Reprinted with permission from
JOURNAL OF PACING AND CLINICAL ELECTROPHYSIOLOGY, Volume 24, No. 10, October 2001

QT Prolongation Associated with Azithromycin/Amiodarone Combination

PADMARAJ SAMARENDRA, SARITA KUMARI,
STEVEN J. EVANS*, TERRENCE J. SACCHI, and VICTOR NAVARRO
From the Department of Cardiology, Long Island College Hospital, Brooklyn and the
*Electrophysiology Laboratory, Beth Israel Medical Center, New York, New York

SAMARENDRA, P., ET AL.: QT Prolongation Associated with Azithromycin/ Amiodarone Combination. *Administration of oral azithromycin, in addition to previously well-tolerated long-term amiodarone therapy, was associated with a marked prolongation of QT interval and increased QT dispersion, both substrates for life-threatening ventricular tachyarrhythmia and torsades de pointes. This is a report of QT prolongation and increased QT dispersion associated with the use of azithromycin. The report assumes an added significance, in view of widespread empirical use of this antibiotic for the treatment of lower respiratory infections and belief of its safety in patients with cardiac diseases. Based on the authors' experience, they would like to emphasize that the combination of azithromycin with other drugs known to prolong QT or causing torsades de pointes be used with caution until the question of the proarrhythmic effect of azithromycin is resolved by further studies. (PACE 2001; 24:1572–1574)*

QT interval, QT dispersion, azithromycin, torsades de pointes, erythromycin

Introduction

Azithromycin, an azalide antibiotic, although derived from erythromycin has not been shown to share the QT interval lengthening effect of the parent compound.

In clinical trials, ventricular arrhythmia or torsades de pointes had not been reported with the use of azithromycin, except for a report from postmarket experience of a patient who developed torsades de pointes.[1]

This report describes a patient, in whom administration of oral azithromycin, in addition to previously well-tolerated long-term amiodarone therapy, was associated with a marked prolongation of QT interval and increased QT dispersion, both substrates for life-threatening ventricular tachyarrhythmia and torsades de pointes.

The report assumes an added significance, in view of widespread empirical use of this antibiotic for the treatment of lower respiratory infections and belief of its safety in patients with cardiac diseases.

Case Report

A 68-year-old hispanic woman with stable congestive heart failure and an aneurysm of the posterior communicating artery was seen in her physician's office for right lower lobe pneumonia.

Address for reprints: Padmaraj Samarendra, M.D., 86 Baltic St., Apt. 3, Brooklyn, NY 11201. Fax: (718) 780-1619; e-mail: Padmaraj@aol.com

Received November 20, 2000; revised January 11, 2001; accepted January 22, 2001.

She was on amiodarone therapy (200 mg/day) for paroxysmal atrial fibrillation for more than a year. She was also taking furosemide (40 mg/day) and enalapril (7.5 mg twice a day) for moderate to severe systolic dysfunction, besides aspirin (325 mg/day). Her thyroid and liver function tests were normal.

Clinical examination revealed a blood pressure of 120/70 mmHg with a regular heart rate of 60 beats/min and normal jugular venous pulse. Cardiac examination showed an iii/vi soft systolic murmur at the apex with short radiation to the axilla. Lung auscultation revealed a few crepitations in the lower zone on the right side anteriorly, while abdominal and neurological examinations were normal.

There was no edema and blood chemistries, potassium, and magnesium were within the normal range.

An electrocardiogram showed a regular sinus rhythm at a rate of 60 beats/min with normal P-R, QRST, and QTc of 510 ms and QT dispersion of 58 ms (measured as the difference between longest and shortest QT intervals in a 12-lead electrocardiogram).

