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CASE REPORT

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Moxifloxacin-induced torsade de pointes

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Abstract

Torsade de pointes (TdP) is increasingly recognized as a complication of drug therapy. The most common cause of drug-induced QT prolongation is inhibition of the rapidly activating component of the delayed potassium current (I_{Kr}). Moxifloxacin, a widely used fluoroquinolone, is a weak I_{Kr} inhibitor and has been associated with QT prolongation. We report a case of marked QT prolongation (618 ms) and TdP associated with moxifloxacin use. Although it is difficult to predict which patients are at risk from TdP, careful assessment of the risk/benefit ratio is important before prescribing drugs known to cause QT prolongation. (Cardiol J 2008; 15: 71–73)

Key words: torsade de pointes, moxifloxacin, QT prolongation

Introduction

Torsade de pointes (TdP), a potentially life-threatening polymorphic ventricular tachyarrhythmia associated with QT prolongation, is increasingly recognized as a complication of drug therapy. The most common cause of drug-induced QT prolongation is inhibition of the rapidly activating component of the delayed potassium current (I_{Kr}). Moxifloxacin, a widely used fluoroquinolone, is a weak I_{Kr} inhibitor and has been associated with QT prolongation [1]. Moxifloxacin has not been commonly associated with drug-induced TdP. We report a case of TdP associated with moxifloxacin use.

Case report

A 74-year-old man presented with coughing and chest pain for three days. Past medical history included coronary artery bypass surgery, congestive heart failure and hypertension. Medications were pantoprazole, lisinopril, levothyroxine, celecoxib, furosemide and atorvastatin. Physical examination was unremarkable except for faint bibasilar crackles. Laboratory data showed K of 4.3 mmol/L and Mg of 1.2 meq/L. First troponin was 0.54 ng/mL (0–0.79 ng/mL), and the second troponin was 0.18 ng/mL. EKG was unremarkable with QTc interval of 461 ms. The patient was started on intravenous moxifloxacin 400 mg as therapy for presumed community-acquired pneumonia. On the second day of admission the patient had an episode of TdP, which progressed to ventricular fibrillation (VF) and was successfully defibrillated (Fig. 1). An ECG done immediately after the arrest showed a QTc of 618 ms (Fig. 2). The patient had one more episode of VF ten minutes later, which was again successfully defibrillated. Moxifloxacin was promptly discontinued and he underwent a cardiac angiogram, which showed patent grafts and no intervention was needed. His QTc upon discharge shortened to 492 ms, close to his baseline value, but still abnormally prolonged. In follow-up for one year following the two TdP/VF arrests, he has had no further recurrence of ventricular tachycardia or syncope.

Discussion

Prolongation of the QT interval has gained increased clinical attention due to its association with

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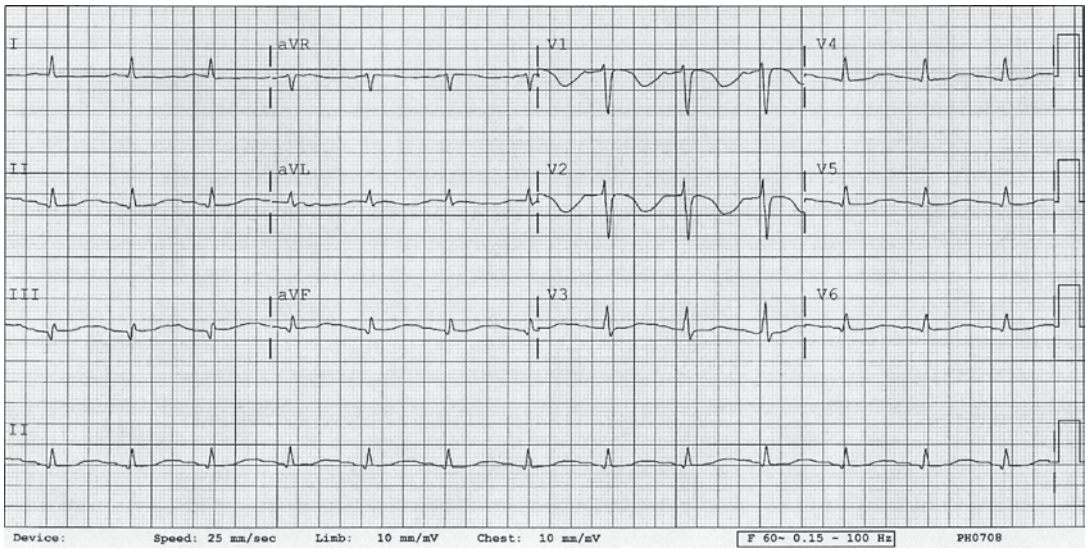

Figure 1. The polymorphic ventricular tachycardia in the acquired form is most commonly precipitated by short--long-short RR intervals (as shown here). This interval is normally caused by a ventricular premature beat followed by a compensatory pause. This can also occur in association with bradycardia or frequent pauses; as a result, the acquired form of long QT syndrome is known as 'pause-dependent' [9].

