-fifth day of Bpd therapy, she developed recurrent syncope. ECG showed QT prolongation, torsades de pointes, and sensing failure. Electrical defibrillation (DF) was performed for ventricular fibrillation or ventricular tachycardia. It was presumed that Bpd had caused not only proarrhythmia but also a transient decrease in the amplitude of ventricular activation at the site of the pacing lead, as the sensing level was gradually restored after the drug was ceased and her plasma concentrations of Bpd decreased. It is also believed that DF had caused a sustained increase in pacing threshold because she developed pacing failure after DF and her pacing threshold had not returned to its prior level although the blood levels of Bpd had been below the minimum detectable level. Although it is well known that torsades de pointes occasionally develops in association with Bpd therapy, it is less evident that pacing and sensing failure may develop in association with Bpd therapy. This case report suggests that we should be aware of this possible outcome when employing Bpd and pacemaker implantation as combination therapy. (Jpn Heart J 2003; 44: 783-788)

Key words: Bepridil, Pacemaker malfunction, Torsades de pointes, Proarrhythmia, Electrical defibrillation

It is well known that torsades de pointes occasionally develops in association with bepridil (Bpd) therapy. However, it has not yet been documented that pacing and sensing failure might develop in association with this drug. This case study describes a patient with sick sinus syndrome who developed torsades de pointes, pacing failure, and sensing failure during administration of Bpd.
CASE REPORT

A 65-year-old Japanese woman was admitted to our hospital on 6 January, 2000 because of palpitations and faintness. Holter ECG showed paroxysmal atrial flutter and fibrillation and sinus arrest. Her heart rate exceeded 150 beats per minute during atrial flutter. Coronary angiography showed no abnormality and a left ventriculogram showed normal contraction. She was diagnosed as having sick sinus syndrome, so a permanent pacemaker (PM) (Ela Medical OPUS G4624 VVI mode) was implanted on 26 January, 2000. At the time of implanta-
tion the pacing threshold was 0.7 V at 0.50 ms and the ventricular sensing thresh-
old was 5.9 mV. Pacing threshold was estimated again on 9 February 2000 and was found to be 0.5 V at 0.49 ms. However, the sensing threshold was not esti-
mated at this time because her native rhythm was not detectable at the pro-
grammed rate of 40 beats/minute. The telemetered generator functions (magnet rate, battery resistance, lead impedance) were within the normal ranges. Because atrial flutter often develops after pacemaker implantation, administration of Bpd (200 mg daily) was started on 18 February, 2000 for the prevention of atrial flut-
ter and fibrillation. Attacks of paroxysmal atrial flutter and fibrillation decreased dramatically after the commencement of Bpd therapy.

However, on the eighteenth day of Bpd therapy, the patient lost conscious-
ness at her residence. On 15 March, 2000 (the twenty-fifth day of Bpd therapy), she developed recurrent syncope and visited the outpatient clinic. An ECG showed brady
cardic atrial fibrillation, QT prolongation (QT interval 0.58 sec-
onds), and failure in sensing function for premature ventricular contraction (Figure 1). She subsequently lost consciousness and developed convulsions. Since the ECG showed ventricular fibrillation, electrical defibrillation (DF) was performed and the patient recovered to atrial fibrillation rhythm. She was anesthetized and intubated intratracheally because of recurrent ventricular tachycardia (VT). After DF, pacing failure also developed (Figure 2). Chest x-rays did not show disloca-
tion of the pacing lead. PM parameters were estimated two hours after initial DF, showing an increase in pacing threshold (2.0 V at 0.49 ms), a decrease in ventric-
ular sensing level (0.8 mV), and lead impedance of 515 ohms. The delivered energy was altered from 2.5 V at 0.49 ms to 3.5 V at 0.49 ms. Although sensing failure remained, we were unable to change from VVI mode to OVO mode and had to observe the patient with the pacemaker running in VVI mode. Lidocaine, mexiletine and magnesium sulfate were all administered in an attempt to termi-
nate VT, but to no effect. There were numerous spontaneous attacks of Tdp (Fig-
ure 3). Multiple DFs were performed for termination of VT. The blood concentration of Bpd on admission was 504 ng/mL, and administration of the drug was discontinued at that point. After cessation of Bpd, attacks of Tdp had
Figure 1. This 12-electrode electrocardiogram (ECG) had been recorded on admission before electrical defibrillation (DF) was performed. Atrial fibrillation rhythm, QT prolongation, premature ventricular contraction (VPC), and sensing failure for VPC (arrow head) were seen on this ECG.

