A Case of QT Prolongation and Rhabdomyolysis on Methadone

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Abstract

A 24-year-old male developed a prolonged QT interval and sinus bradycardia along with dark red urine due to rhabdomyolysis and resultant myoglobinuria while on methadone treatment for opiate addiction. In patients taking methadone, we recommend paying special attention to medication history, screening for risk factors associated with long QT syndrome and rhabdomyolysis, counseling patient about potential drug interactions and close and continuous monitoring of QT interval before and during methadone treatment.

Keywords: QT interval prolongation; Sinus bradycardia; Methadone; Rhabdomyolysis

Introduction

Methadone is a synthetic long-acting opiate used in the detoxification and maintenance of patients dependent on opiates—mainly heroine and management of chronic pain. Over 180,000 patients are enrolled in methadone maintenance program for heroin addiction in the United States [1]. For the purpose of treatment of opiate dependence, methadone’s accessibility is restricted to physicians, clinics and pharmacies licensed by the United States-FDA (US-FDA). Methadone maintenance has reduced heroine use, reduced the incidence of HIV/hepatitis through decreased needle sharing and has also helped to reduce mortality with simultaneous improvement in social outcome [2]. Due to its increased consumption, the toxicities and facilities associated with methadone has also increased.

Methadone is independently associated with a prolonged QT which may herald torsade de pointes. In animal studies it has been found that methadone augments the inotropic response to sympathetic stimulation, increases his functional refractory, and decreases the maximum rate of depolarization along with increase in action potential duration. These effects cause prolongation of QT/QTc interval [3]. These effects are mainly dose-related. Structure of methadone has also been compared to verapamil by virtue of its ability to cause calcium channel blockade by acting on the same receptors. It has been reported to block the cardiac human ether-a-go-go-related gene potassium channel. Thus, it has also been seen to cause sinus bradycardia [4]. Methadone can also be nephrotoxic and can have both direct and indirect effects on the kidney. At high doses it can induce rhabdomyolysis and acute tubular necrosis. It can also induce volumetric changes, renal lipodosis, amylodiosis and kidney transplant rejection [5].

We describe a case of a young male on high-dose methadone maintenance that developed a prolonged QT interval and sinus bradycardia along with severe rhabdomyolysis. Although the patient had multiple risk factors that could have likely contributed to both rhabdomyolysis and QTc prolongation, we believe that methadone played a major role in simultaneous occurrence of these entities.

Case Report

On 26th of January, 2017 a 24-year-old Caucasian male on maintenance methadone 135mg daily for opiate drug abuse including Oxycontin and oxycodone/acetaminophen presented to the emergency department after noticing two episodes of dark red urine overnight. Patient was on gradually tapering dose of methadone for last 4 years. On admission, patient was noted to have creatinine kinase (CK) of 39125, LDH=1195, CK-MB=49.5, AST=140, AST 381. His serum potassium, magnesium and creatinine were normal. Calcium was 9.3 and
phosphorus 6.9. He had a past medical history of two episodes of rhabdomyolysis of unclear etiology in 2015. His genetic testing for glycogen storage disease type V was negative. He had a normal alpha-1 antitrypsin level, negative ANA, normal ceruloplasmin, negative antimitochondrial antibody, negative anti-dsDNA antibody and negative Jo antibody. Muscle biopsy was not done. On admission, he was noted to have sinus bradycardia with the heart rate as low as 38bpm in the telemetry. His QTc was 483ms, rate 55bpm in twelve-lead electrocardiogram (ECG) (Figure 1). He complained of mild dizziness overnight. His previous ECG in March 2015 revealed normal sinus rhythm with QTc=431ms, rate of 67bpm (Figure 2) while ECG in December 2015 showed sinus bradycardia (58bpm) with QTc=456ms (Figure 3). On examination, BP was 123/85mmHg, hear rate=46bpm, regular, temperature=98.6°F, RR=14/min. Cardiovascular examination revealed normal S1 and S2 with no murmur, rub orgallop. Neck was supple with no carotid bruits. There was no prior history of cardiac illnesses and the family history for cardiac disease was negative. He didn’t have history of excessive exercise or direct trauma to the body. Patient was not an avid athlete. There was no evidence of infection. His urine drug screen was negative for any other substance except opiates. Echocardiography showed no evidence for intracardiac masses, vegetations or thrombus. There was 1+ mitral and pulmonic insufficiency, 1+tricuspid regurgitation with PA systolic pressure of 34. Ejection fraction was 50%. Cardiolite stress test was negative for any evidence of myocardial ischemia and cardiac dysrhythmias. Patient received aggressive intravenous hydration with normal saline and CK level, AST/ALT and serum electrolytes were trended. In view of gradually prolonging QTC with persistent sinus bradycardia over the period of last 18 months along with recurrent episodes of rhabdomyolysis of unclear etiology, dose of methadone was decreased gradually over the period of next 2 days to 100mg per day. Patient’s QTc decreased to 452ms with tapering of methadone (Figure 4). His CK level also trended down to 5798. Patient was recommended to be gradually tapered off the methadone under close supervision of his methadone clinic. He was also referred to the neuroscience clinic at a higher center for a possible muscle biopsy. During the follow-up on 10th of February, 2017, ECG revealed QTc=460 and his sinus bradycardia resolved with a rate of 72bpm (Figure 5). Patient has no recurrence of rhabdomyolysis so far since last hospital discharge.

