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Case Report Open Access

Acquired QT Interval Prolongation & Methadone: The Risk of Pharmacological Interaction

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Abstract

Methadone is known to be associated with acquired long QT (LQT) syndrome and the subsequent development of Torsades de Pointes (TdP). We describe a case of acquired LQT and TdP in a patient taking methadone maintenance therapy (MMT) in conjunction with medications known to prolong QT interval, and in the setting of hypokalemia and hypomagnesemia. We highlight the risk of QT interval prolongation when polypharmacy and electrolyte imbalances coexist, demonstrate the importance of early and effective therapy of LQT and suggest potential future alternatives to MMT that appear to have less QT prolonging properties in patients with multiple risks for LQT and TdP.

Keywords: Long QT interval; Polypharmacy; Methadone; Torsades de Pointes; Drug interaction

Abbreviations: LQT: Long QT; TdP: Torsades de Pointes; QTc: corrected QT interval; MMT: Methadone Maintenance Therapy

Introduction

Acquired long QT interval (LQT) is a high-risk condition that can be associated with the ingestion of drugs that alter the action potential by different mechanisms [1]. Prolongation of the QT interval increases the risk for development of Torsades de Pointes (TdP), an often life-threatening ventricular dysrrhythmia [1]. Its occurrence is primarily seen in the setting of corrected QT (QTc) interval prolongation usually greater than 500 ms [2].

Methadone maintenance therapy (MMT) is the first choice treatment for opiate addiction [3]. Though infrequent, there have been reports of TdP occurring with long-term use of high dose methadone [4]. There are other causes of LQT and TdP, with some of the most common etiologies being drugs and electrolyte imbalances that delay repolarization time. In susceptible individuals, the use of methadone may trigger the development of ventricular arrhythmias.

We report a case in which the use of methadone, citalopram and a diuretic, in the setting of an electrolyte imbalance, led to the development of LQT and TdP.

Case Report

A 53 year-old male presented to the emergency department with sudden onset palpitations and shortness of breath. He had prior history of hypertension, chronic back pain, depression, gastroesophageal reflux disease and a 35-pack year history of cigarette smoking. He also admitted to a previous history of heroin use, but adamantly denied any recent consumption and was receiving methadone for opiate addiction. His methadone dose at admission was 85 mg daily and he had been receiving methadone for approximately one and a half years at the time of admission. He was not known to have any communicable diseases, such as hepatitis, and there were no signs or symptoms of hepatic failure. He had no known drug allergies. His medications at admission are listed in Table 1.

At initial presentation, his heart rate was 58 bpm, blood pressure was 156/80 mmHg and the rest of the physical examination was unremarkable. A 12-lead ECG showed sinus rhythm, ventricular bigeminy, and a QTc interval of 520 ms (Figure 1, Panel A and B). Initial

On Admission	*On Discharge*
Methadone 85 mg daily	Methadone 65 mg daily
Hydrochlorothiazide 25 mg daily	Spironolactone 25 mg daily
Telmisartan 40 mg daily	Perindopril 8 mg daily
Citalopram 20 mg daily	Amlodipine 10 mg daily
Pantoprazole 40 mg daily	Pantoprazole 40 mg daily
Ibuprofen 600 mg TID	

Table 1: List of medications.

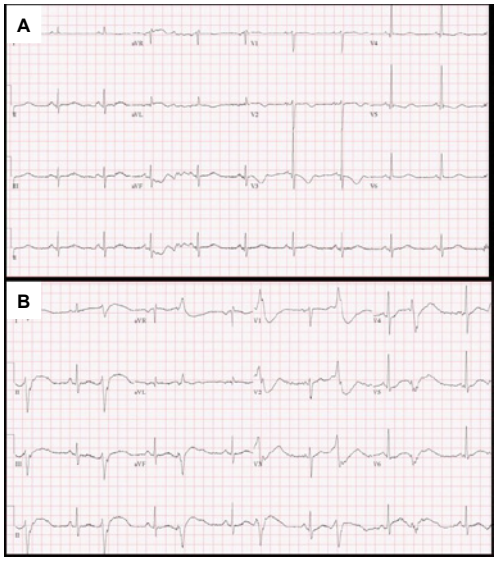

Figure 1: Panel A) Admission electrocardiogram demonstrating prolonged QTc (QTc 520 ms). **Panel B)** Ventricular bigeminy. Long QTc.

