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Published In/Presented At

Routhier DD, Katz KD, Brooks DE. QTc prolongation and torsades de pointes associated with methadone therapy. J Emerg Med. 2007 Apr;32(3):275-8. doi: 10.1016/j.jemermed.2006.07.027. Epub 2007 Feb 2.

The Journal of Emergency Medicine, Vol. 32, No. 3, pp. 275–278, 2007

0736-4679/07 $–see front matter

ELSEVIER

doi:10.1016/j.jemermed.2006.07.027

Clinical Communications

QTc PROLONGATION AND TORSADES DE POINTES ASSOCIATED WITH METHADONE THERAPY

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□ **Abstract—Oral methadone therapy is an effective and increasingly popular treatment for opioid dependency and chronic pain. Although it is not typically considered pro-dysrhythmic, we present the unique case of a 52-year-old HIV-positive woman without underlying cardiac disease who developed QTc prolongation and pulseless Torsades secondary to high dose methadone therapy.** © 2007 Elsevier Inc.

□ **Keywords—methadone; QTc prolongation; Torsades de Pointes; HIV; dysrhythmia**

INTRODUCTION

Methadone is commonly used for opioid dependency and chronic pain, often at high daily doses. Though not considered a pro-dysrhythmic drug, there are reports of patients taking methadone (typically higher than 100 mg/day) who develop prolongation of the QT interval and Torsades de Pointes (TdP) (1). We report a case of a patient with methadone-induced QTc prolongation and TdP.

CASE REPORT

A 52-year-old woman with a past medical history significant for human immunodeficiency virus (HIV), Hepatitis B and C, opioid dependency, and anxiety presented to the Emergency Department (ED) with fever and syncope. She complained of tactile fever, frontal headache, and a syncopal episode the night before presentation. Vital signs on presentation were: temperature 40.2°C (104.3°F), heart rate 86 beats/min, respiratory rate 20 breaths/min, blood pressure 142/72 mm Hg; her physical examination had no significant findings. Her prescribed medications included: methadone (145 mg daily), acyclovir, zidovudine, lamivudine, amoxicillin, ranitidine and alprazolam. While in the ED, the patient experienced ventricular ectopy with a self-terminating run of TdP with a prolonged QTc of 517 milliseconds (ms). She complained of nausea and lightheadedness during this episode, but remained hemodynamically stable. Laboratory data: Na^+ 140 mEq/L, K^+ 3.2 mEq/L, Cl^- 102 mEq/L, CO_2 31 mEq/L, BUN 19 mg/dL, Cr 1.1 mg/dL, Glucose 98 mg/dL, Ca^{++} 9.4 mg/dL, Mg^{++} 1.3 mEq/L, PO_4 1.3 mg/dL, WBC 5.5 K/uL, Hgb 9.5 g/dL, Hct 28.1, Plt 190 K/uL. Urine drug screen was positive for cocaine, methadone, and benzodiazepines. She was treated with 2 g i.v. magnesium and 100 mg i.v. lidocaine and experienced no further dysrhythmias in the ED. Blood and urine cultures were obtained, lumbar puncture performed, and ceftriaxone was administered.

On hospital day 2, the patient experienced pulseless polymorphic ventricular tachycardia (Figure 1). Cardiopulmonary resuscitation was performed and the patient was successfully cardioverted with 200 Joules. At the time of arrest, her QTc was 618 ms and serum electrolytes were normal. Troponin after the arrest peaked at 0.28 ng/mL. A transthoracic echocardiogram was per-

