Ivabradine-Induced Torsade de Pointes in Patients with Heart Failure Reduced Ejection Fraction

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Summary

Ivabradine is a selective inhibitor of the sinoatrial node “funny” current, prolonging the slow diastolic depolarization. As it has the ability to block the heart rate selectively, it is more effective at a faster heart rate. It is recommended for the treatment of heart failure reduced ejection fraction in the presence of beta-blocker therapy for the further reduction of the heart rate. However, previous reports have shown the association of Torsade de pointes (TdP) with concurrent use of ivabradine and drugs resulting in QT prolongation or blockage of the metabolic breakdown of ivabradine. In this article, we report two cases of patients with heart failure reduced ejection fraction who developed TdP after ivabradine use. Our report highlights the need to exercise caution with the administration of ivabradine in the presence of a reduced repolarization reserve, such as QT prolongation or metabolic insufficiency.

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Key words: Polymorphic ventricular tachycardia, QT prolongation

Ivabradine is a selective “funny” current (If) inhibitor that reduces heart rate through inhibition of the If channel in the sinoatrial (SA) node. Owing to its beneficial ability to selectively decrease heart rate and thereby decrease myocardial oxygen demand, it is used in the treatment of patients with coronary artery diseases (CAD) and heart failure (HF) reduced ejection fraction, demonstrating an ineffectively controlled heart rate. However, some cases have reported an arrhythmogenic effect of ivabradine, especially with the concurrent use of drugs resulting in QT prolongation-associated Torsade de pointes (TdP). We present two cases of patients who developed TdP after ivabradine use with coexistent beta-blocker and loop diuretics.

Case Report

Case 1: A 48-year-old male patient was admitted with New York Heart Association classification II dyspnea. He reportedly suffered from upper respiratory symptoms three days before and then worsened to dyspnea. He has diagnosed with ST-elevation myocardial infarction with cardiogenic shock three months prior and underwent primary percutaneous coronary intervention at the left descending artery with an intra-aortic balloon pump. After recovering the patient from the cardiogenic shock and stabilizing him, we started ivabradine 5 mg b.i.d because he showed beta-blocker intolerance (e.g., symptomatic hypotension). After starting carvedilol 3.125 mg, he complained of dizziness and dyspnea. Blood pressure (BP), which was around 90/60 mmHg before starting, dropped to around 70/50 mmHg, and congestion was observed to have aggravated on chest radiography. As the patient showed improvement after changing the medication, he was discharged with conventional HF medications and ivabradine.

On present admission, physical examination revealed jugular vein engorgement, and chest radiography revealed cardiacomegaly (cardiothoracic ratio = 0.61) with pulmonary edema. On the initial vital signs, BP was 87/63 mmHg, and the heart rate (HR) was 91 beats per minute (bpm). Echocardiography revealed severe left ventricular dysfunction (left ventricular ejection fraction [LVEF] = 28%). Electrocardiography (ECG) showed sinus rhythm with deep pathologic Q wave at the precordial lead (HR = 86 bpm, corrected QT [QTc] = 502 ms, Figure 1A). Laboratory findings revealed normal kidney and liver function (blood urea nitrogen [BUN], 14.9 mg/dL; creatinine [Cr], 1.03 mg/dL; estimated glomerular filtration rate [eGFR],
Figure 1. Serial electrocardiogram (ECG) of 48-year-old male patient. A: Baseline ECG at present admission shows heart rate is 86 beats per minute and corrected QT (QTc) is 502 ms. B: Telemetry reveals “polymorphic ventricular tachycardia owing to R-on-T phenomenon” after bigeminy (red arrows), which is compatible with Torsade de pointes (TdP). C: After recovery of sinus rhythm, ECG shows a heart rate of 58 beats and markedly prolonged QTc with 692 ms. D: Follow-up ECG 24 hours after recovery shows heart rate elevated at 109 beats per minute, and QTc recovered to 458 ms. The paper speed is 25 mm/second, and the amplitude is 10 mm/mV.

83 mL/minute/1.73 m²; aspartate transaminase [AST], 23 IU/L; alanine aminotransferase [ALT], 10 IU/L; total bilirubin, 0.8 mg/dL; albumin, 3.6 g/dL; and prothrombin time [PT], 1.00 INR). N-terminal pro-brain natriuretic peptide (NT-proBNP) level was 2817 pg/mL. The electrolyte levels were as follows: sodium, 138 mEq/L; potassium, 3.23 mEq/L; and chloride, 97 mEq/L.

Our medical diagnosis was determined to be acute decompensated HF, and we then started concomitant oral torsemide and intravascular (i.v.) furosemide. Ivabradine was used continuously at the previous dose. The symptoms were improving. However, on the 12th day in the hospital, he developed syncope. Telemetry demonstrated polymorphic ventricular tachycardia. After several attempts of DC cardioversion, VT disappeared and was converted to a sinus rhythm. Laboratory studies, including electrolytes, were within the normal range. Telemetry recording showed polymorphic VT owing to “R-on-T” phenomenon after QTc prolongation with bigeminy premature ventricular complex (Figure 1B). Post-event ECG showed a ventricular rate of 58 bpm with QTc of 692 ms (Figure 1C). Ivabradine was discontinued, and the 24-hour follow-up ECG showed normalization of QTc (458 ms, Figure 1D).

