

Sudden cardiac death due to ciprofloxacin induced torsade de pointes

Semir Usmael¹ and Teferi Seyoum¹

¹Haramaya University College of Health and Medical Sciences

April 08, 2024

Introduction

Long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG). This syndrome is associated with an increased risk of polymorphic ventricular tachycardia (VT) and a characteristic life-threatening cardiac arrhythmia also known as torsade de pointes (TdP). TdP is an uncommon and fatal polymorphic ventricular tachyarrhythmia, which often occurs in association with a prolonged QT interval. It is usually asymptomatic and terminates spontaneously; nevertheless it can cause syncope, dizziness, palpitations, seizures, and sudden cardiac death (SCD).

QT prolongation has traditionally been separated into two general categories: congenital LQTS and acquired LQTS. The acquired causes include drugs (antiarrhythmic, antibiotic, antipsychotic, antihistamines, and antiemetic), electrolyte abnormality (hypokalemia, hypocalcemia, and hypomagnesemia), bradycardia, ischemia, stroke, and structural heart disease [1-3].

Quinolone antibiotics are frequently prescribed agents due to their broad-spectrum antimicrobial efficacy. QT prolongation is a class effect of fluoroquinolones, but there are great differences between the various members of this group in their proarrhythmic potential. Ciprofloxacin is considered to be safer than the other agents in this class [4]. Current clinical studies suggest that among quinolones, ciprofloxacin has no effect on QT interval in healthy subjects with no predisposing factors [5-6] and a weak effect in patients with preexisting risk factors for torsade de Pointes [4, 7].

We report a case 40-years old Ethiopian man with no previous history of cardiac disease who died due to recurrent cardiac arrest secondary to ciprofloxacin-induced torsade de pointes.

Case presentation

A 40-year-old Ethiopian man with no previous history of cardiac disease presented with a 7-days history of profuse watery diarrhea associated with vomiting and crampy abdominal pain. He denied a history of shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, and palpitation. He had no family history of sudden cardiac death and cardiac illness.

On physical examination, the patient appeared acutely ill and his vital signs were as follows: blood pressure (BP)-70/50 mmHg, pulse rate (PR)-104 beat per minute which was feeble, respiratory rate-20, temperature-35-degree Celsius, and saturation of 96% on room air. There was conjunctival pallor. There were signs of peripheral hypoperfusion such as cold extremities and delayed capillary refill. Cardiac and nervous system examinations were non-revealing.

Laboratory work-up revealed; serum potassium: 2.27mmol/L, sodium: 127mmol/L, chloride: 99.7mmol/L, serum creatinine: 2.33mg/dl, and blood urea nitrogen: 108.8 mg/dl. White cell count (WBC) level was 8800 and Hemoglobin (Hgb) was 10.2 g/dl. Liver enzymes were within the normal range and total and direct

bilirubin level was 1.62 mg/dl and 1.05 mg/dl, respectively. There were numerous puss cells on microscopic stool exam. Blood and stool culture were sent.

With this finding, a working diagnosis of septic shock of GI focus, acute kidney injury, severe hypokalemia, and hypovolemic hyponatremia was established.

The patient was admitted and managed as follows: intravenous (IV) epinephrine infusion was started after BP failed to respond to initial fluid resuscitation, IV ceftriaxone 1 gram BID and metronidazole 500 mg TID, IV potassium chloride infusion 40 meq in 400 ml of normal saline TID, and Oral rehydration solution 300 ml per loss.

Despite the above management, there was poor clinical response, and laboratory work-up 2 days after admission revealed a high WBC level (28, 080) and Hgb level of 6.2 g/dl. Serum potassium became 3.72 mmol/l. There was no growth on blood and stool culture. Subsequently, the initial antibiotics were discontinued and IV ciprofloxacin 400 mg BID and vancomycin 1g BID was initiated. He was transfused with 2 units of packed red blood cell and given IV hydrocortisone 100mg TID. IV potassium chloride infusion was discontinued. The remaining treatment was continued.

Within 16 hours of ciprofloxacin initiation, he developed sudden onset shortness of breath followed by loss of consciousness. On examination, he was unresponsive, pulse was not palpable, BP was unrecordable, and had no spontaneous breathing effort. The random blood sugar level was 195 mg/dl. ECG done at this time revealed a sustained polymorphic tachycardia with a feature of torsade de pointes (Figure 1).