### Discussion

The interval between ventricular depolarization (Q wave) and end of repolarization (T wave) is referred to as QT interval in an ECG. A QT interval that is corrected for heart rate refers to QTc. It is often calculated based on Bazett's formula (QTc =QT interval ÷ square root of the RR interval in sec). This is inaccurate at extreme heart rates and results in over...
correcting at high rates and under correcting at low rates [6]. QTc duration >450ms is considered prolonged. There is more than 70% risk of syncope or sudden death with QTc>500ms [7]. Prolonged QT interval may herald onset of torsades de pointes (TdP) which is a form of polymorphic ventricular tachycardia that has rates faster than 100bpm with frequent variations of the QRS axis, morphology or both. TdP generally terminates spontaneously but at times can degenerate to ventricular fibrillation and sudden cardiac death [8]. The prevalence of QTc prolongation and TdP in methadone treated patients is not clear. Between 1969 and 2002, only 43 cases of methadone associated TdP and 16 cases of QTc prolongation were reported to the US-FDA Med Watch program. The mean methadone dose in the reported cases was 410mg/day (range, 29-1680mg/day). Only 1 individual was found to be receiving less than 40mg/day of methadone [9,10]. In a cross sectional study by Fanoe et al. [11], out of 452 individuals undergoing methadone treatment in Copenhagen, Denmark; one third of methadone users taking 100mg/day had prolonged QTc interval. The QTc prolongation has been found to be associated with higher daily methadone dose (average 100mg/day), a lower potassium level, lower prothrombin level and concomitant use of cytochrome P450 (CYP) 3A4 inhibitors [12]. Several protease inhibitors used simultaneously as part of active antiretroviral therapy have also been reported to cause QT prolongation in patients on methadone. HIV-associated autonomic dysfunction and hepatitis C co infection have also been reported to have increased the prevalence of prolonged QTc in HIV patients on methadone therapy [13]. Genetic predisposition for cardiac arrhythmias such as congenital long QT syndrome may also significantly increase the chances of methadone induced QT interval prolongation and TdP. Our patient did not have any such coexisting factors that could have prolonged QTc apart from high-dose methadone which most likely independently caused QTc prolongation and sinus bradycardia.

Methadone can cause muscle injury and elevated CK as a result of direct toxicity. It can also induce rhabdomyolysis indirectly due to prolonged immobilization in a comatose patient or as a result of respiratory depression causing hypoxemia. Unconsciousness causes increased muscular demand for oxygen as well as secondary ischemia which may cause rhabdomyolysis. Acute tubular necrosis due to direct effect of myoglobin is the major cause for acute kidney injury in methadone toxicity and this is mainly dose-dependent [5]. In our case, there was no clear reason for recurrent episodes of rhabdomyolysis in spite of extensive diagnostic workup. High dose maintenance methadone might be the culprit for it.

Methadone is effective in treating opiate addiction and decreases high mortality rates seen in untreated illicit opiate users [14]. Risk of serious cardiac conduction effects and nephrotoxicity with methadone was treated carefully weighed against the potential benefits before the initiation of treatment with methadone. A baseline ECG management, personal and family history of unexplained syncope, review of comorbid medical conditions and a complete medication history should be obtained on all patients. Regular follow-up with a cardiologist should be emphasized in individuals with prolonged QTc and on high-dose methadone. Patients on methadone should be educated to promptly report any symptoms of syncope/presyncope or palpitations. It is also crucial to be aware about the relationship between renal function and opiates, especially in patients on high-dose methadone. Close monitoring of kidney function with down titration of dose may help to avoid potentially serious nephrotoxicity. In opioid dependent patient, switching methadone to buprenorphine/naloxone or naltrexone has been reported to resolve TdP. This may be easier in an acute hospital setting compared to outpatient clinic due to federal regulations [14,15]. Patients who continue taking methadone after initial episodes of TdP are at high risk for recurrent arrhythmic events. Such patients might be good candidates for implantable cardioverter defibrillators (ICD) implantation [16]. In cases of prolonged state of TdP, IV magnesium, temporary cardiac pacing, maintenance of normal serum electrolyte level and discontinuation of methadone is helpful [14].

**Conclusion**

This case emphasizes about the need for close and continuous cardiac and renal monitoring in patients on methadone. Screening for risk factors associated with prolonged QTc including personal or family history of long QT syndrome, arrhythmias and structural heart disease; detail medication history, review of comorbid medical conditions and patient education about drug interaction with methadone are extremely important before its initiation. Gradual tapering of methadone is prudent in patients with significant adverse effects.

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