Hydroxyzine-induced Torsade de Pointes in a Patient with Complete Atrioventricular Block

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Abstract:
An 82-year-old woman was admitted to our hospital because of dyspnea and bradycardia during exertion. Electrocardiography revealed complete atrioventricular block. During pacemaker implantation, a small dose (12.5 mg) of hydroxyzine was injected for sedation, and torsade de pointes (Tdp) occurred. The QT interval was prolonged after administration of hydroxyzine, and Tdp was observed after the R on T phenomenon occurred, indicating that hydroxyzine was capable of prolonging the QT interval and causing Tdp. Therefore, we must be cautious when administering hydroxyzine for sedation during surgery, especially in patients with bradycardia.

Key words: hydroxyzine, torsade de pointes, QT prolongation, bradycardia

Introduction

Hydroxyzine is among the most potent first-generation histamine 1 receptor antagonists (1). This drug is widely used in daily clinical practice for various conditions, such as skin allergies, pruritus, urticaria, and sedation during operation. Antihistamines, including hydroxyzine, have been reported to prolong the QT interval (2) and cause ventricular tachyarrhythmias (3, 4). These drugs delay myocardial repolarization and prolong the QT interval in a dose-dependent manner. Hydroxyzine is one of the most potent drugs for prolonging the QT interval (2).

We herein report a case of complete atrioventricular block with torsade de pointes (Tdp) induced by hydroxyzine administered during pacemaker implantation.

Case Report

An 82-year-old woman was admitted to our hospital with shortness of breath on physical exertion for the past 2 months. Her medical history included hypertension and asthma. She routinely took amlodipine for hypertension and verapamil for paroxysmal supraventricular tachyarrhythmia but no other medications that were known to prolong the QT interval.

Her height and weight were 140 cm and 45 kg, respectively. A physical examination revealed a pulse rate of 45 beats per minute, blood pressure of 145/45 mmHg, respiratory rate of 18 breaths per minute, oxygen saturation of 97% at room air, and temperature of 37.0 °C. There was no heart murmur. The cardiothoracic ratio was 55%; chest radiography revealed lung congestion (Fig. 1). Electrocardiography revealed complete atrioventricular block (CAVB), the heart rate was 46 beats per minute (bpm), and the QT/QTc interval was 570/482 ms (Fig. 2). Echocardiography revealed no abnormal findings, and the left ventricular ejection fraction was 70%. The serum potassium level was 4.0 mmol/L, magnesium level was 2.0 mg/dL, and other electrolyte levels were normal. The brain natriuretic peptide and troponin I levels were 399.5 pg/mL and 0.01 ng/mL, respectively.

Verapamil was discontinued after admission; however, the CAVB did not improve, and the patient underwent pacemaker implantation on the day after admission. The QT interval was 565 ms at the beginning of the operation. After she entered the operation room, 12.5 mg hydroxyzine was injected for sedation. However, 10 minutes later, she developed Tdp and convulsions. As chest compressions were performed within seconds, Tdp recovered to sinus rhythm, and
immediate temporary pacing was inserted. Tdp did not recur after temporary pacing at 70 bpm, and the pacemaker was successfully implanted. Just before Tdp occurred, the QT interval was prolonged to 636 ms, and R on T waves were observed (Fig. 3). We were unable to measure the QT interval of her own pulse after washout of hydroxyzine, as temporary pacing had been performed during pacemaker implantation, and all ventricular pacing was required for complete atrioventricular block after pacemaker implantation. The patient was discharged nine days later without incident.

Discussion

Various drugs, such as antiallergic drugs, antibiotics, and antipsychotic drugs, have been reported to prolong the QT interval (5-10). Among these, antihistamines, such as hydroxyzine, have been reported to cause ventricular tachyarrhythmias due to QT prolongation (2-4). Antihistamines slow cardiac repolarization and prolong the QT interval in a dose-dependent manner; hydroxyzine is one of the most potent drugs prolonging the QT interval (2).

Cardiomyocytes are repolarized mainly through the activation of potassium channels. The main channels involved in repolarization are IKs channels, which are slowly activated and deactivated, and IKr channels, which are rapidly activated and deactivated (11). Drug-induced QT prolongation typically occurs due to delayed myocardial repolarization, in which activation of IKr channels is blocked, and slow activation of IKs channels is more accentuated (12). During bradycardia, repolarization takes longer because there is sufficient time for the IKs channels to deactivate until the next depolarization after repolarization (13). In contrast, when the heart rate is increased by temporary pacing, the next depolarization begins before the IKs channel is completely deactivated, which advances the IKs current accumulation. Consequently, repolarization occurs easily, and the QT interval is shortened.

According to a recent review on QT prolongation and Tdp induced by hydroxyzine (3), most patients take 100 to 300 mg of hydroxyzine regularly. Only four cases of Tdp caused by injecting hydroxyzine as pre-medication during operation have been reported; however, the doses of hydroxyzine were high, ranging from 25 to 400 mg. The use of other drugs that prolong the QT interval in elderly patients and women has been reported as a risk factor for hydroxyzine-induced Tdp. In the present case, the dose of hydroxyzine was only 12.5 mg; however, the patient was an elderly woman with a small physique who had bradycardia due to CAVB. Therefore, even a small dose of hydroxyzine carried a risk of causing Tdp. Genetic mutations are reportedly associated with drug-induced QT prolongation (14). Unfortunately, we have no data on any mutations in the long QT syndrome gene in this case. However, genetic screening may be useful, as examining a patient for a genetic mutation can lead to the early detection of the risk of drug-induced QT prolongation in family members.

This is the first report to include an electrocardiogram clearly demonstrating that the QT interval was prolonged after injection of hydroxyzine and that Tdp was triggered by...
An electrocardiogram during pacemaker implantation. A: The electrocardiogram showed the moment of R on T and Tdp. B: The QT interval (arrow) was 565 ms at the beginning of the operation. C: The QT interval (arrow) was prolonged to 636 ms after the injection of hydroxyzine and just before Tdp.

R on T coincident with premature ventricular contraction.

**Conclusion**

Hydroxyzine is frequently used for sedation during operations in daily clinical practice. We should recognize that these conventional drugs have a QT-prolonging effect and be alert for the appearance of ventricular arrhythmia. Even small doses of hydroxyzine should not be administered to bradycardia patients, especially elderly women with small physiques.

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

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