Treatment with azithromycin (500 mg) on day 1, followed by 250 mg/day for 4 days was started. On day 3 she was seen again for not feeling well and intermittent dizziness of short durations. Clinical examination remained unchanged except disappearance of previous lung findings. Blood chemistries, including renal parameters and cardiac enzymes, remained within normal limits with magnesium at 2.0 mg/mL and potassium at 4.3 mmol/L. However, the electrocardiogram now

showed sinus bradycardia at a rate of 53/min with marked prolongation of the QT interval (QT 676 ms, QTc 660 ms) and increased QT dispersion (140 ms) (Fig. 1).

Since azithromycin was the only new medication added to patient's preexisting long-term treatment, it was discontinued. Four days after the discontinuation of azithromycin, QT decreased to 541 ms, QTc to 523 ms, and QT dispersion to 60 ms, the baseline values for the patient (Fig. 2).

Discussion

There are no available data on azithromycin's effects on QT interval, QT dispersion, or the interaction of this antibiotic with other potentially arrhythmogenic compounds especially antiarrhythmic agents, capable of causing QT prolongation.

The patient in this report experienced dizziness and showed a prolonged QTc and increased QT dispersion, thus cardiac arrhythmia as one of the possible causes of her symptoms was considered besides others.

Although clinical trials have demonstrated a relatively safe arrhythmogenic profile, one postmarket experience report has shown association of azithromycin with torsades de pointes.[1]

Since searching *Medline* by using the key words azithromycin, zithromax, QT prolongation, torsades de pointes, or cardiac effects yielded no literature, the authors presume that this is an early report of QT prolongation and increased QT dispersion associated with the use of azithromycin.

Substantial QT prolongation (18%–20%) is expected with amiodarone,[2,3] and may be used as an indirect measure of therapeutic amiodarone effect,[4,5] however, increased QT dispersion is not a feature of amiodarone therapy. Amiodarone has been shown to decrease QT dispersion or not to affect it.[6,7]

Incidence of torsades de pointes associated with QT prolongation is a well-recognized but an unusual proarrhythmic complication of amiodarone therapy (overall incidence $< 1\%$).[8]

The arrhythmia associated with antiarrhythmic drugs usually occurs during the first several weeks of therapy but has occasionally been reported after long-term use.[9] While the early incidence of torsades de pointes is considered an idiosyncratic reaction to the antiarrhythmic drugs, the late occurrence is thought to be related to the introduction of a second risk factor such as hypokalemia, bradycardia, or change in the dose of antiarrhythmic medication.[10]

In the present case the patient was at no time hypokalemic or hypomagnesemic nor was there a change in her usual amiodarone dose. Therefore, it seems unlikely that amiodarone was responsible for the symptoms or increased QTc and QT dispersion from the baseline in this patient. Alternatively, since repolarization abnormalities resolved to baseline values after cessation of azithromycin therapy, it seems possible that azithromycin was casually related to these events. However, a possible interaction between azithromycin and amiodarone can not be ruled out.

The possible mechanism of the QT prolonging effect of azithromycin in this patient is difficult to define, however, one can speculate that perhaps azithromycin shares properties of erythromycin (the parent compound) of prolonging action potential duration in M cells and subsequent increase in transmural dispersion of repo-