RECEIVED: 3 June 2005; FINAL SUBMISSION RECEIVED: 10 March 2006;
ACCEPTED: 5 July 2006

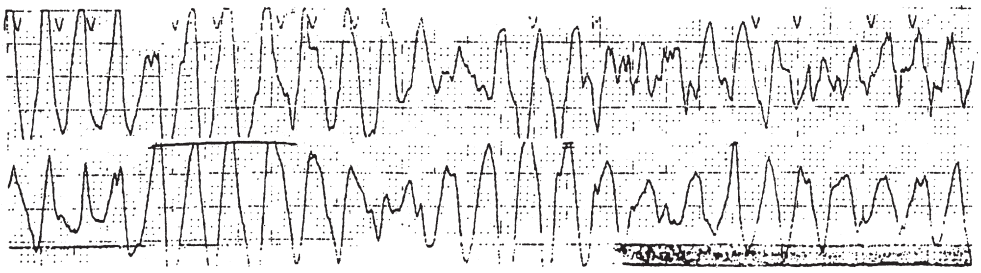

Figure 1. Torsades rhythm strip at the time of pulseless cardiac arrest.

formed, which revealed: a nondilatated left ventricle with hypokinesis involving the anterior and inferior septum and inferior wall, ejection fraction 50% to 55%, mild mitral regurgitation, mild to moderate tricuspid regurgitation, and no vegetations. Blood cultures grew *Streptococcus viridans* of unidentifiable origin, and she completed a 2-week course of Ceftriaxone and Vancomycin. No further cardiac testing was performed. No other cause for the QTc prolongation or dysrhythmia was elucidated. The patient was still receiving 145 mg methadone daily at the time of her arrest. However, her methadone dose was then gradually reduced to 80 mg daily, and subsequent electrocardiograms (ECG) revealed narrowing of the QTc interval (503 ms) on hospital day 4. The QTc was normal at the time of discharge of hospital day 19 (454 ms).

DISCUSSION

This case demonstrates QTc prolongation and TdP subsequent to high-dose methadone therapy. As in this and most cases of drug-induced Torsades, there is a confluence of potential factors, including underlying cardiac, hepatic, electrolyte abnormalities or other medications that may contribute to dysrhythmia development (2). Methadone may cause TdP by blockade of the rapid component of the delayed rectifier potassium current (I_{Kr}), a common mechanism of drug-induced QT prolongation and Torsades (3). Methadone also shares a chemical structure similar to verapamil and may induce bradycardia through calcium channel blockade (4). It has demonstrated negative chronotropic effects in vitro and, therefore, may cause bradycardia and early after-depolarizations with the potential to deteriorate into Torsades (3,5). In HIV-positive patients there exists potential for underlying dilatated cardiomyopathy or myocarditis, which may further predispose to dysrhythmias. However, this patient demonstrated normal ECGs both before methadone was prescribed and after reduction of high-dose methadone therapy (Figure 2), and her echocardiogram revealed normal ejection fraction with only mild hypokinesis thought to be secondary to arrest-induced myocardial stunning.

Methadone seems to exhibit a dose-dependent effect on QTc prolongation but only at high doses. Krantz et al. reported a series of 17 patients who had Torsades while on high dose methadone (400 mg daily). Multiple linear regression indicated that only daily methadone dose was predictive of the QTc interval (3). Martel et al. followed serial ECGs during methadone induction of 132 patients, revealing a statistically significant QTc prolongation. Patients receiving higher doses (110–150 mg) had the longest prolongations (6). Kornick et al. studied i.v. methadone both clinically and in vitro and demonstrated: 1) a statistically significant increasing QTc interval with increasing methadone doses, and 2) concentration-dependent blockade of methadone on cardiac potassium channels (7). As methadone's usage for opiod dependency and chronic pain increases, there is a trend to prescribe high dose therapy (8). Consequently, there may be a higher incidence of QTc prolongation and TdP in this patient population.

A potential contributing factor for the development of TdP is the concomitant use of cocaine. Although our patient's urine drug screen was positive for cocaine, she demonstrated no evidence of sympathomimetic toxicity upon presentation. In low concentrations, cocaine, like methadone, selectively blocks I_{Kr}, causing prolongation of the action potential and QTc interval. Isolated case reports have described TdP in recreational cocaine users. However, all patients had evidence of prolonged QTc after abstinence from cocaine (9).