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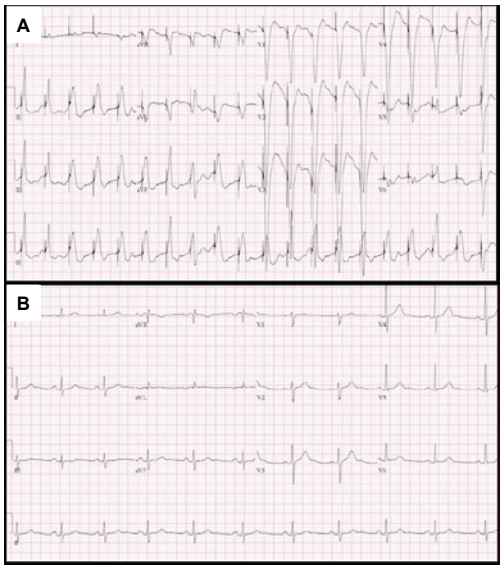

Figure 2: Panel A) Ventricular pacing at 120 bpm. **Panel B)** 12-lead ECG 3 months follow-up (QTc 434ms).

investigations revealed serum potassium of 2.4 mmol/L and serum magnesium of 0.74 mmol/L. Shortly after his initial ECG, the patient's heart rate decreased to 32 bpm followed by a spontaneous, but self-terminating, episode of TdP. The origin of the ventricular tachycardia was initially thought to be ischemic in nature, which prompted the administration of two boluses of intravenous amiodarone at 150 mg and 300 mg, respectively. The amiodarone further prolonged his QT interval and lead to recurrent TdP. He was transferred to the catheterization laboratory, where only minor coronary artery disease was revealed. A temporary percutaneous pacing wire was placed for overdrive pacing (at 120 bpm for the first 2 hours and then reduced to 90 bpm) and suppression of ventricular arrhythmia (Figure 2A).

The patient was then transferred to the Coronary Care Unit medications associated with prolongation of the QT interval were discontinued (methadone, citalopram and amiodarone). Electrolytes were corrected within 12 hours of presentation; an average potassium of 4.0 was reached and maintained, though daily magnesium supplementation continued to be necessary for 4 days after presentation due to persistent hypomagnesemia, likely secondary to diuretic use. The patient's intermittent episodes of TdP subsequently resolved and percutaneous pacing was able to be discontinued at this time. However, with cessation of methadone treatment, he began to develop significant pain, which prompted the resumption of methadone treatment on the second day of admission at 85 mg/day and tapered down by 5 mg/day to 65 mg/day. An in-hospital exercise stress test demonstrated a prolonged QTc interval of 554 ms at rest but appropriate shortening to 422 ms with exertion.

The patient's QTc remained prolonged for several days, even after cessation of TdP. In fact, at the time of termination of percutaneous pacing, the QTc was 486 ms, though it gradually corrected to 436 ms at the time of discharge. A new medication regimen was devised for discharge (Table 1). In follow-up clinic almost three months later, the patient had no recurrence of arrhythmias, and his ECG demonstrated a normal QTc of 434 ms (Figure 2, Panel B).

Discussion

This case illustrates the multiple risk factors that can be involved in acquired LQT and TdP. Not only was the patient on long-standing MMT, which has been found to lead to LQT in up to 9.2% of patients [5, 6], but he was also taking non-toxic doses of citalopram and presented with a severe electrolyte disturbance that was likely diuretic-induced. All of these factors likely contributed to QTc interval prolongation and development of TdP.

Methadone is an opioid agonist that works via stimulation of μ-receptors as well as antagonism of glutaminergic N-methyl-D-aspartate (NMDA) receptors [4]. It was initially used in the 1950s and 1960s as a substitution therapy in opioid addicts as a response to the post-WWII heroin epidemic in America. Since then, methadone has also been used to manage chronic pain and has even been described for use as an analgesic in diabetic neuropathy [2,7].

Methadone acts to inhibit the rapid delayed rectifier (repolarization) potassium current channel, I_{Kr}. Specifically, methadone blocks the human "Ether à-go-go Related Gene (hERG)", which encodes I_{Kr} channels, resulting in fewer repolarizing currents and a lengthening of the QT interval [4]. Consequently, parts of the mid-myocardial layer may continue to be refractory to depolarization, and any premature depolarization can lead to a blocked impulse. This impulse then circulates until excitable tissue is found, establishing re-entrant circuits and leading to TdP [2].