Case 2: A 51-year-old male was admitted due to cardiomegaly. He had chronic heavy alcoholism. His echocardiography revealed dilatation of all cardiac chambers (LV end-diastolic diameter/LV end-systolic diameter = 63/52 mm) with severe LV dysfunction (LVEF = 30%) and moderate functional mitral regurgitation compatible with dilated cardiomyopathy. His initial ECG showed sinus tachycardia with right bundle branch block (HR = 143 bpm, QRS duration = 154 ms, QTc = 466 ms, Figure 2A). His chest radiograph revealed marked cardiomegaly (cardiothoracic ratio = 0.65), without pulmonary congestion. Laboratory study revealed elevated BUN (26.6 mg/dL) and Cr (1.47 mg/dL) with decreased eGFR (54 mL/minute/1.73 m²). In the liver enzyme assay, AST was determined to be slightly elevated (123 IU/L), whereas other tests were within normal limits (ALT, 42 IU/L; total bilirubin, 1.1 mg/dL; albumin, 3.5 g/dL; and prothrombin time, 1.10 INR). NT-proBNP was elevated (27482 pg/mL). Electrolyte level was as follows: sodium, 135 mEq/L; potassium, 4.61 mEq/L; and chloride, 98 mEq/L.

We started HF medication, including 40 mg of valsartan, 6.25 mg of carvedilol, 12.5 mg of spironolactone, and 20 mg of furosemide orally. Three days after admission, we added 5 mg of ivabradine due to uncontrolled tachycardia (HR > 100 bpm). However, his HR continued to be over 70 bpm after ivabradine. Therefore, we increased carvedilol to 12.5 mg, seven days after admission, and ivabradine to 10 mg, nine days after admission (Figure 2B). After up-titration of these drugs, his HR was controlled around 70 bpm. However, on the 14th hospital day, he developed syncope. The electrical rhythm showed bigeminy premature ventricular complex (PVC) followed by polymorphic VT, which was consistent with TdP (Figure 2C). After several attempts of DC cardioversion, his rhythm recovered. ECG immediately after the event showed 64 bpm with bigeminy PVC and markedly prolonged QTc (790 ms, Figure 2D), and, 12 hours after follow-up, ECG from the last TdP showed slightly short-
Figure 2. A: Baseline electrocardiogram (ECG) shows sinus tachycardia with right bundle branch block and corrected QT interval (QTc) of 466 ms. B: ECG follow-up nine days after admission shows controlled heart rate for 87 bpm, but also shows prolongation of QTc (539 ms). C: ECG confirmed by the defibrillator at the time of syncope demonstrates polymorphic ventricular tachycardia owing to the “R-on-T” phenomenon (red arrow) following bigeminy with markedly prolonged QTc (689 ms). D: ECG immediately after the event showed 64 bpm with bigeminy and further prolonged QTc (790 ms). E: Twelve hours after follow-up ECG from last TdP showed sinus bradycardia with QTc prolongation. However, QTc was slightly shortened (657 ms). F: ECG follow-up three days after discontinuing of ivabradine shows shortened QTc from 689 ms to 546 ms.

Discussion

This report describes the clinical course, diagnostic features, and management of two patients who developed TdP after ivabradine use with concomitant beta-blocker and loop diuretics.

Increased HR was determined to be independently related to worse clinical outcomes in various cardiac diseases, including hypertension, CAD, and HF. Ivabradine can reduce HR that inhibits the If channel in the SA node to produce dose-dependent bradycardia.1,2) The BEAUTIFUL and SIGNIFY studies showed the beneficial effect of ivabradine in CAD with HR ≥ 70 beats per minute.3,4) Meanwhile, the SHIFT trial showed reduced hospital admission rates and mortality in patients with HF reduced ejection fraction.5) Previously published studies have demonstrated that ivabradine is effective and relatively safe for patients with acute decompensated systolic HF.6,7) Further, they suggested that early co-administration of ivabradine and beta-blockers during hospitalization for acute HF was feasible and safe.8) In actual clinical practice, achieving the maximum tolerated dose of beta-blockers is not easy owing to intolerance.9,10) "Intolerance" in a broad sense may include the selective nature of trial enrollment, provider disgust, therapeutic inertia, real or perceived side effects, and clinically significant adverse effects. Especially, the potential side effects, such as bradycardia, hypotension and/or orthostasis, fatigue, and especially acute decompensation, can lead to under prescription or low-dose prescription.11) As a result, many patients are unable to reach the target. Therefore, the combined use of ivabradine before achieving the maximal beta-blocker dose
is feasible.

Despite the beneficial effect of ivabradine, it is known to increase the relative risk of atrial fibrillation.\(^1\) In addition, although ivabradine is known not to cause QT prolongation directly, it is recommended to avoid ivabradine in patients with congenital long QT syndrome or those receiving known QT-prolonging medications. Further, electrolyte abnormalities, which may be induced by co-administration of diuretics or drugs that block the metabolic breakdown of ivabradine, may increase the conditional risk of TdP.\(^2,3\) A previous in vivo study demonstrated that ivabradine inhibits hERG channels, which strongly affect ventricular repolarization and susceptibility to TdP.\(^4\) Therefore, we speculate that impaired ivabradine metabolism owing to concomitant use of other drugs leads to increased concentrations or tissue accumulation, and this process enhances the intrinsic bradycardic effects of ivabradine and directly affects repolarization by hERG potassium channel inhibition, resulting in TdP. In Case 1, it is presumed that the above process enhanced the bradycardic effects of ivabradine during decongestion therapy using diuretics. In Case 2, the bradycardia-induced TdP may have occurred by enhancing the intrinsic bradycardic effects due to the synergistic effect with beta-blocker.\(^5\)

Our cases imply that ivabradine should be administered with caution in the presence of a reduced repolarization reserve, such as QT prolongation or condition with metabolic insufficiency.

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Conflicts of interest: The authors have no conflict of interest to declare.

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