

# Clarithromycin-Induced Prolonged QT Syndrome

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Conduction delays sufficient to cause QT-prolongation and the development of polymorphic ventricular tachycardia (torsade de pointes) can be life-threatening and require prompt treatment. The effect of medications on conduction within the ventricles can be assessed by measuring the QT interval, or QTc which is the measured QT normalized for the current heart rate. A longer than normal QTc is an indication of slowing of conduction in the ventricles and is associated with the development of torsade de pointes. Recognition of the potential for certain medications to cause such conduction delays is an important component of management. Since identifying drug-induced polymorphic ventricular tachycardia allows prompt initiation of corrective treatment without necessitating additional or unnecessary testing, it is important for the clinician to be familiar with medications causing this arrhythmia. As new medications are being developed and incorporated into common practice on a regular basis, it is important for clinicians to be aware of the potential cardiovascular toxicities of these new agents. The following case report illustrates the potential for clarithromycin to cause symptomatic QT-prolongation.

## CASE

A 70 year-old woman was admitted for the investigation of syncope after collapsing at home while watching television. Her past medical history included coronary artery disease, requiring angioplasty approximately one and three years prior to presentation, paroxysmal atrial fibrillation, obstructive hypertrophic cardiomyopathy, as well as rheumatoid arthritis. Her ischemic heart disease had been well controlled recently and she was not limited in any of her activities. Her anti-anginal and atrial fibrillation prophylaxis therapy prior to admission included sublingual nitroglycerin tablets taken as required for chest pain, and sotalol 160 mg twice daily which she had been taking for three months. Treatment for arthritis included prednisone 5 mg twice daily, hydroxychloroquine 200 mg twice daily, and methotrexate 2.5 mg once weekly. Four days prior to admission,

she presented to the Emergency Department for evaluation of a cough, low grade fever, and a left lung infiltrate. At the time, she had a heart rate of 77 beats/minute and a QT/QTc of 440/498 msec with no signs of ischemia (Figure 1). She was prescribed clarithromycin 250 mg orally bid for a presumed respiratory infection and discharged from the Emergency Department.

The admission electrocardiogram from four days later showed a heart rate of 50 beats/minute, QT/QTc of 696/641 msec and no signs of ischemia or atrial fibrillation. Laboratory measurements on admission included a serum potassium of 4.5 mEq/L, sodium of 137mEq/L, and a serum creatine phosphokinase concentration of <20 units/L. The serum magnesium concentration was not measured. She denied the ingestion of additional sotalol over her prescribed regimen or the use of any anti-histamine products. No episodes of torsade de pointes or atrial fibrillation were documented at any time.

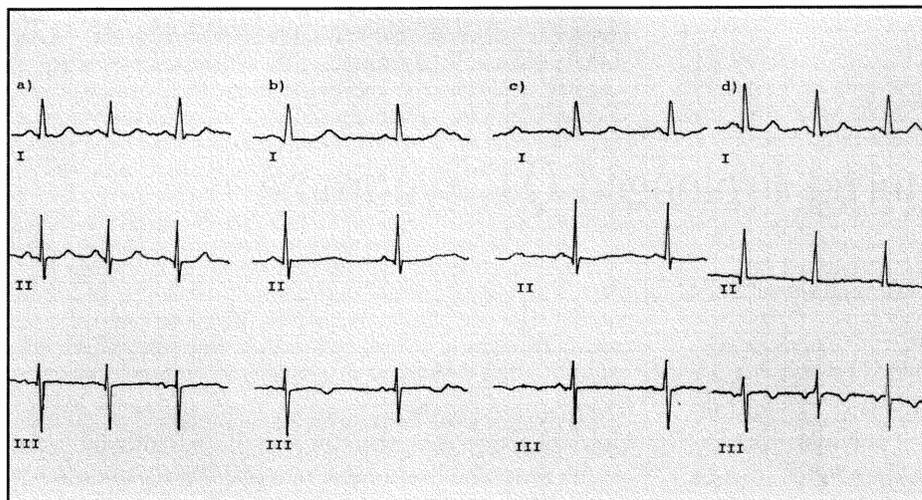
Upon admission, she was alert and cooperative with no further syncopal episodes. The sotalol and clarithromycin were held while her other medications (as above) were continued. No evidence of worsening of the obstructive hypertrophic cardiomyopathy, ischemic heart disease, or atrial fibrillation was detected as the cause for the syncopal attack and no treatment was initiated. Over the next five days the QT/QTc returned to normal values, the resting heart rate increased, and the patient had no syncopal or ischemic pain episodes. She was discharged on her previous medications with the exception of clarithromycin and sotalol. The patient was not rechallenged with either clarithromycin or sotalol. A follow-up electrocardiogram at two months after discharge demonstrated no evidence of a conduction delay (QT/QTc 440/496 msec) (Figure 1).

