Papaverine-induced QT Interval Prolongation and Ventricular Fibrillation in a Patient with a History of Drug-induced QT Prolongation

Masayuki Goto¹, Masahito Sato¹, Hitoshi Kitazawa¹, Minoru Takahashi¹, Koichi Fuse¹, Atsushi Saito¹, Masaaki Okabe¹ and Yoshifusa Aizawa²

Abstract

A 64-year-old woman underwent a coronary flow reserve evaluation using intracoronary-administered papaverine into the left anterior descending artery. Her baseline electrocardiogram (ECG) was normal, but toward the end of papaverine administration, the QTU intervals were excessively prolonged and torsade de pointes occurred, leading to ventricular fibrillation. Ten months previously, the patient’s ECG showed mildly prolonged QTc (480 ms¹/²), which normalized after the cessation of bepridil. This case report suggests that a history of drug-induced QT prolongation can be a risk factor for papaverine-induced fatal ventricular arrhythmia.

Key words: coronary flow reserve, papaverine, QT prolongation, torsade de pointes

Case Report

We herein describe a case of a 64-year-old woman who had been treated for hypertension and paroxysmal atrial fibrillation. Ten months previously, she had developed chest pain and cold sweats and was transferred to our hospital. Upon admission, her electrocardiogram (ECG) showed mild ST depression in the leads V4-6. Her ECG showed normal sinus rhythm and a normal QT interval of 440 ms, but it showed mildly prolonged QTc (480 ms¹/²), which normalized after the cessation of bepridil (100 mg/day), which had been administered for atrial fibrillation (Fig. 1A, B). After providing informed consent, the patient underwent coronary angiography, which revealed 90% stenosis in the right coronary artery, 75% stenosis in the left anterior descending artery (LAD), and 99% stenosis in the left circumflex artery. A drug-eluting stent was placed, and the lesion of the left circumflex artery was dilated to 0% of stenosis. The patient became asymptomatic and was administered antihypertensive drugs (bisoprolol 2.5 mg/d and imidapril 2.5 mg/d) and antiplatelet agents (aspirin 100 mg/d and clopidogrel 75 mg/d) and followed in the outpatient clinic. The patient was re-admitted for coronary artery re-evaluation. At the time of catheterization, her blood pressure was 113/73 mmHg, and her heart rate was 56 beats/min. Her serum potassium was 4.2 meq/L. No re-stenosis was observed at the stenting site. Then, the stenosis of the LAD was evaluated using the coronary fractional flow reserve (FFR) method (1, 2). Briefly, a pressure wire (Pressure Wire, Radi Medical Systems, Wilmington, USA) was passed through the stenotic lesion, her blood pressure was recorded during a pull-back, and FFR was calculated as the ratio of the mean coronary pressure distal to the stenosis divided by the mean aortic pressure. FFR <0.80 was considered to be an indication for coronary intervention therapy. We administered papaverine hydrochloride to induce the maximal dilatation: 12 mg was administered into LAD in 15 seconds, and FFR was determined at the end of administration (3,4).

The patient’s baseline ECG was normal (Fig. 2A), but toward the end of the papaverine administration, the QT and QTU intervals were excessively prolonged, and this was soon followed by torsade de pointes (TdP) and ventricular fibrillation (VF) (Fig. 2B). Her sinus rhythm was resumed.
Figure 1. QT prolongation induced by bepridil. A: The patient was administered bepridil for atrial fibrillation. Her heart rate was 70 bpm, and QTc was mildly prolonged (480 ms\(^{1/2}\)). B: After the cessation of bepridil, QTc normalized in a few days (419 ms\(^{1/2}\)). HR: heart rate, bpm: beats per minute.

Figure 2. TdP induced by papaverine hydrochloride. A: The patient’s ECG was normal before the administration of papaverine: QT and QTc were 410 ms and 404 ms\(^{1/2}\), respectively, in lead II and 430 ms and 424 ms\(^{1/2}\), respectively, in lead V4. B: Soon after intracoronary papaverine was administered at a dose of 12 mg, the T and U waves were merged, forming a giant T-U wave, and the QTU (QTUc) interval was excessively prolonged to 610 ms (729 ms\(^{1/2}\)) in lead II, and 700 ms (836 ms\(^{1/2}\)) or longer in V4 with ST-T alteration. Soon after, TdP developed and degenerated to fibrillation.

by a DC shock delivery at 300 W.

Because the FFR value was borderline (0.80), we performed intervention therapy to the LAD lesion, which resulted in 0% stenosis with stenting. The patient has since been followed uneventfully in the outpatient clinic.

### Discussion

The FFR study has been established as a tool to guide coronary intervention therapy with beneficial outcomes (1, 2). In the present patient, we employed papaver-
ine hydrochloride for the FFR study because it can be administered intracoronary and induces a relatively steady-state of maximal hyperemia (3, 4).

However, it is known that papaverine may induce fatal ventricular tachyarrhythmia (VTA) (4-7). The mechanism of papaverine-induced VTA is not fully understood (8), but the drug has been shown to inhibit delayed rectifying potassium currents (IKr) and to prolong the action potential duration (9). When the action potential duration is excessively prolonged, early after-depolarization is expected to provoke triggered activity and subsequent VF, as observed in congenital or drug-induced QT prolongation (10, 11).

Several risk factors have been suggested for papaverine-induced VTAs, including female gender (4, 6), hypokalemia, and alkalosis (6, 7). In this report, the patient was female, but she had a normal serum potassium level and sinus rate. However, her history was remarkable for bepridil-induced QT prolongation. Bepridil has been shown to inhibit delayed rectifying potassium currents (IKr and IKs) in animals (12). Bepridil is now used to prevent atrial fibrillation recurrence in Japan, and TdP might rarely develop as an adverse effect (13). Through a common class III action, papaverine and bepridil can cause QT prolongation and TdP, and a history of bepridil-induced QT prolongation can be a risk factor for papaverine-induced VTAs during coronary fractional reserve studies.

A female patient developed TdP and VF following the intracoronary administration of papaverine during a coronary FFR study. A history of drug-induced VTAs during coronary fractional reserve studies may be a risk factor for papaverine-induced VTA.

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

References