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CASE REPORT

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Ciprofloxacin induced acquired long QT syndrome in a patient under class III antiarrhythmic therapy

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Abstract

We report one case of cardiac arrest related to ciprofloxacin administration. One female patient (aged 70 years old) developed a marked QTc prolongation (QTc = 0.62 s) within 24 hours of ciprofloxacin administration, with documented torsades de pointes and recurrent syncope that required defibrillation. The patient was under amiodarone and sotalol therapy for atrial fibrillation, with no obvious QT prolongation prior to ciprofloxacin therapy. QT prolongation and subsequent torsades de pointes appeared only after initiation of ciprofloxacin and normalized after drug discontinuation. Even though ciprofloxacin is thought to be safer than other agents in its class, it may cause QT prolongation and torsades de pointes, particularly in high risk patients with predisposing factors.

Prolongation of the QT interval related to the effect of fluoroquinolones on rapid potassium channels (IKr) may result on potentially serious proarrhythmic effect, leading to torsades de pointes. (Cardiol J 2009; 16, 2: 172–174)

Key words: ciprofloxacin, torsades de pointes, amiodarone, sotalol, long QT

Introduction

Fluoroquinolones are frequently used antibacterial agents with a wide efficacy spectrum [1]. However, prolongation of the QT interval related to the effect of these drugs on rapid potassium channels (IKr) may result on potentially serious proarrhythmic effect, leading to torsades de pointes [2]. Several quinolones, including sparfloxacin and grepafloxacin have been withdrawn from the market by the manufacturer, when associated with QT-related arrhythmias [3]. Current clinical studies suggest that among quinolones, ciprofloxacin has no effect on QT interval in healthy subjects with no predisposing factors [4, 5] and weak effect in patients with pre-existing risk factors for torsades de pointes [6, 7]. Ciprofloxacin is given to selected patients because is considered to be safer than other agents in its class.

The upper limit for duration of the normal QT interval corrected for heart rate (QTc) is often given as 0.44 s. However, the normal QTc may actually be longer (0.46 for men and 0.47 for women) with a normal range of plus or minus 15% of the mean value [8]. Prolonged QT interval may be associated with a polymorphic ventricular tachycardia known as torsades de pointes. Congenital long QT syndromes, female gender, hypokalemia and use of sympathomimetics drugs increase the risk of torsades. Antiarrhythmics that block the potassium

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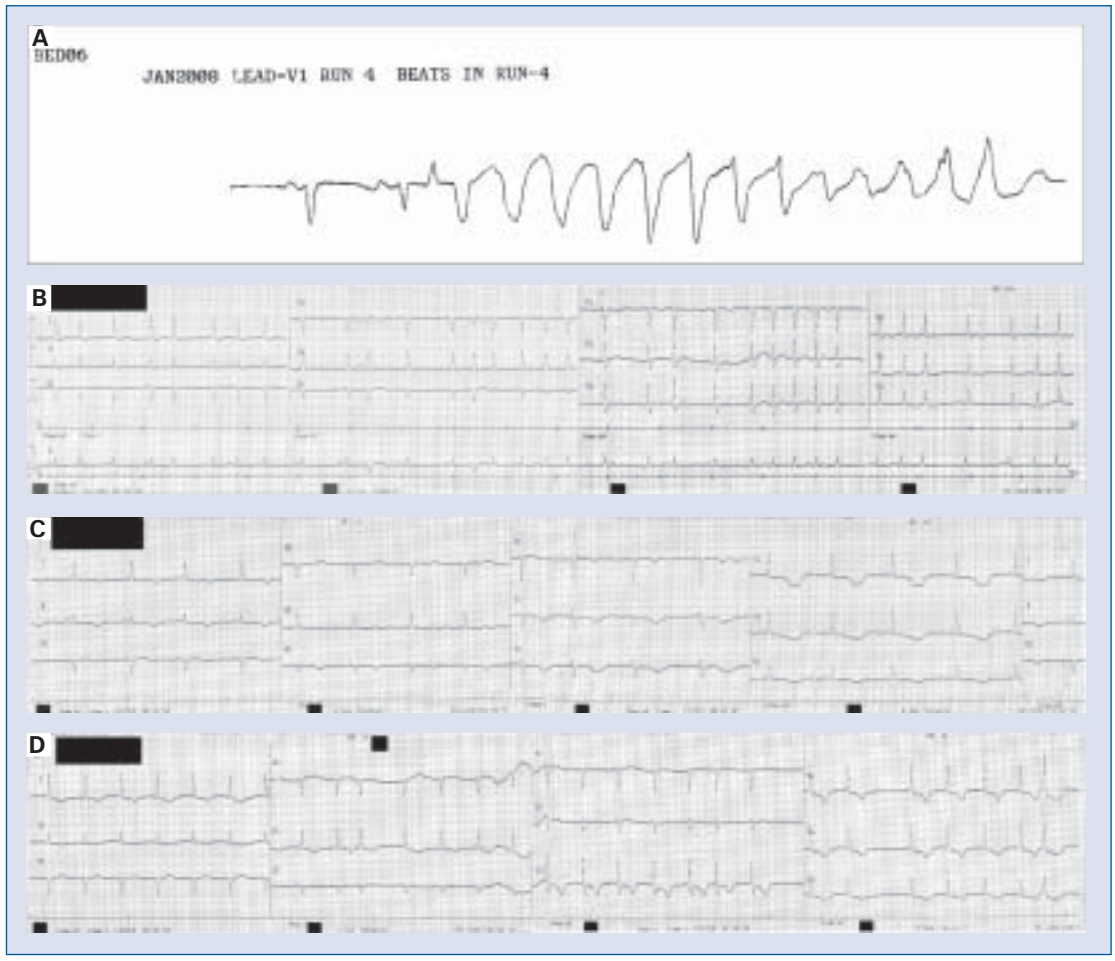