Examination of the patient's prescribed medication regimen did not reveal any other drug known to cause QTc prolongation or significant CYP3A4 interaction. The patient was prescribed zidovudine and lamivudine (NRTIs); however, there is no current association between antiretrovirals and long QT (1). Methadone is metabolized by CYP3A4, and NRTIs neither induce nor inhibit this enzyme system. Studies have failed to show any increase in serum methadone concentration with concurrent NRTI use (10). The patient was prescribed alprazolam, which shares CYP3A4 metabolism and may theoretically competitively inhibit methadone metabo-

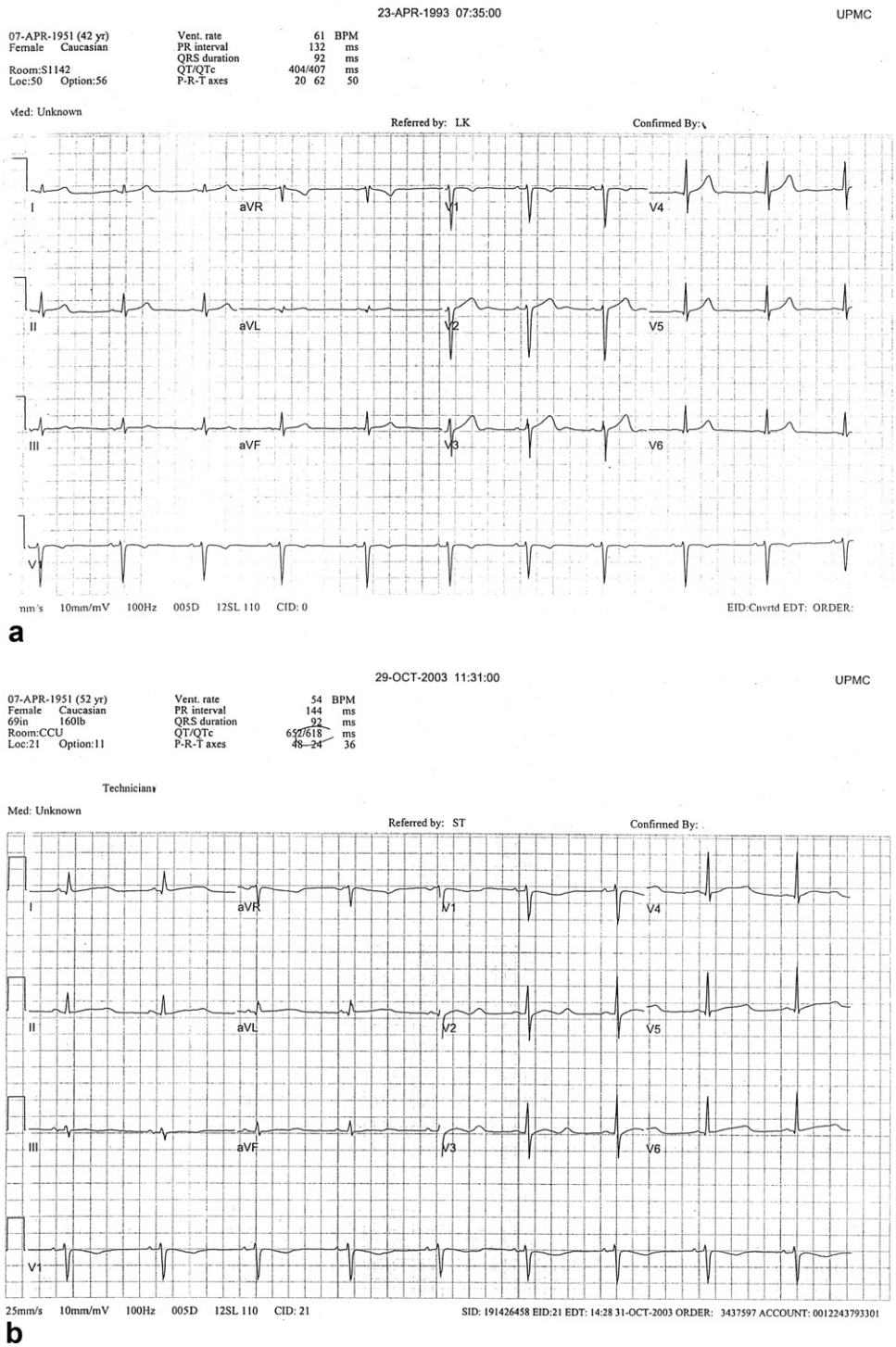

Figure 2. ECG (a) before methadone therapy, QTc interval 407 ms; (b) during methadone therapy, QTc 618 ms; (c) after reduction of methadone dose, QTc 454 ms.

lism. However, this phenomenon has neither been demonstrated in vitro nor in vivo (11).