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**Figure 1: Electrocardiogram from a) initial emergency room visit (QT/QTc 440/498); b) upon presentation (QT/QTc 696/641); c) the following day (QT/QTc 620/558); and d) two months following hospitalization (QT/QTc 440/496).**

## DISCUSSION

The suggestion that clarithromycin contributed to the QT prolongation is supported by the lack of symptoms over the three months of sotalol therapy prior to initiation of clarithromycin; the rapid prolongation of the QT following clarithromycin initiation; and reversal upon stopping of clarithromycin and sotalol. The potential for the QT prolongation to result in torsade de pointes which caused the syncopal episode is hypothesized, although no episode of torsade was documented on any electrocardiogram. Sotalol alone has been reported to cause a prolonged QT resulting in torsade de pointes and collapse.<sup>1</sup> This effect is seen soon after initiating therapy and is dose related. No explanation is available for the apparent delay (three months) in onset of the effects of sotalol in this patient.

The potential for macrolides, particularly erythromycin, to produce a long QT syndrome as a result of its direct electrophysiologic actions has been well documented.<sup>2</sup> *In vitro* experiments show that erythromycin increases action potential duration in a concentration-related fashion which is believed to explain its propensity to produce an acquired long QT syndrome.<sup>3</sup> These reports have resulted in the recommendation that erythromycin should be avoided in patients with a history of the long QT syndrome.

The potential for clarithromycin to have produced a similar conduction delay in our patient is favoured by its structural similarity to erythromycin. Clarithromycin is a 14-membered macrolide antibiotic that differs from erythromycin only in the substitution of an O-methyl group for the hydroxy group at position six of the lactone ring. Consequently, clarithromycin has improved acid stability which results in improved

oral bioavailability which may also lead to increased intracellular bioactivity over erythromycin, including myocardial tissues. Two patients have been reported to have experienced severe cardiac toxicity (arrhythmia and ventricular fibrillation) to clarithromycin during early clinical trials.<sup>4</sup> However, the extensive use of clarithromycin in Europe without frequent reports of cardiac toxicities, suggests that this effect is rare.

An alternate hypothesis for the mechanism of the QT prolongation in this patient could include clarithromycin-induced inhibition of sotalol metabolism. Clarithromycin

is metabolized by hepatic cytochrome P450 enzymes, and inhibition of drug metabolism by clarithromycin has been demonstrated.<sup>5</sup> For example, when clarithromycin is combined with carbamazepine treatment, there is a significant increase in the mean area-under-the curve (AUC) of the carbamazepine concentration-time curve, suggesting impairment of carbamazepine clearance.<sup>5</sup> However, the primary route of sotalol elimination is renal excretion with approximately 80-90% of a dose being excreted unchanged in the urine.<sup>6</sup> Hepatic dysfunction has no effect on the pharmacokinetics of sotalol, and drug interactions involving impairment of the hepatic clearance of sotalol are not available. Therefore, it is unlikely that a clarithromycin-induced reduction in sotalol elimination contributed to this patient's sudden prolonged QT interval.

This case report suggests that clarithromycin may result in symptomatic conduction delays. The clinician should consider this possibility in any patient presenting with syncopal symptoms or prolonged QT while receiving clarithromycin, especially those patients taking other medications which may prolong conduction. The rapid acceptance of clarithromycin for the treatment of a wide range of infectious conditions has the potential to increase the frequency in which clinicians may encounter this drug-induced toxicity. ☒

## REFERENCES

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