Figure 2. This ECG was recorded after defibrillation (DF). Although sensing failure (arrow head) had been evident before DF, pacing failure (arrow) developed after DF.
ceased by the end of the second hospital day. The QT interval gradually became shorter. Blood levels of Bpd had fluctuated between 387 and 793 ng/mL during the initial 6 hospital days and then decreased. After the cessation of Bpd, the sensing level was apparently restored from 0.8 to 2.0 mV, but there was no significant change in the pacing threshold (1st hospital day, 2.9 V at 0.49 ms; 27th hospital day, 2.0V at 0.49 ms) (Figure 4), so the pacing lead was exchanged. Ten days after exchange of the pacing lead, the pacing threshold and sensing level were 1.0 V at 0.20 ms and 8.0 mV, respectively. The telemetered generator functions were within the normal ranges.

**DISCUSSION**

Bepridil was synthesized in France as an antianginal drug. The drug also possesses cellular membrane effects. The effect of Bpd in suppressing both ventricular and supraventricular arrhythmia can be explained by several mechanisms. Bpd has an inhibitory action on slow calcium channels that is related to depression of automaticity and conduction in the sinus and atrioventricular nodes. It also inhibits cardiac fast sodium channels in a manner similar to
lidocaine, and inhibits sodium-calcium exchange. This effect tends to prolong the action potential duration and may contribute to QT prolongation. In addition to its effects on sodium-calcium exchange, Bpd also demonstrates an ability to inhibit repolarizing potassium currents.\textsuperscript{1-3})

A nine-year French study has reported a low incidence of Tdp with Bpd.\textsuperscript{4)} On the other hand, in a study of treatment of refractory atrial fibrillation with Bpd and amiodarone, Bpd was associated with the development of ventricular arrhythmia in 8 of 14 patients, and 2 had torsades de pointes. The authors state that Bpd seemed to be an effective antiarrhythmic agent for the management of atrial fibrillation, but its arrhythmogenic action makes it unsuitable for this purpose.\textsuperscript{5)}

In our case, Bpd toxicity seemed to be associated not only with Tdp and QT prolongation but also with abnormalities in both the capture and sensing function of the PM. In addition, the sensing level was restored with a reduction in blood concentrations of Bpd as shown in Figure 4. It is therefore believed that Bpd caused a decrease in the sensing level of the pacemaker. In accordance with this hypothesis, in the present study, the sensing level did improve with a reduction in blood concentrations of Bpd, but the pacing threshold was not completely restored to its prior level (Figure 4). Several antiarrhythmic agents have been

\textbf{Figure 4.} This graph shows the transition of each parameter. Both pacing threshold and sensing level had improved somewhat by the second hospital day. Sensing level had virtually improved with a reduction in blood concentrations of Bpd but pacing threshold did not completely return to its prior level.
found to change the thresholds of pacemakers but no such effect has been documented for Bpd. In these reports changes in the pacing threshold have been mentioned, yet the sensing thresholds are much less commonly recognized as being affected by cardioactive drugs, and significant clinical sensing problems have not been recognized with any of the drugs discussed in relation to pacing thresholds. The sensing capacity of a pacemaker depends on depolarization of the myocardium at the site of the pacing lead. It is believed that the amplitude of ventricular activation was altered by Bpd toxicity and that a decrease in the sensing level might culminate in sensing failure. It is also thought that DF had caused a sustained increase in pacing threshold that did not recover to its former level despite blood levels of Bpd being below the level of detectability. Several other reports that refer to the effect of DF on pacemaker threshold indicate an increase in stimulation threshold. These reports postulate thermal burn at the site of the ventricular electrode-endocardial junction secondary to DF.

The possibility of pacemaker malfunction occurring in association with antiarrhythmic therapy has not been fully explored. However, combination therapy with antiarrhythmic drugs and permanent pacemaker implantation is a popular treatment option for patients with sick sinus syndrome. This case report suggests that an inadequate use of antiarrhythmic drugs in conjunction with permanent pacemaker implantation may represent a serious hazard, and should be considered with caution.

REFERENCES