Figure 1. ECG from the patient shows sinus rhythm on sotalol 40 mg bid (baseline, QTc = 0.38) (**A**), during torsades de pointes (rhythm strip) (**B**), immediately after resuscitation (QTc = 0.62) (**C**) and 72 hours after discontinuation of ciprofloxacin and antiarrhythmic therapy (QTc = 0.42) (**D**).

channel prolong the QT and increase the risk for torsades (amiodarone, sotalol, quinidine, disopyramide, procainamide, ibutilide). Additionally, some macrolide and fluoroquinolone antibiotics, antipsychotic and antidepressant drugs, serotonin agonists of the triptan class, cisapride, dolasetron and others, have been reported to be associated with QT prolongation or cases of torsades [9].

Quinolones are common antibiotic agents with wide antimicrobial efficacy spectrum having effect on IKr. Ciprofloxacin is often used in high risk patients for QT mediated arrhythmia because of its lower rate of QT prolongation and torsades de pointes.

Case presentation

A 70-year-old woman with no previous cardiac history was admitted to the hospital for new onset atrial fibrillation with rapid ventricular response. On admission she was on amiodarone 450 mg *i.v.* in 30 minutes loading dose and 650 mg in 24-hour infusion rate and digoxin 0.25 mg/day. The patient converted to sinus rhythm within 48 hours of admission. Digoxin and amiodarone was discontinued and sotalol 40 mg *p.o.* bid was administered. Next day the patient presented with with jaundice, fever, and right abdominal pain diagnosed by ultrasound as cholecystitis. Laboratory test results revealed high WBC level (20,730), high total and direct bilirubin (3.82 mg/dL and 1.98 mg/dL, respectively) and low potassium levels (3.00 mmol/L). Ciprofloxacin 400 mg *i.v.* bid was administered. Within 12 hours, she had syncope with a documented torsades de pointes requiring defibrillation (Fig. 1A). Prior to initiation of ciprofloxacin QTc was 0.38 (Fig. 1B). After resuscitation, QTc was markedly increased at 0.62 (Fig. 1C). Intravenous magnesium was administered. Sotalol and ciprofloxacin was discontinued. QT normalized to 0.42 within 3 days of drug cessation (Fig. 1D).

Conclusions

Fluoroquinolones are common antibacterial agents that directly inhibit the synthesis of DNA by inactivation of two enzymes [1]. They are commonly used because of their wide antimicrobial efficacy in common respiratory, gastrointestinal and genitourinary infections. Among fluoroquinolones, moxifloxacin appears to have the greatest risk of QT prolongation and it should be used with caution in patients with predisposing factors. Gemifloxacin, levofloxacin and ofloxacin are related with lower risk of prolongation of QT. However, they should be used with caution in high risk patients [10–12]. Ciprofloxacin has been associated with the lowest risk for QT prolongation and torsades de pointes [2]. The case presented here demonstrates ciprofloxacin's involvement in generation of QT mediated proarrhythmia. It is of notice, that many predisposing and risk factors were present in this case. Nevertheless, initiation of ciprofloxacin had a clear temporal effect in QT prolongation and QT mediated arrhythmia.

Frothingham compared the rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin and moxifloxacin administraton in a retrospective study between 1/1/1996 and 2/5/2001. Ciprofloxacin was associated with a significantly lower rate of torsades de pointes (0.3 cases/10 million prescriptions, 95% confidence interval (CI) 0.0–1.10 than levofloxacin 95.4/10 million, 95% CI 2.9–9.3, $p < 0.001$) or gatifloxacin (27/ /10 million, 95% CI 12–53, $p < 0.0.001$ for comparison with ciprofloxacin or levofloxacin) [6]. Thus, ciprofloxacin is commonly administered due to its low potential to cause QT mediated arrhythmias.

In an open label crossover study, 13 healthy participants received 3 standard treatment courses with ciprofloxacin, levofloxacin and moxifloxacin. No difference was seen in baseline QTc (0.48) or QTd (0.92). Following 7 days of moxifloxacin, the QTc was prolonged by 6ms relative to baseline (408 ms, $p = 0.0022$) and 11 ms from 2 hour measurement (403 ms, $p = 0.003$). Ciprofloxacin and levofloxacin had no effect on QTc and no fluoroquinolone changed the QTd [5].

In another study, changes in QT and QTc interval from baseline values were assessed before and after a single high dose of levofloxacin, moxifloxaxin and ciprofloxacin [4]. Increases in QT and QTc interval compared with placebo were consistently greater after moxifloxacin compared with either levofloxacin or ciprofloxacin. The mean post dose change from baseline QTc intervals for the 24 hours period after treatment with moxifloxacin ranged from 16.34 to 17.83 ms ($p < 0.001$). For levofloxacin, this change ranged from 3.53 to 4.88 ms ($p < < 0.05$) and for ciprofloxacin this change ranged from 2.27 to 4.93 ms ($p < 0.05$). Greater changes in QT and QTc intervals after treatment with moxifloxacin compared with levofloxacin or ciprofloxacin are consistent with in vitro observations related to the effect of these drugs on rapid potassium channels (IKr).

Although rare, ciprofloxacin must be used with caution because its potential to cause QT prolongation and life threatening arrhythmias, especially in patients with other risk factors.

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