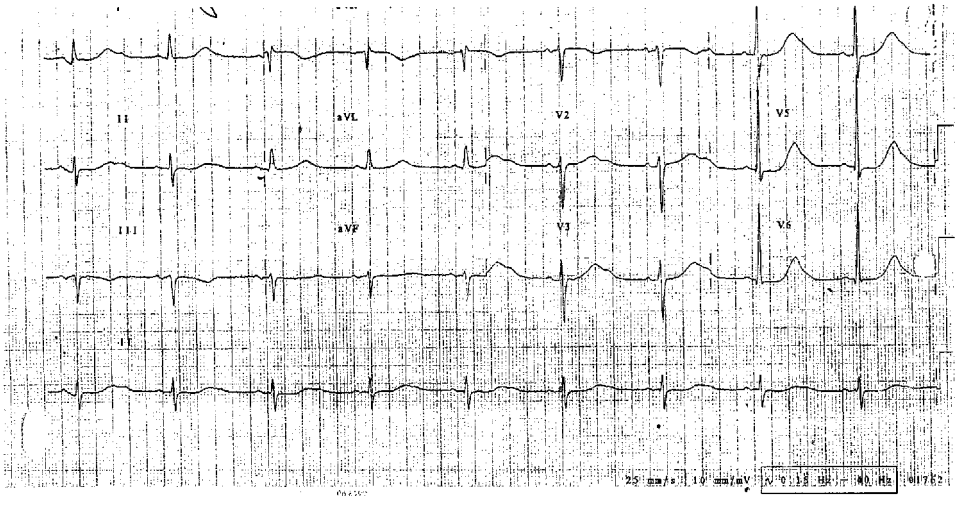

Figure 1. *ECG showing sinus bradycardia, QT 676 ms, QTc 660 ms, and QTd 140 ms while on a combination of azithromycin, amiodarone therapy.*

Figure 2. *ECG 4 days after discontinuation of azithromycin but continued amiodarone therapy. QT 541 ms, QTc 523 ms, and QTd 60 ms.*

larization by inhibiting potassium channels.[11] Alternatively, it inhibits the CYP3A4 isoenzyme affecting metabolism of amiodarone. Likewise, it is difficult to say if female sex predisposed this patient to the QT lengthening effect of azithromycin, as a sex difference in cardiac repolarization response has been reported to be a potential contributing factor for QT prolongation and torsades de pointes in response to erythromycin.[12]

In conclusion, it should be emphasize that the concurrent use of azithromycin with other drugs known to prolong QT or causing torsades de pointes be used with caution until the question of possible proarrhythmic effects of azithromycin is resolved by further studies.

References

1. Azithromycin PDR, 54 Ed 2000.
2. Middlekauff HR, Stevenson WG, Saxon LA, et al. Amiodarone and torsade de pointes in patients with advanced heart failure. Am J Cardiol 1995; 76:499–502.
3. Debbas NMG, du Cailar C, Bexton RS, et al. The QT interval: A predictor of the plasma and myocardial concentrations of amiodarone. Br Heart J 1984; 51:316–320.
4. Carry PVL, Holt P, Way B, et al. Intravenous amiodarone: An effective antiarrhythmic agent. (abstract) Br Heart J 1982; 47:191.
5. Nademanee K, Singh BN, Stevenson WG, et al. Amiodarone and post-MI patients. Circulation 1993; 88:764–774.
6. Cui G, Sen L, Sager P, et al. Effect of amiodarone, sematilide and sotalol on QT dispersion. Am J Cardiol 1994; 74:896–900.
7. Hii JT, Wyse DG, Gillis AM, et al. Precordial QT interval dispersion as a marker of torsade de pointes. Disparate effects of class Ia antiarrhythmic drugs and amiodarone. Circulation 1992; 86:1376–1382.
8. Singh BN, Venkatesh N, Nademanee K, et al. The historical development, cellular electrophysiology and clinical pharmacology of amiodarone. Prog Cardiovasc Dis 1989; 31:249–437.
9. Vrobel RT, MillerPE, Mostow DM, et al. A general overview of amiodarone toxicity: Its prevention, detection and management. Prog Cardiovasc Dis 1989; 31:393–426.
10. Oberg KC, O'Toole MF, Gallastegni Jl, et al. "Late" proarrhythmia due to quinidine. Am J Cardiol 1994; 74:192–194.
11. Antzelevitch C, Sun ZQ, Zhang ZQ, et al. Cellular and ionic mechanism underlying erythromycin induced long QT intervals and torsade de pointes. J Am Coll Cardiol 1996; 28:1836–1848.
12. Drici MD, Knollmann BC, Wang WX, et al. Cardiac actions of erythromycin: Influence of female sex. JAMA 1998; 280:1774–1776.