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A Case of Ciprofloxacin-Induced QT Prolongation and Torsade de Pointes

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ABSTRACT

Prolongation of the QT interval is a recognized adverse effect of fluoroquinolone antibiotics. This effect on ventricular repolarization can potentially lead to life-threatening arrhythmias such as Torsade de pointes. Torsade de pointes is a polymorphic form of ventricular tachycardia identified by twisting of the QRS axis around an isoelectric point. We report a case of torsade de pointes induced by ciprofloxacin treatment. The patient experienced an acquired QT interval prolongation followed by Torsade de pointes arrhythmia with ciprofloxacin administration for ileostomy closure surgery and unfortunately expired.

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Introduction

A range of drugs from antiarrhythmic to antibiotics can cause Torsade de pointes (TdP) arrhythmia (1). Fluoroquinolones are broad-spectrum antibiotics with specific activity against gram-negative organisms. Although safety profile of fluoroquinolones is comparable with those of other antimicrobial classes, they may occasionally cause significant adverse events (1, 2). Life-threatening arrhythmias such as TdP can occur due to effect of fluoroquinolones on ventricular repolarization (3). The marked oscillation of the axis in TdP is preceded by a lengthening of the QT interval, the electrocardiographic interval that shows ventricular repolarization (4). Although the rhythm is often self-limiting, there is potential to progress to ventricular fibrillation or sudden cardiac death (5).

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Although QT prolongation seems to be a class effect of fluoroquinolones, the significance of prolongation, and thus the probability of TdP, varies between individual agents (6). The fluoroquinolones with the most potent adverse effects were Grepafloxacin and Sparfloxacin that led to their removal from the market (7).

Among the most frequently used fluoroquinolones (Ciprofloxacin, Levofloxacin, Gatifloxacin, and Moxifloxacin), 25 cases of TdP were reported in the United States between the dates 1996 and 2000, and ciprofloxacin was associated with only two reports. The scarcity of ciprofloxacin-associated events was made more obvious when one acknowledges an estimated 66 million prescriptions for ciprofloxacin written during this 5-year interval in United States (6).

When concern exists about QT-mediated arrhythmias, ciprofloxacin is generally the best choice in fluoroquinolone class because of its weak clinical correlation with QT prolongation and TdP (6, 8-12). However, there are several case reports of ciprofloxacin-induced QT prolongation and TdP.

Table 1. Serum electrolytes.

Days of admission	1	3	5	7	8	9	10	11	12	13
Potassium (mEq/L)	4.3	4	3.4	2.8	3.5	4.7	4.7	4.7	5.7	4.1
Magnesium (mg/dL)	2.1	2.2	2.1	2	2.3	2.3	2.7	1.9	2.2	1.7

Case Report

A 46-year-old male who underwent a temporary ileostomy surgery last year, was admitted for ileostomy closure at Imam Khomeini Hospital Complex, Tehran, Iran. His past medical history was negative for cardiac disease but family history was remarkable including a sudden death of his mother at the age of 45. At the first day of admission, the patient laboratory analysis (complete blood count, biochemical test, and electrolytes) as well as vital sign (blood pressure, pulse rate, respiratory rate, and temperature) were normal. The electrocardiography (ECG) showed normal sinus rhythm. His serum magnesium was 2 mg/dL (adult reference range: 1.7–2.4 mg/dL) and serum potassium was 4.3 mEq/L (adult reference range: 3.5-5.1 mEq/L). The patient was started on intravenous ciprofloxacin (400 mg, q12h) and metronidazole (500 mg, q6h) before surgery. After surgery a thorough evaluation of his condition confirmed hemodynamic stability and normal laboratory data without fever and discharge of wound. He was continued on the same antibiotic therapy until the sixth day in which metronidazole was discontinued.

On seventh day of admission, the patient experienced ventricular tachycardia (VT) and cardiac arrest three hours after ciprofloxacin administration. An ECG showed a lengthening of QT interval. His serum potassium was 2.8 mEq/L and serum magnesium was 2 mg/dL (Table 1). He survived after 5 minutes of cardiopulmonary resuscitation (CPR).

Intravenous lidocaine (1 mg/min, over 24 hours) and magnesium sulfate (50 grams, over 12 hours) were given. Ciprofloxacin was discontinued because of concerns of drug-induced QT prolongation. Due to hypokalemia, he received potassium chloride (20 cc, potassium chloride 15%) in hospital days of six to nine. On hospital day 10, the patient again experienced VT. His serum potassium was 4.7 mEq/L and serum magnesium 2.7 mg/dL. He was continued on lidocaine and magnesium sulfate and because of sustained VT, amiodarone (150 mg over 10 minutes, then 1 mg/minute for 6 hours) was started. On hospital day 13, the patient started to experience VT and lost his consciousness consequently. After immediate DC shock of 200 joules, the patient reverted to sinus rhythm. However, after about 10 seconds, he showed signs of VT and repeated episodes of TdP. In spite of 45 minutes of CPR and repeated DC shock, the patientexpired.

