

Giant inverted T waves and substantial QT interval prolongation induced by azithromycin

In an elderly woman with renal insufficiency

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Azithromycin is widely used for respiratory tract infections involving atypical organisms. As a newer type of macrolide, azithromycin is usually better tolerated than other macrolides, and it has a good safety profile. However, side effects involving long QT intervals, torsade de pointes (TdP), polymorphic ventricular tachycardia, and sudden cardiac death have been reported.¹⁻⁸ We describe a case of an elderly patient with renal insufficiency who developed severe giant inverted T waves and QT interval prolongation as an adverse effect of azithromycin. Unlike in previous studies, coronary angiography was performed in this patient, and no coronary artery lesions were found. The patient was not taking any other medications simultaneously that were known to cause QT prolongation.

Case

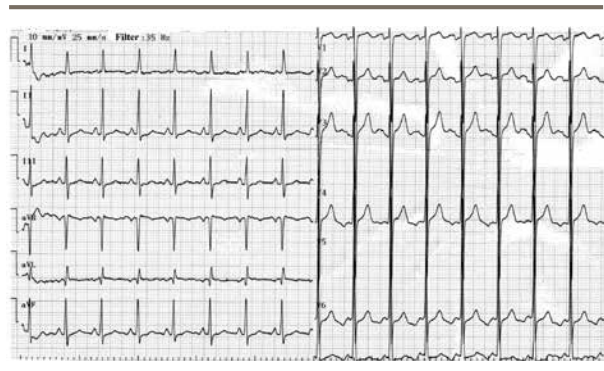
A 65-year-old woman presented with cough, chest tightness, and shortness of breath. She had a 2-year history of recurrent episodes of headache and dizziness. She denied having other symptoms, including chest pain or palpitations.

Upon presentation, the patient's blood pressure was 220/140 mm Hg, her heart rate was 94 beats/min, her respiratory rate was 16 breaths/min, her temperature was 38.2°C, and her oxygen saturation measured by pulse oximetry was 98% on room air. Lung auscultation revealed a few moist rales in the lower zones, while cardiac, abdominal, and neurologic examination findings were normal.

An electrocardiogram showed normal sinus rhythm at a rate of 97 beats/min with a QT interval of 346 milliseconds and a QTc of 400 milliseconds (Figure 1). The QTc was manually calculated using the Bazett formula: $QTc = QT / (RR^{1/2})$.⁹ Computed tomography of the chest revealed infiltrates throughout both lung fields. The white blood cell count was $13.6 \times 10^9/L$, with 88.3% neutrophils. The creatinine level was 362 $\mu\text{mol/L}$, the troponin I level was 0.16 $\mu\text{g/L}$, and the brain natriuretic peptide level was 4681.8 ng/L. Serum electrolyte levels and liver function were normal.

The patient was admitted with a diagnosis of community-acquired pneumonia and was given 0.5 g of intravenous azithromycin per day. Her other medications included arotinolol, nifedipine extended-release tablets, furosemide, spironolactone,

Figure 1. An electrocardiogram at admission showed normal sinus rhythm with a QT interval of 346 ms and QTc of 400 ms



EDITOR'S KEY POINTS

- Azithromycin is a newer subclass of macrolide antibiotic that is reported to be better tolerated than other macrolides. Although reports of azithromycin-induced QT prolongation and torsade de pointes have been intermittently published, cases with giant inverted T waves are rare.
- Clinicians should be aware of the dangerous and even potentially lethal side effects of azithromycin. Alternative antibiotics should be considered for those potentially at increased risk.

POINTS DE REPÈRE DU RÉDACTEUR

- L'azithromycine est une sous-classe plus récente d'antibiotiques macrolides qui, selon les rapports, est mieux tolérée que d'autres macrolides. Quoiqu'on ait occasionnellement signalé des cas d'allongement de l'intervalle QT et de torsades de pointes induits par l'azithromycine, les cas d'ondes T inversées de grande amplitude sont rares.
- Il faudrait que les cliniciens soient au courant des effets secondaires dangereux et potentiellement mortels de l'azithromycine. D'autres antibiotiques devraient être envisagés pour les personnes potentiellement à risque plus élevé.

