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CASE REPORT

Azithromycin as a cause of QT-interval prolongation and torsade de pointes in the absence of other known precipitating factors

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Abstract During treatment with azithromycin, a 55 year-old woman developed a newly prolonged QT interval and torsade de pointes in the absence of known risk factors. Female gender and acute renal failure may be considerations in patients treated with azithromycin.

Keywords Azithromycin · QT interval · Torsade de Pointes · LQTS

1 Introduction

The long QT syndrome (LQTS) is characterized by prolongation of the QT interval, which can be congenital or acquired. The acquired form has a long QT interval caused by various cardiovascular and non-cardiovascular drugs, electrolyte abnormalities, central nervous system lesions and other medical conditions. [1]

Q-T prolongation, whether congenital or acquired, is associated with the development of the malignant arrhythmia torsade de pointes (a polymorphic ventricular tachycardia), that may result in sudden death [2]. We are reporting a case of QT-interval prolongation and torsade de pointes apparently precipitated by azithromycin. Unlike previous reports, this patient was not taking other medications known to cause QT prolongation or have other risk factors for LQTS.

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2 Case report

A 55-year-old female who had a pacemaker for intermittent symptomatic bradycardia presented elsewhere with headache, generalized body weakness and chills for 2 days. Cultures were positive for *Staphylococcus aureus*. She was started on gentamicin and vancomycin and transferred to Montefiore. On admission, she reported no chest pain, shortness of breath, nausea or vomiting. Her past medical history included hypertension and symptomatic bradycardia. Her medications included atorvastatin, quinapril, metoprolol, niacin, aspirin and multivitamins. She did not take any opiates, herbal or antipsychotic medications. Physical examination revealed a flushed face with no evidence of fever on gentamicin and vancomycin. Breath sounds were normal. Cardiac auscultation showed normal heart sounds without murmurs or gallops. The patient's baseline 12-lead ECG taken a week before admission showed normal sinus rhythm at 40 beats per minute, normal axis, normal PR interval of 160 ms, QT 520 ms, QTc 420 ms (Fig. 1). Because of methicillin-resistant staphylococcus aureus sepsis, extraction of the permanent pacemaker was scheduled. Intravenous gentamicin and vancomycin were continued. The pacemaker system was successfully extracted on the second hospital day. A transthoracic echocardiogram showed an ejection fraction of 50% and normal cardiac valves, without vegetations. In the presence of sepsis-related hypotension and antibiotics, the patient developed acute renal failure requiring transient hemodialysis. Gentamicin was discontinued.

On the seventh hospital day the patient developed cough and shortness of breath and was started on oral azithromycin at 500 mg daily for atypical pneumonia. On the 14th hospital day, after the seventh daily dose of azithromycin, telemetry showed two brief episodes of torsade de pointes

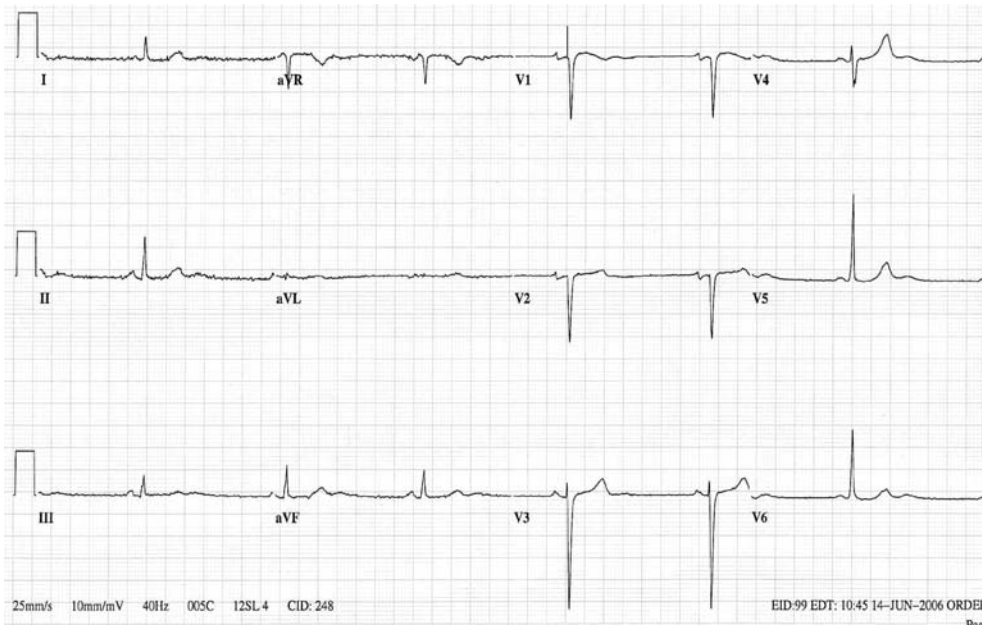

Fig. 1 Pre-admission electrocardiogram 7 days prior to admission during a pacemaker check with pacing inhibited