Other possible etiologic factors implicated in Torsades include electrolyte abnormalities and liver dysfunction (a decreased ability to metabolize pro-dysrhythmic drugs). In this case, the serum K^+ and Mg^{++} concentrations were initially low on presentation, which may have contributed to the patient's dysrhythmia, however, they were normal at the time of the arrest. Despite a known history of viral hepatitis, liver function tests were normal with-

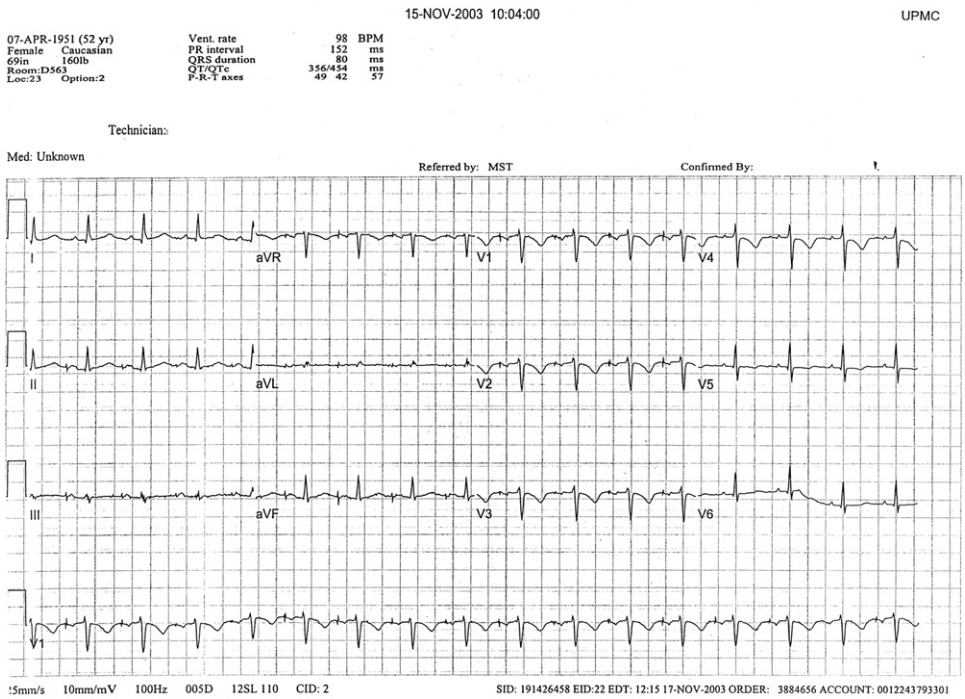

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Figure 2. (continued).

out evidence of synthetic dysfunction. Additionally, the QTc clearly decreased in a temporal fashion with the decrease in methadone dosage.

CONCLUSION

This case report suggests the ability of methadone to induce QTc prolongation and Torsades de Pointes in an apparent dose-dependent manner. Physicians should be aware of methadone's potential cardiotoxicity, particularly when considering its increased use and dosing for opioid dependency and chronic pain. Additionally, it may be prudent to obtain ECGs in methadone users who are prescribed additional medications known to inhibit methadone metabolism or effect.

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