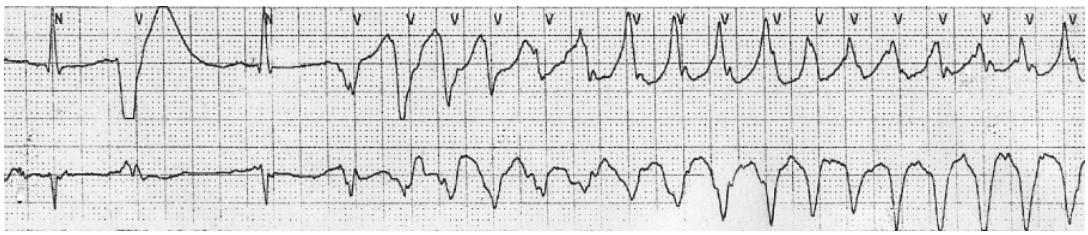

Figure 2. 12-Lead ECG after torsade de pointes showing QTc interval of 618 ms.

degeneration into a potentially fatal ventricular arrhythmia known as torsade de pointes. Clinicians need to be alert to QT prolongation when using certain pharmacologic agents, especially in patients with certain identified risk factors for QT prolongation.

Understanding normal cell cardiac cell electrophysiology is required in order to appreciate fully the proposed alteration in ion currents and electrophysiological mechanisms that underlie congenital or acquired long QT syndrome (LQTS). The normal depolarization of cardiac cells involves a rapid inflow of sodium ions. Repolarization follows when the outflow of potassium ions exceeds the declining influx of sodium and calcium ions. In the family of long QT syndromes, there is a delay in repolarization due to malfunction of ion channels. The most common mechanism for LQTS due to drug therapy is through inhibition of the rapid component of the delayed rectifier, potassium current (I_{Kr}), that is chiefly responsible for phase 3 repolarization [2]. The proposed mechanism for drug-induced TdP is the development of early afterdepolarizations (EAD) when the balance of repolarization and depolarization becomes perturbed in phase 3 of the action potential. An EAD may lead to a triggered response or action potential. Moxifloxacin is a weak I_{Kr} inhibitor and has been shown to prolong ventricular repolarization time in healthy individuals at standard (400 mg) and supratherapeutic (800 mg) doses [1]. In the range of doses tested, this lengthening was not dose dependent but was correlated to plasma moxifloxacin concentration. Moxifloxacin is implicated in this patient's TdP as it was the only new medication administered to him that has previously been associated with QT interval prolongation. Although he had pre-existing risk factors for TdP, including prolonged QTc, further QTc interval prolongation and TdP did not occur until moxifloxacin

was initiated, and the QTc improved after moxifloxacin discontinuation. The patient did not have any recurrent arrhythmia over one year of follow up. The proarrhythmic risks of fluoroquinolones are receiving attention because of the increasingly widespread use of this class of antibiotics [3]. Ciprofloxacin, levofloxacin and gatifloxacin have been reported to be associated with TdP [4]. Grepafloxacin was withdrawn from the market because of QTc prolongation and risk of TdP. The reason that some patients develop this side effect while receiving a drug from this class whereas most patients do not is probably due at least in part to subclinical mutations and polymorphisms. Recent data have confirmed that some cases of drug-induced LQTS and TdP may have 'silent' genetic defects in cardiac ion channel genes [5]. This may create a vulnerable substrate that, in the presence of appropriate triggers such as I_{Kr} blockers, may precipitate LQTS and TdP in non-penetrant or weakly penetrant gene mutation carriers. Our patient had mildly prolonged QTc even before the initiation of QT prolonging medication, which could be due to a 'silent' genetic defect in the ion channel. In all published cases of TdP associated with fluoroquinolones, patients had one or more concomitant risk factors including QTc interval > 500 ms, QTc prolongation > 60 ms from pretreatment value, hypokalemia, hypomagnesemia, female gender, left ventricular dysfunction, advanced age, bradycardia and a possible genetic predisposition for this arrhythmia [6, 7].

Management of patients with acquired LQTS and TdP requires immediate measures to suppress the tachyarrhythmia. Intravenous magnesium sulphate has been shown to suppress the TdP without directly shortening the prolonged QT interval [8]. Increasing the heart rate by administration of either atropine or isoproterenol or, preferably in a controlled fashion, by temporary ventricular pacing is often successful in suppressing the arrhythmia. An increased heart rate results in shortening of the action potential duration and QT interval and suppression of EADs. Long-term measures include correction of underlying electrolyte abnormalities and, particularly, discontinuation of the offending agent.

Conclusions

Although it is difficult to predict which patients are at risk from TdP, careful assessment of the risk/benefit ratio is important before prescribing drugs known to cause QT prolongation.

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