(Fig. 2). Two ECG's on the day before and after the episode were recorded with heart rates of 55 and 53 bpm and QT/QTc intervals of 620/580 and 640/610 ms, respectively, (Fig. 3). The patient remained hemodynamically stable. Two days later, another episode of torsade de pointes occurred when the heart rate was 58 and the QT/QTc 680/670. Blood chemistries during this period were normal other than blood urea nitrogen ranging from 26 to 98 mg/dl and creatinine ranging from 2.4–6.7 mg/dl. Potassium ranged from 3.8 to 4.9 mEq/l and CO2 ranged from 20 to 27 mEq/l. Her in-patient medications overlapping (at least for some days) with azithromycin were: heparin, methylprednisolone, furosemide, pantoprazole, darbapoetin, guafenisine, moxifloxacin, and ciprofloxacin. Of these, moxifloxacin has a weak QT prolongation effect without increasing dispersion; this medication was stopped 1 day after azithromycin was begun, and 6 days prior to torsades. Ciprofloxacin was started the day of the first torsades; there is no definite proclivity of this drug to cause QT prolongation, and the patient's QT prolongation had begun 7 days before, with initiation of azithromycin.

Azithromycin was discontinued at that point. There were no further episodes of torsade de pointes. Hemodialysis was discontinued as patient's creatinine and urine output improved. The cough and shortness of breath resolved. The patient was discharged home on intravenous vancomycin to complete the course of the treatment for four weeks.

3 Discussion

It is well established that individuals with a long QT interval are at an increased risk of developing torsade de pointes and sudden death [2]. Certain drug classes have been shown to be associated with prolongation of the QT interval. Of particular interest is the macrolide class of