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Cet article a fait l'objet d'une révision par des pairs.

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atorvastatin, and salicylic acid. Two hours after receiving the first dose of azithromycin, the patient developed mild chest tightness and shortness of breath. Serum electrolyte levels remained within normal limits, with magnesium at 1.04 mmol/L, calcium at 2.30 mmol/L, and potassium at 3.85 mmol/L. The troponin I level was 0.14 µg/L. However, an electrocardiogram showed normal sinus rhythm at 56 beats/min with a QT interval of 640 milliseconds, a QTc of 618 milliseconds, and giant inverted T waves (**Figure 2**). Subsequently, the QT interval became longer, with electrocardiograms recording a QT interval of 680 milliseconds and a QTc of 633 milliseconds (**Figure 3**) and then a QT interval of 660 milliseconds and a QTc of 676 milliseconds (**Figure 4**). The accompanying T-wave inversions became deeper. Myocardial infarction was ruled out using coronary angiography (**Figure 5**). Acute cerebrovascular disease was also excluded using computed tomography of the head. Normal echocardiogram findings without wall motion abnormalities initially ruled out takotsubo cardiomyopathy.¹⁰ However, no follow-up echocardiogram is available. Two days after discontinuation of azithromycin, the QT interval and QTc had reduced to 440 milliseconds and 443 milliseconds, respectively. The giant inverted T waves disappeared (**Figure 6**). Three days after discontinuation, the QT interval and QTc had reduced to 400 milliseconds and 429 milliseconds, respectively (**Figure 7**).

Discussion

It is recognized that QT prolongation, which can be congenital or acquired, is associated with the development of TdP and even sudden death.¹¹

Azithromycin is a newer subclass of macrolide antibiotic that is reported to be better tolerated than other macrolides. It has surpassed erythromycin as the most widely used macrolide.¹² However, a recent large-scale observational study found that a 5-day course of azithromycin was associated with a small absolute

increase in the risk of cardiovascular death, which was most pronounced for patients in the highest decile of the baseline risk of cardiovascular disease. Twenty-two of 29 cardiovascular deaths, 64.6 per 1 million courses, were sudden cardiac deaths, likely related to malignant arrhythmia.⁸

Our patient also developed an obvious QT prolongation with giant inverted T waves associated with administration of intravenous azithromycin. Using the Naranjo scale, a method for estimating the probability of adverse

Figure 3. An electrocardiogram showed a QT interval of 680 ms and a QTc of 633 ms 1 d after azithromycin administration

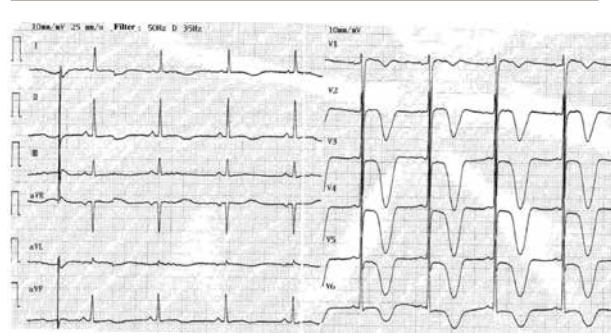


Figure 4. An electrocardiogram showed a QT interval of 660 ms and a QTc of 676 ms 2 d after azithromycin administration (1 d after discontinuation)