Discussion

TdP is an uncommon form of arrhythmia caused by congenital long QT syndrome or drug-induced arrhythmia. The use of several antibiotics in the clinical setting may cause QT prolongation and rarely to TdP (13). Evidence suggests that fluoroquinolones can prolong the QT interval by blocking the cardiac voltage-gated potassium channels specially the rapid component (I_{Kr}) of the delayed rectifier potassium current, but weak evidence relates ciprofloxacin with QT-mediated arrhythmias. From all available quinolones in clinical practice, ciprofloxacin seems to be related to the lowest risk of QT prolongation and a lower rate of TdP (14).

Only a few case reports have linked ciprofloxacin therapy with QT prolongation or episodes of TdP. Two cases were female patients who concomitantly received sotalol and amiodarone for supraventricular arrhythmia and developed TdP within 24 hours of ciprofloxacin administration (15). Another case was a 76-year-old male patient with acute renal failure and hypocalcaemia, who developed QT prolongation and TdP provoked by hemodialysis, 24 hours after completion of oral ciprofloxacin therapy (16). In a case reported by Letsas et al, an elderly woman receiving a long-term medication with olanzapine and valsartan showed an obvious QT interval prolongation after intravenous administration of ciprofloxacin on the third day of hospital admission (17). Arcea et al., (18) represented a male case of prolonged QT interval and TdP due to ciprofloxacin (400 mg q12h) in a 77-year old patient with the diagnosis of cholangitis. Manolis et al., (19) described a male case of ciprofloxacin-induced cardiac arrest in an 87-year-old patient on chronic amiodarone therapy (for paroxysmal atrial fibrillation but no precedent history of ventricular tachyarrhythmias). He showed an episode of cardiac arrest following polymorphic ventricular tachycardia in the form of typical torsade des pointes, 24 hours after ciprofloxacin administration (400 mg q12h). Keivanidou et al., (20) reported ciprofloxacin-induced acquired long QT syndrome in a female patient (aged 70 years old) under amiodarone and sotalol therapy after 24 hours of ciprofloxacin administration (400 mg q12h), who developed TdP and syncope. Ibrahim et al., (21) identified a case (65-year-old man) of ciprofloxacin-induced TdP in a 65-year-old man on the fourth day of oral ciprofloxacin therapy (500 mg q12h), which resolved 7 days later after ciprofloxacin discontinuation. Flanagan et al., (5) published a 22-year-old active duty marine with

a mild baseline prolonged QTc in ECG, with a proceeding lengthening of the QTc after three days of treatment with ciprofloxacin (10 hours after the last dose administration).

Knorr et al., (22) illustrated a 16-year-old healthy boy experiencing bradycardia and mildly prolonged QT interval and low heart rate within 48 hours of ciprofloxacin administration (400 mg q12h) and metronidazole (500 mg q6h). The patient's QT interval normalized after seven days of ciprofloxacin discontinuation.

In previous studies of fluoroquinolones-induced TdP, it was obvious that risk factors for TdP had been frequent prior to antibiotic therapy (7, 15, 17, 19). A literature review by Justo et al., represented that the most frequently established risk factor for TdP among these patients were advanced heart disease (76%), female gender (68%), concomitant use of a QT interval-prolonging drug (40%), and hypokalemia (20%) (23).

Hypokalemia as an electrolyte disturbance affecting cardiac repolarization has been proved to prolong the QT interval, precipitate TdP, and cause sudden cardiac death. A common effect of many drugs developing TdP is blockade of I_{Kr}. Enforcement of drug-induced I_{kr} block by low extracellular potassium is of most importance in clinical settings, suggesting a mechanism to clarify the link between hypokalemia and TdP (24).

The mechanism of ciprofloxacin cardio-toxicity has not been fully understood yet. Some authors claim that it could be related to blocking of cardiac voltage-gated potassium channels especially I_{kr}. In vitro studies suggest that fluoroquinolones block HERG (the human ether-ago-go-gene) responsible for the I_{kr} and subsequently prolong QT and TdP (8,24و 25). Further animal studies explained that ciprofloxacin might have caused myocardiotoxicity in rats by inducing oxidative stress in heart and nitric oxide may play a role in this toxicity (26).

Regarding to temporal relationship between cardiovascular events and ciprofloxacin, Clark et al., previously demonstrated that a higher number of potentially dysrhythmic cardiovascular events were reported during the first 6 weeks of ciprofloxacin therapy (irrespective of whether or not treatment was continued). Moreover, the majority of overall deaths recorded with ciprofloxacin happened in days 1 to 8 (27).

Using Naranjo Adverse Drug Reaction probability scale (28) to determine the likelihood that the QT prolongation and subsequent TdP were drug-related, we demonstrate this case as a "possible" ciprofloxacin-induced event (the score was 3 out of 13). Since the QT prolongation and subsequent TdP was occurred within a plausible temporal link to ciprofloxacin administration, a causal relationship cannot be ruled out. Also our case had family history of sudden cardiac death and hypokalemia as risk factors, therefore being at high risk of developing TdP. However, further investigation by other types of study is required to specify exact mechanisms underlying these rare cardiovascular events by ciprofloxacin.

It is essential to raise awareness of healthcare professionals about drugs that can potentially induce QT prolongation, their interactions, and patient risk factors. Baseline ECG and electrolyte correction is recommended before initiation of ciprofloxacin administration in high-risk individuals with recognized risk factors predisposing to TdP.

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