

# QT Interval Prolongation Associated with Azithromycin/Methadone Combination

S Amer, S Hassan, M Shariffi, L Chueca

## ABSTRACT

*This report documents the occurrence of QT prolongation in a 57-year old man, on methadone replacement therapy, treated with azithromycin for community acquired pneumonia. This case highlights a hitherto unknown drug interaction. In light of ever-increasing use of azithromycin, it is imperative that azithromycin be used with caution in patients who are already on drugs that are known to cause QT prolongation or that cause torsades de pointes.*

**Keywords:** Azithromycin, methadone, QT prolongation, *torsades de pointes*

## Prolongación del Intervalo QT Asociada con Combinación de Azitromicina/Metadona

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## RESUMEN

*Este reporte documenta la ocurrencia de la prolongación del intervalo QT en un hombre de 57 años, en la terapia de reemplazo con metadona, tratado con azitromicina por pulmonía adquirida en la comunidad. Este caso destaca una interacción de medicamentos desconocida hasta ahora. En vista del uso cada vez mayor de la azitromicina, resulta absolutamente necesario usarla con precaución en pacientes que ya están bajo tratamiento con medicamentos de los cuales se sabe que causan prolongación del intervalo QT o que causan torsades de pointes.*

**Palabras claves:** Azitromicina, metadona, prolongación del intervalo QT, *torsades de pointes*

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## INTRODUCTION

Methadone has been widely used as a replacement therapy in the management of opioid-dependent patients (1, 2). However, it has been historically known to cause QT prolongation, leading to *torsades de pointes* and even death (3). Several reports of drug interactions involving methadone causing cardiac arrhythmias have been reported (4–6). An interaction between methadone and azithromycin causing QTc prolongation has not been described previously. This case report documents the potentially fatal cocktail of azithromycin and methadone.

## CASE REPORT

A 57-year-old male, with past medical history of chronic obstructive pulmonary disorder (COPD), hypertension and intravenous drug use, presented to the emergency department

with a three-day history of fever, chills, shortness of breath and dry cough. He had been on methadone 60 mg daily for the last five years. He was subsequently diagnosed with COPD exacerbation and was treated with two courses of nebulization along with a single dose of 500 mg of azithromycin. Six hours later, he complained of chest pain, palpitations and diaphoresis. On examination, he was found to have tachycardia with other vitals remaining stable. Electrocardiogram (ECG) was done and it showed a sinus rhythm with QTc interval of 542 ms [milliseconds] (Figure). On reviewing his earlier ECGs that were done during his ongoing treatment with methadone, there was never an ECG recorded with QTc interval greater than 450 ms. Methadone and azithromycin were immediately withdrawn and he was then transferred to the telemetry floor for close observation. Within 24 hours, the patient improved clinically and his QTc reduced to 471 ms. He was subsequently monitored for another 24 hours and discharged with a prescription for ceftriaxone to be completed for seven days for his COPD exacerbation, along with other medications. A permanent

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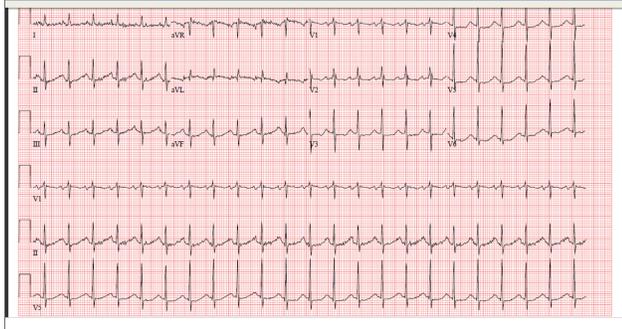


Figure: Electrocardiogram of patient showing QTc interval of 542 milliseconds while on a combination of azithromycin and methadone therapy.

annotation was put in his records on this kind of drug interaction and to maintain a high degree of caution for use of any drugs that are known to cause QTc prolongation, given his dependence on methadone.

## DISCUSSION

The QTc interval prolongation was most likely due to the result of a drug interaction between methadone and azithromycin as the patient presented with no other risk factors. This report underscores the risk of cardiac arrhythmias due to drug interactions in those receiving methadone substitution therapy. Methadone is often known to cause QTc prolongation and *torsades de pointes*. Methadone is presumed to cause cardiac arrhythmias *via* blockade of cardiac K<sup>+</sup> channels, subsequently prolonging the QT interval and thereby precipitating ventricular arrhythmias (7). Usually these adverse effects are reported in those on high-dose methadone – mean daily dosage of 397 mg (8). In this case, the patient developed QTc prolongation on a rather low dose of 60 mg daily.

The mechanism of azithromycin leading to QT prolongation is difficult to speculate. It could possibly be due to azithromycin being similar to erythromycin in prolonging the duration of action potential in M cells and thereby increasing the transmural dispersion of repolarization by inhibition of K<sup>+</sup> channels (9). Moreover, azithromycin being an inhibitor of CYP3A4 could affect the metabolism of methadone. Interestingly, in less than two weeks we got two cases (unrelated patients) that were on methadone therapy for management of opioid dependence, who received azithro-

mycin after being diagnosed with community acquired pneumonia. Both of them complained of chest pain, palpitations and diaphoresis within hours of azithromycin administration. Electrocardiogram showed QTc prolongation in both. The two drugs were eventually discontinued in both patients and within hours the QTc interval returned to normal. Had there been a delay in identifying this fatal drug interaction, it would have progressed to *torsades de pointes*, a potentially fatal ventricular tachyarrhythmia.

This case report assumes great significance in view of increasing use of azithromycin for lower respiratory tract infections. It is thus imperative that azithromycin be used with caution in patients who are already on drugs that are known to cause QT prolongation or that cause *torsades de pointes*. Nevertheless, in the opioid dependent patients on treatment with methadone who develop a prolonged QT interval or *torsades de pointes*, buprenorphine may be considered as a safe alternative (10).

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