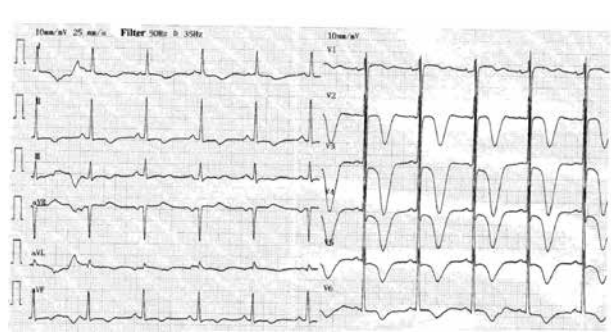


Figure 2. An electrocardiogram showed prominent QT interval prolongation (QTc = 618 ms) and giant inverted T waves 2 h after intravenous azithromycin administration

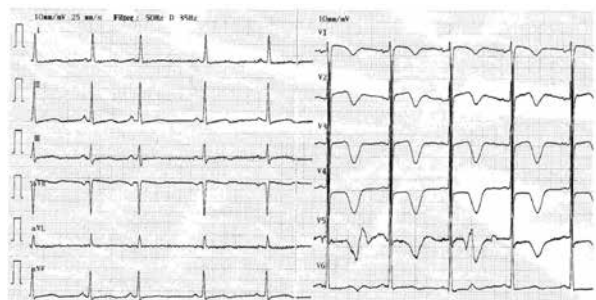


Figure 5. Coronary angiography showed no coronary artery lesions

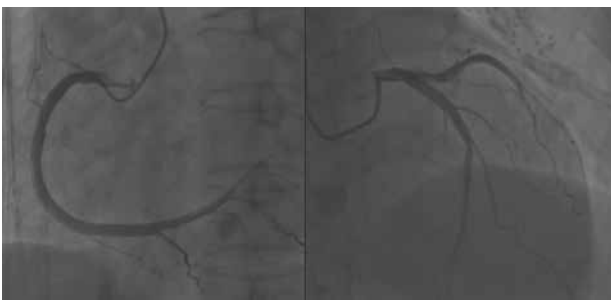


Figure 6. Two days after the discontinuation of azithromycin, the QT interval and QTc were reduced to 440 ms and 443 ms, respectively, and the giant inverted T waves disappeared

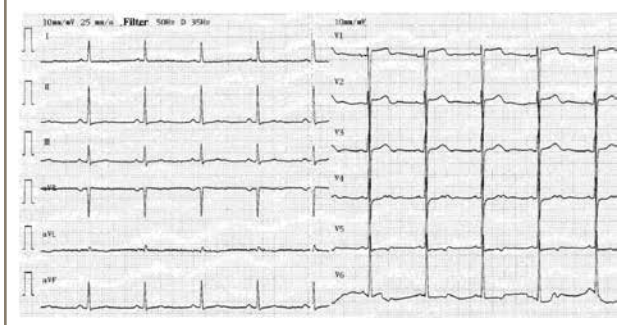
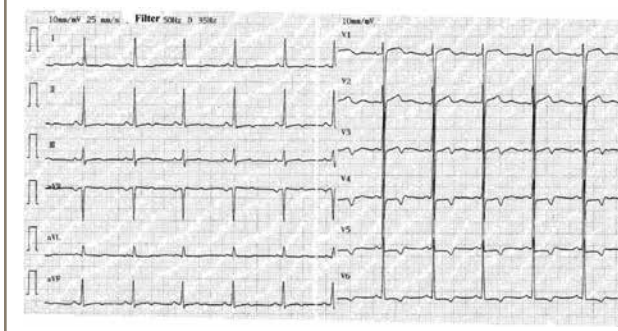


Figure 7. Three days after discontinuation of azithromycin, the QT interval and QTc were reduced to 400 ms and 429 ms, respectively



drug reactions, the patient had a score of 3, indicating a possible adverse reaction to azithromycin.¹³ Although reports of azithromycin-induced QT prolongation and TdP have been intermittently published, cases with such giant inverted T waves are rare. Because elevated troponin I level, coronary T waves, and QT prolongation are also induced by myocardial ischemia, this was excluded in our patient using coronary angiography. At the time of admission, the patient's troponin I level was elevated, but her electrocardiogram findings were normal.