With a diagnosis of sudden cardiac arrest due to polymorphic ventricular tachycardia induced by ciprofloxacin, cardiopulmonary resuscitation (CPR) was started immediately; epinephrine infusion at a rate of 0.3 microgram/kg/minute commenced and amiodarone 150 mg IV bolus was administered. After 5 cycles of CPR and defibrillation return of spontaneous circulation was achieved. However, 30 minutes later he developed additional episodes of recurrent torsade de pointes and cardiac arrest. CPR and defibrillation were attempted but it was not successful and the patient passed away. The possible cause of death was cardiac arrest secondary to torsade de pointes induced by ciprofloxacin.

Discussion

Fluoroquinolones are commonly used antimicrobial agents because of their wide antimicrobial efficacy in common respiratory, gastrointestinal, and genitourinary infections. However, cardiac toxicity can occur as an unintended consequence of therapy with quinolone. Case reports and other studies have reported several quinolone-induced arrhythmia-related cardiac effects, including QT interval prolongation, TdP, ventricular tachycardia, ventricular fibrillation, and SCD [4, 8-9]. Fluoroquinolones prolong the QT interval by blocking the cardiac voltage-gated rapid potassium channels (IKr). This adverse effect can be potentiated by the presence of predisposing factors such as female gender, structural heart disease, concomitant use of QT-interval-prolonging medication, reduced drug elimination (due to drug interaction, renal, or hepatic dysfunction), electrolyte abnormalities (hypokalemia, hypomagnesemia), bradycardia, prolonged QTc interval before therapy, and congenital LQTS.

The risk of QT prolongation and TdP varies among quinolones; moxifloxacin appears to have the greatest risk followed by levofloxacin and ofloxacin. Ciprofloxacin has been associated with the lowest risk for QT prolongation and torsade de pointes [4-6, 9-10]. Even though ciprofloxacin is considered to be the safest quinolone in terms of TdP, there are several case reports on ciprofloxacin-induced TdP [11-15]. This case report suggests that ciprofloxacin should be used with great caution in patients who are at risk for QT prolongation and QT-mediated arrhythmias.

The diagnosis of quinolone-induced TdP requires the presence of a clear temporal relationship between exposure and onset of the ECG features. Typical ECG features of TdP include an antecedent prolonged QT interval, particularly in the last heartbeat preceding the onset of the arrhythmia. Additional typical features include a ventricular rate of 160 to 250 beats per minute, irregular RR intervals, and cycling of the QRS

axis through 180 degrees every 5 to 20 beats. In our case, TdP developed within 16 hours of ciprofloxacin administration and the patient had predisposing factors such as hypokalemia and acute kidney injury.

Prevention of ciprofloxacin-induced QT-interval prolongation and TdP in a high-risk patient includes, whenever possible alternative antibiotics that don't prolong QT interval should be used, serum potassium and magnesium should be maintained in the normal range, and monitoring the QT-interval before and at least every 8 to 12 hours after initiating the drug [16].

The management of quinolone-induced QT-interval prolongation includes discontinuation of the offending drug and aggressive correction of any metabolic and electrolyte abnormalities. Prompt defibrillation in hemodynamically unstable and in those with syncope due to torsade de pointes. In conscious patients' treatment with intravenous magnesium infusion, beta-blockers, and temporary transvenous pacing are indicated [17].

The major limitations in the management of this case were; initiation of full dose of ciprofloxacin in the presence of acute renal failure and severe hypokalemia, inadequate monitoring of QT interval after starting culprit drug, failure to withdraw ciprofloxacin, and inappropriate treatment of TdP namely failure to administer IV magnesium sulfate and inappropriate administration of IV amiodarone. Since there is no baseline ECG before administration of ciprofloxacin, congenital LQTS can't be ruled out completely.

Conclusion

Cardiac arrest due to TdP in the acquired form of drug-induced LQTS is a rare but potentially catastrophic event. Although fluoroquinolone is well tolerated, and effective, they are associated with various cardiac toxicities. Even though ciprofloxacin is considered to be the safest agent in this class, it may cause QT-interval prolongation, torsade de pointes, and sudden cardiac death, especially in the presence of predisposing factors. This case emphasizes the importance of prevention, early recognition, and treatment of QT-interval prolongation and TdP induced by ciprofloxacin.