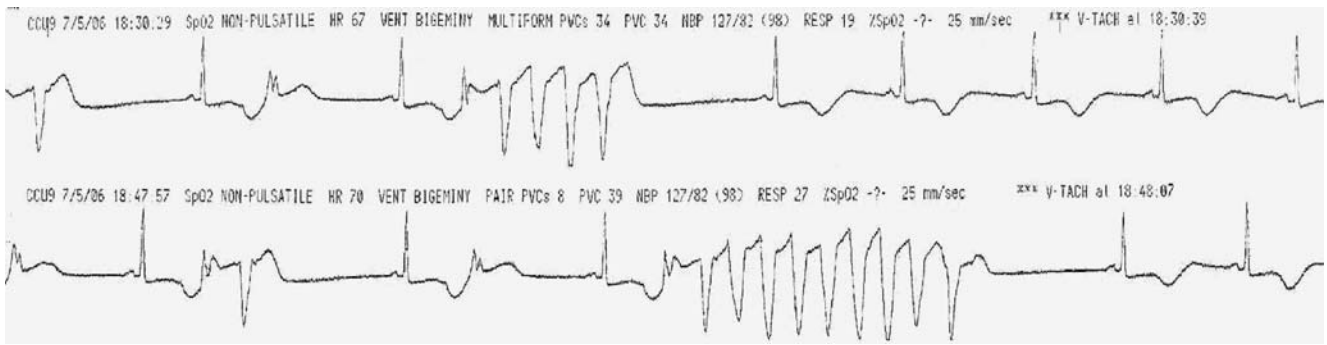

Fig. 2 Telemetry recording of torsade de pointes

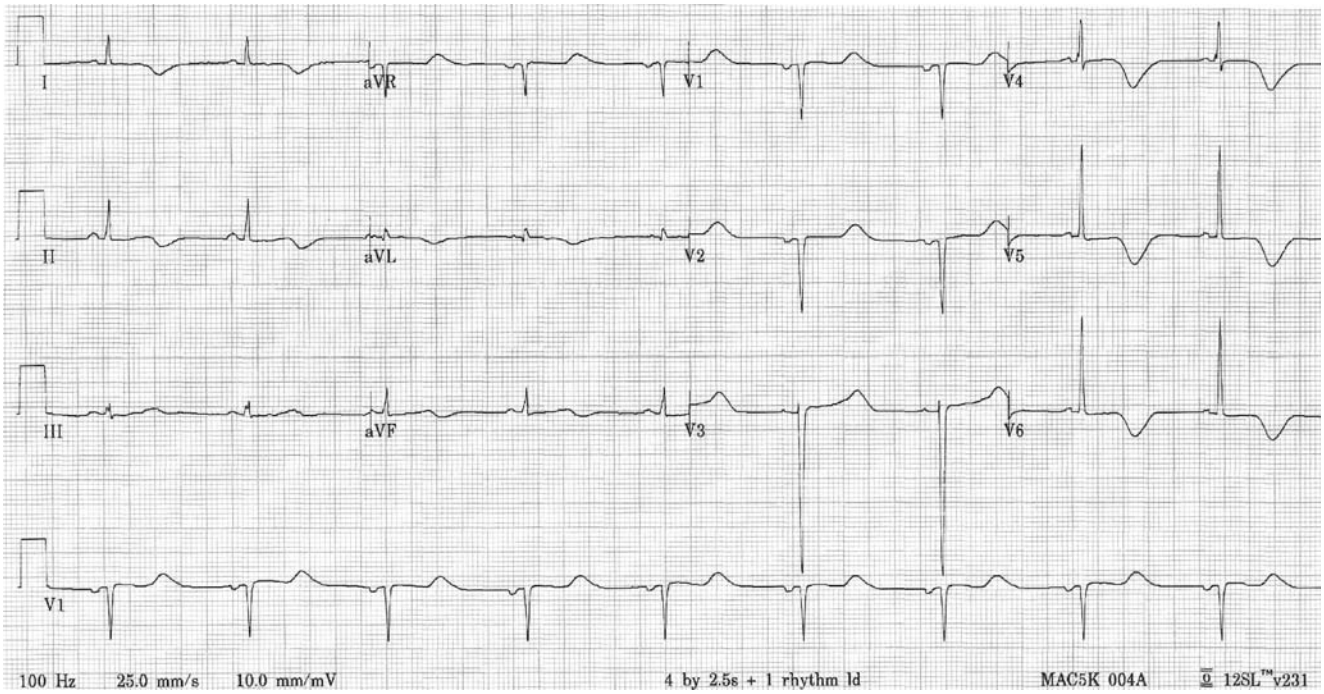

Fig. 3 Electrocardiogram while taking azithromycin

antibiotics. Semi-synthetic azithromycin has surpassed erythromycin as the most widely used macrolide. It may be better tolerated than other macrolides that are known to prolong the QT. [3–5] To our knowledge all previous reports of LQTS with azithromycin have been associated with additional known LQT risk factors. Samarendra reported a case of QT prolongation in a patient after administration of oral azithromycin, in addition to previously well-tolerated long-term amiodarone therapy. [6] Arellano-Rodrigo reported azithromycin-induced torsade de pointes and cardiorespiratory arrest in a patient with congenital long QT syndrome. [7] Matsunaga reported a case of QT prolongation associated with the use of azithromycin in a patient with pre-existing prolonged QTc and dilated cardiomyopathy. [8] In another study involving previously healthy persons, a modest statistically insignificant prolongation of the QTc interval without clinical consequences was observed after completion of a course of 3 g of azithromycin administered over a period of 5 days. [9] Finally, in a study by Kim [10], one dose of azithromycin was followed by polymorphic ventricular tachycardia, but no QT prolongation was noted and the patient was also reported to be hypokalemic. In animal studies, the "torsadogenic" potential of azithromycin was found to be remarkably low compared to clarithromycin and erythromycin [11]. In the Langendorff-perfused rabbit heart model of TdP, azithromycin did not display the pro-arrhythmic profile typical for blockers of the rapid component of delayed rectifier potassium current I_{Kr} such as erythromycin or sotalol. [12] Azithromycin, unlike many drugs causing torsade de pointes is not a substrate for CYP 450 3A4. Azithromycin is principally eliminated via liver and its non-renal clearance is not known to be affected by renal insufficiency [13] (GFR was 7 and 22 for the first and second event, respectively).

Could it be that the patient really had LQTS at baseline that was masked by her medications? We do not think so. Although the patient was initially taking atorvastatin and metoprolol, both of which may cause mild shortening of the QT interval, [14] her QT/QTc remained short for several days after both drugs were discontinued at admission.

Our case is unique in that this patient developed several bouts of torsade de pointes after seven days of azithromycin use without any other factors known to prolong QT interval. All her medications were checked against all the drugs known to prolong QT. [15] The patient's electrolytes were stable throughout. The echocardiogram was normal.

4 Recommendations

There is known to be female predominance in the FDA reports of erythromycin-associated cardiac arrhythmias [16, 17]. However, it is unknown whether there is a sex difference in cardiac repolarization response to azithromycin. In the meantime, it would seem prudent to consider all macrolides as a potential risk factor for LQT. There are several reports of QT prolongation in chronic renal failure [18, 19], and a report in acute renal failure where there were significant electrolyte abnormalities [20] (electrolytes

were normal in our patient). It remains unknown whether acute renal failure may be a potential risk factor for developing QT-interval prolongation in patients taking azithromycin.

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