Other studies have reported similar adverse effects with azithromycin use. Kezerashvili et al¹ have reported a case of azithromycin-related QT interval prolongation and TdP in the absence of other known precipitating factors. Russo et al² have reported a case of azithromycin-induced QT prolongation in an elderly patient with idiopathic dilated cardiomyopathy. Samarendra et al³ reported a case of QT prolongation associated with an azithromycin-amiodarone combination. Arellano-Rodrigo et al⁴ reported a case of azithromycin-induced TdP and cardiorespiratory arrest in a patient with congenital long QT syndrome. Matsunaga

et al⁵ reported QT prolongation associated with the use of azithromycin in a patient with pre-existing prolonged QTc and dilated cardiomyopathy. In another study, Strle and Maraspin⁶ observed a modest but not statistically significant prolongation of QTc without clinical consequences in otherwise healthy participants after completion of a course of 3 g of azithromycin administered over 5 days. Further, in a case reported by Kim et al,⁷ a single dose of azithromycin was associated with polymorphic ventricular tachycardia. The patient had no QT prolongation but had hypokalemia.

Risk factors for development of QT prolongation and TdP include electrolyte level abnormalities (hypokalemia, hypocalcemia, hypomagnesemia), myocardial ischemia or infarction, myocarditis, bradycardia, left ventricular dysfunction, mitral regurgitation, use of antiarrhythmic agents, and idiopathic long QT syndrome.¹⁴ Data also suggest that female sex is a risk factor for TdP. In our case, the patient was an elderly woman with renal insufficiency.

Female predominance has been observed in a significant percentage of reports of medication-associated cardiac arrhythmias ($P < .001$).^{15,16} Even healthy women have slightly longer QT intervals than men, and idiopathic long QT syndrome predominantly affects women.^{17,18} Liu et al found that female rabbit heart models are more likely to develop TdP arrhythmias, despite a similar degree of QT prolongation with a potassium channel block by 4-aminopyridine.¹⁹ However, Johansson et al found no association between ibutilide-induced QT prolongation and female sex in *in vivo* rabbit models of acquired long QT syndrome.²⁰ At present, it is unknown whether the sex difference is a potential contributing factor for QT prolongation and TdP in response to azithromycin, and the pathophysiologic basis for the sex disparity should be further investigated.

The mechanisms of erythromycin-induced changes in cardiac repolarization remain unclear, but the prolongation of the action potential duration might be related to erythromycin-induced suppression of the delayed rectifier potassium current.^{21,22} However, azithromycin did not display the proarrhythmic profile typical of blockers of the rapid component of the delayed rectifier potassium current (eg, erythromycin) in the Langendorff-perfused rabbit heart model of TdP.²³

Azithromycin is principally eliminated via the liver. This nonrenal clearance is not known to be affected by renal insufficiency.²⁴ However, Kezerashvili et al¹ reported a case of QT interval prolongation and TdP caused by azithromycin in a patient with acute renal failure and normal electrolyte levels. In our case, the patient had renal insufficiency, but the electrolyte levels were also normal. It remains unknown whether renal insufficiency is a potential risk factor for developing QT interval prolongation in patients taking azithromycin.

Conclusion

Our case and the findings of others indicate that clinicians should be aware of the dangerous and even potentially lethal side effects of azithromycin. We suggest that patients receiving intravenous macrolides should be monitored closely. Alternative antibiotics should be considered for those potentially at increased risk—for example, as in our case, elderly women with renal insufficiency. 🌿