Abbreviation

ECG, electrocardiogram; IV, intravenous; LQTS, long QT syndrome; SCD, sudden cardiac death; TdP, torsade de pointes; VT, ventricular tachycardia

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and accompanying image. A copy of written consent is available for review by an editor in chief of this journal.

Ethical approval and consent to participate

Not applicable.

Competing interest

The authors declare no competing interest.

Funding

None.

Availability of data and material

Not applicable.

Acknowledgement

We thank the patient and her family for information provided and their approval for publication of this case.

Authors' contribution

SA and TM contributed to the acquisition of history, laboratory investigation, and interpretation of the case and the patient data. SA carried out a literature review and was a major contributor to the writing of the manuscript. All authors have read and approved the final manuscript.

References

1. Roden DM (2004) Drug-Induced Prolongation of the QT Interval. *N Engl J Med* 350: 1013-1022.
2. Passman R, Kadish A (2001) Polymorphic ventricular tachycardia. Long QT syndrome, and torsades de pointes. *Med Clin North Am* 8: 32.
3. Yap YG, Camm AJ (2003) Drug induced QT prolongation and torsades de pointes. *Heart* 89: 1363.
4. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy*, 2001; 21: 1468–1472.
5. Noel GJ, Natarajan J, Chien S, Hunt TL, Goodman DB, Abels R. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther*, 2003; 73: 292–303.
6. Tsikouris JP, Peeters MJ, Cox CD, Meyerrose GE, Seifert CF. Effects of three fluoroquinolones on QT analysis after standard treatment courses. *Ann Noninvasive Electrocardiol*, 2006; 11: 52–56.
7. Makaryus AN, Byrns K, Makaryus MN, Natarajan U, Singer C, Goldner B. Effect of ciprofloxacin and levofloxacin on the QT interval: Is this a significant “clinical” event? *South Med J*, 2006; 99: 52–56.
8. Anderson ME, Mazur A, Yang T, et al. Potassium current antagonist properties and proarrhythmic consequences of quinolone antibiotics. *J Pharmacol Exp Ther* 2001;296:806–10.
9. Liu X, Ma J, Haung J, et al. Fluoroquinolones increase the risk of serious arrhythmias. A systematic review and meta-analysis. *Medicine*, 96:44.
10. Falagas ME, Rafailidis PI, Rosmarakis ES. Arrhythmias associated with fluoroquinolone therapy. *Int J Antimicrob Agents*, 2007; 29:374–379.
11. Prabhakar M, Krahn AD. Ciprofloxacin-induced acquired long QT syndrome. *Heart Rhythm*. 2004;1(5):624-626. doi:10.1016/j.hrthm.2004.06.020.
12. Keivanidou A, Arnaoutoglou C, Krommydas A, et al. Ciprofloxacin induced acquired long QT syndrome in a patient under class III antiarrhythmic therapy. *Cardiol J*. 2009;16(2):172-174.
13. Flanagan MC, Mitchell ES, Haigney MC. Ciprofloxacin-induced torsade de pointes. *Int J Cardiol*. 2006; 113(2):239-241. doi:10.1016/j.ijcard.2005.08.048.
14. Nair MK, Patel K, Starer PJ. Ciprofloxacin-induced torsades de pointes in a methadone-dependent patient. *Addiction*. 2008;103(12):2062-2064. doi:10.1111/j.1360-0443.2008.02390.x
15. Ibrahim M, Omar B. Ciprofloxacin-induced torsade de pointes. *Am J Emerg Med*. 2012; 30(1):252.e5-252.e2.52E9. doi:10.1016/j.ajem.2010.09.039
16. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2010; 55(9):934-947. doi:10.1016/j.jacc.2010.01.001
17. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society [published correction appears in *Heart Rhythm*. 2018 Sep 26;]. *Heart Rhythm*. 2018; 15(10):e190-e252. doi:10.1016/j.hrthm.2017.10.03.

Figures

Figure 1. ECG taken during episode of cardiac arrest showing feature of Torsade de pointe: initiation of the arrhythmia after a short-long-short cycle sequence PVC that falls near the peak of the distorted T-wave, irregular RR interval, and abrupt switching of QRS morphology from predominately positive to predominately negative complexes (A). Note the change in polarity of QRS complex about the isoelectric line (B)

Hosted file

ECG figure.docx available at <https://authorea.com/users/511482/articles/771220-sudden->

cardiac-death-due-to-ciprofloxacin-induced-torsade-de-pointes