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Polymorphic Ventricular Tachycardia with a Normal QT Interval Following Azithromycin

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Introduction

Macrolide antibiotics have been associated with ventricular tachycardia and torsade de pointes. Azithromycin is a commonly prescribed azalide, a subclass of macrolide antibiotics. There were no reports of significant ventricular arrhythmias during clinical trials. Post-marketing safety surveillance noted torsade de pointes in a patient with a history of "arrhythmias" who had a myocardial infarction while on azithromycin.[1] Other reports describe ventricular arrhythmias with azithromycin while on disopyramide[2] or in congenital long QT syndrome.[3] There are no reports of ventricular arrhythmias associated with azithromycin in otherwise healthy individuals.

Case Report

A 51-year-old woman was prescribed azithromycin for an upper respiratory tract infection. Standard "over the counter" dose pseudoephedrine was taken shortly before the azithromycin. Two hours after her first dose of azithromycin (500 mg), she had sudden loss of consciousness. She awoke with a clear sensorium. Shortly thereafter, another syncopal event prompted a hospital evaluation. Her past medical history was significant for hypothyroidism and bladder cancer. Medications consisted of aspirin, synthroid, and vitamins. She had taken pseudoephedrine before without sequelae, but had no prior exposure to azithromycin. There was no family history of sudden death and no history of substance abuse. She was a nonsmoker.

Minutes after arriving at the emergency room, syncope recurred. Telemetry revealed polymorphic ventricular tachycardia (PMVT) (Fig. 1) in the absence of a prolonged QT, long-short sequence, or bradycardia. Her QT and QT_c (range 420–440 ms) intervals were normal. A very short coupling interval prior to the PMVT was noted. Defibrillation restored normal sinus rhythm. Multiple episodes of PMVT and ventricular flutter ensued, some requiring defibrillation. Initial laboratory values were notable for a potassium of 2.8. Magnesium, potassium, isoproterenol, and lidocaine were administered in the emergency department. All repeat potassium values, including the repeat sample 3 hours after the first, were normal. Cardiac enzymes were negative. Azithromycin was discontinued and her ventricular arrhythmias ceased 10 hours after presentation. No clinical evidence of ST segment elevation or coronary vasospasm was seen. Cardiac catheterization and transthoracic echocardiogram were normal. The patient was monitored for 7 days and was arrhythmia-free. Multiple electrocardiograms revealed normal QT and QT_c (range 410–420 ms) intervals and no significant abnormalities. The patient refused an implantable cardioverter defibrillator. Genetic testing for any Long QT variants was declined. No further syncopal events were noted at follow-up 1 year later.

Discussion

This case details the possibility that azithromycin, one of the most commonly prescribed antibiotics, contributed to the development of a potentially lethal ventricular arrhythmia in an otherwise healthy individual. The clinical events (syncope and ventricular arrhythmias) occurred about the time of peak azithromycin tissue penetration. Of significance is that no pronounced QT prolongation was noted. There was a slight (5%) increase in QT_c earlier in the hospitalization, but the overall QT and QT_c values were normal.

Most reports of macrolide-related ventricular arrhythmias have been in the setting of a prolonged QT interval, although its occurrence with a normal QT interval has been described with erythromycin.[4] The currently available macrolide antibiotics including erythromycin, clarithromycin, and azithromycin all prolong cardiac repolarization, but in a different manner.[5] The prolongation in monophasic action potential (MAP) duration when these macrolides were compared showed a different pattern of MAP configuration for azithromycin in comparison to erythromycin and clarithromycin and thus a lowered proarrhythmic potential. This finding has clinical

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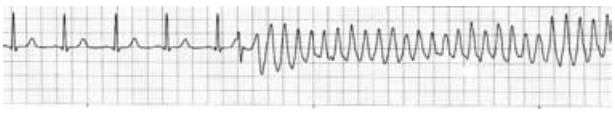

Figure 1. *Rhythm strip of sustained polymorphic ventricular tachycardia.*

relevance in that the ventricular arrhythmias reported have been more commonly associated with erythromycin and clarithromycin. Nevertheless, the potential for proarrhythmia, although very low, exists for azithromycin due to its effects on increasing the action potential duration. QT prolongation is not necessarily clinically manifest despite an increase in the action potential duration.

Although this patient had transient hypokalemia, it seems somewhat unlikely that this caused her arrhythmias in the absence of QT prolongation. Only rare case reports have noted PMVT in the setting of hypokalemia without QT prolongation.[6] In addition, the PMVT continued after potassium repletion. An etiology for the initial hypokalemia was not found and hypokalemia has not recurred during follow-up. Potentiation by pseudoephedrine or an undiagnosed ion channelopathy is difficult to exclude. However, the association of the PMVT at the time of peak azithromycin tissue penetration is notable.

This case does have some similarities, specifically the normal QT, no structural heart disease, and short coupling interval (Fig. 1), to the short-coupled variant of torsade de pointes, a form of idiopathic ventricular tachycardia.[7] The association of the clinical events to the administration of azithromycin would argue against the presence of idiopathic ventricular tachycardia.

This case suggests that the ventricular arrhythmia may have been caused by an adverse reaction to azithromycin. The potential, albeit very rare, for azithromycin as a contributing factor in life threatening ventricular arrhythmias should be considered in healthy individuals who present with syncope and/or PMVT (torsades de pointes).

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