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Competing interests

None declared

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References

1. Kezerashvili A, Khattak H, Barsky A, Nazari R, Fisher JD. Azithromycin as a cause of QT-interval prolongation and torsade de pointes in the absence of other known precipitating factors. *J Interv Card Electrophysiol* 2007;18(3):243-6. Epub 2007 Jun 2.
2. Russo V, Puzio G, Siniscalchi N. Azithromycin-induced QT prolongation in elderly patient. *Acta Biomed* 2006;77(1):30-2.
3. Samarendra P, Kumari S, Evans SJ, Sacchi TJ, Navarro V. QT prolongation associated with azithromycin/amiodarone combination. *Pacing Clin Electrophysiol* 2001;24(10):1572-4.
4. Arellano-Rodrigo E, García A, Mont L, Roqué M. Torsade de pointes and cardiorespiratory arrest induced by azithromycin in a patient with congenital long QT syndrome [article in Spanish]. *Med Clin (Barc)* 2001;117(3):118-9.
5. Matsunaga N, Oki Y, Prigollini A. A case of QT-interval prolongation precipitated by azithromycin. *N Z Med J* 2003;116(1185):U666.
6. Strle F, Maraspin V. Is azithromycin treatment associated with prolongation of the Q-Tc interval? *Wien Klin Wochenschr* 2002;114(10-11):396-9.
7. Kim MH, Berkowitz C, Trohman RG. Polymorphic ventricular tachycardia with a normal QT interval following azithromycin. *Pacing Clin Electrophysiol* 2005;28(11):1221-2.
8. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366(20):1881-90.
9. Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal". *J Cardiovasc Electrophysiol* 2006;17(3):333-6.
10. Prasad A. Apical ballooning syndrome: an important differential diagnosis of acute myocardial infarction. *Circulation* 2007;115(5):e56-9.
11. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, et al. The long QT syndrome. Prospective longitudinal study of 328 families. *Circulation* 1991;84(3):1136-44.
12. Rubinstein E. Comparative safety of the different macrolides. *Int J Antimicrob Agents* 2001;18(Suppl 1):S71-6.
13. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239-45.
14. Jackman WM, Friday KJ, Anderson JL, Aliot EM, Clark M, Lazzara R. The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. *Prog Cardiovasc Dis* 1988;31(2):115-72.
15. Drici MD, Knollmann BC, Wang WX, Woosley RL. Cardiac actions of erythromycin: influence of female sex. *JAMA* 1998;280(20):1774-6.
16. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. *JAMA* 1993;270(21):2590-7.
17. Moss AJ, Schwartz PJ, Crampton RS, Locati E, Carleen E. The long QT syndrome: a prospective international study. *Circulation* 1985;71(1):17-21.
18. Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. *Am J Cardiol* 1993;72(6):23B-5B.
19. Liu XK, Wang W, Ebert SN, Franz MR, Katchman A, Woosley RL. Female gender is a risk factor for torsades de pointes in an in vitro animal model. *J Cardiovasc Pharmacol* 1999;34(2):287-94.
20. Johansson M, Carlsson L. Female gender does not influence the magnitude of ibutilide-induced repolarization delay and incidence of torsades de pointes in an in vivo rabbit model of the acquired long QT syndrome. *J Cardiovasc Pharmacol Ther* 2001;6(3):247-54.
21. Stanat SJ, Carlton CG, Crumb WJ Jr, Agrawal KC, Clarkson CW. Characterization of the inhibitory effects of erythromycin and clarithromycin on the HERG potassium channel. *Mol Cell Biochem* 2003;254(1-2):1-7.
22. Volberg WA, Koci BJ, Su W, Lin J, Zhou J. Blockade of human cardiac potassium channel human ether-a-go-go-related gene (HERG) by macrolide antibiotics. *J Pharmacol Exp Ther* 2002;302(1):320-7.
23. Eckardt L, Breithardt G, Haverkamp W. Electrophysiologic characterization of the antipsychotic drug sertindole in a rabbit heart model of torsade de pointes: low torsadogenic potential despite QT prolongation. *J Pharmacol Exp Ther* 2002;300(1):64-71.
24. Höfler D, Koeppel P, Paeske B. Pharmacokinetics of azithromycin in normal and impaired renal function. *Infection* 1995;23(6):356-61.