Furthermore, methadone has unique pharmacological properties that contribute to unintentional toxicity. Due to the lengthy time to reach steady state concentrations of methadone, clinicians will increase dosing to effect, which may lead to toxicity [2]. There is also suggestion that methadone's effect on the QTc interval may be dose-dependent based on a review of a number of studies summarized by Andrews et al [2]. Additionally, Krants et al reported that daily methadone dose correlated positively with the QTc interval in a series of patients presenting with TdP while receiving high daily doses of methadone [8] and another prospective observational trial showed that when patients were separated by tertile of methadone dose, those patients in the tertile of highest methadone doses had the greatest prolongations in QT interval [9]. One study reported that the QTc increased by about 0.140 ms per 1 mg increase in daily methadone dose [10]. However, the extent to which the dose-dependent relationship holds true at lower methadone levels is still unclear. Since methadone is metabolized by hepatic cytochromes CYP3A4, CYP2B6 and CYP2D6 of the p450 enzyme system, use of drugs which inhibit these cytochromes may result in increased serum concentrations of methadone and increased susceptibility to ventricular arrhythmias [4]. Other medications may additionally block hERG channel currents, magnifying methadone's effect [11]. These factors may explain why our patient's ECG normalized after reducing the methadone dose, but also suggests that citalopram, a known hERG channel blocker, may have also contributed to the development of LQT and TdP.

The use of methadone may predispose certain individuals to LQT, however, the development of LQT is complex and multifactorial, and the extent of methadone's effect is dependent on many other covariates [1,12,13]. Some patients may have a "forme fruste" of congenital LQT syndrome in which a mutation of one of the LQT syndrome genes is clinically unapparent until the patient is exposed to a particular drug [14]. Other risk factors for LQT include older age, female gender, cardiac ischemia, congestive heart failure, liver disease, HIV infection, lower prothrombin level and anorexia nervosa [2,10]. Bradycardia is also a well known QTc interval prolonger and may have played a role in generating TdP in our case. Finally, sleep apnea is associated with bradycardia and QT interval prolongation, and methadone, acting as

a central nervous system and respiratory depressant, may contribute to this phenomenon [2].

In this case, methadone likely served as a predisposing factor for the development of LQT and TdP. Due to lack of data, it is difficult to determine whether the moderate dose of methadone this patient was receiving would be sufficient to cause LQT and TdP on its own. However, citalopram likely magnified this risk by additionally blocking the hERG channel. This effect, in combination with diuretic-induced electrolyte abnormalities, bradycardia, and treatment with amiodarone unfortunately provided the optimal combination for LQT and TdP to become manifested.

There are few alternatives for the treatment of opioid addiction, and many patients remain on MMT despite its cardiac risks. Orman et al. reviewed buprenorphine, a μ-opioid agonist, and naloxone, an opioid antagonist, as a combination treatment [7]. They found no significant difference in the relapse rate of opioid-dependent patients compared with methadone use alone. More importantly, this review stated that neither buprenorphine alone, nor the buprenorphine and naloxone combination, appear to be associated with clinically significant QTc prolongation [7]. This combination could prove to be an alternative to MMT for patients at higher risk of developing LQT and TdP. One recent study demonstrated successful transition of three patients to buprenorphine therapy from MMT and found normalization of QT intervals and lack of recurrence of arrhythmias, suggesting that buprenorphine alone could be a useful and effective alternative to methadone in a select group of patients [15]. Another future alternative therapy that has been suggested, though not yet available, is the non-racemic R-enantiomer methadone formulation, which appears to exhibit less hERG channel blockade [2].

Until safer alternatives become available, it is important to recognize the potential risks associated with MMT use. A scientific consensus statement was recently published with recommendations to counsel patients about the risks of TdP, to conduct a baseline ECG prior to beginning treatment to identify those with QTc ≥450 ms, and to repeat ECGs at one month and yearly intervals, or when the dose exceeds 100 mg [2]. Whether ECGs should be recommended to patients being treated with drugs that interfere with CYP3A4 and CYP2D6 continues to be debated [16].

As highlighted by this case, amiodarone is another drug that health care practioners must be especially wary of in the setting of LQT. Amiodarone is thought to prolong QT interval and generate ventricular arrhythmias by blocking the I_{kr} delayed rectifier current and prolonging the duration of the ventricular action potential, thereby increasing refractoriness [17]. Even so, amiodarone is thought to have a low incidence of adverse cardiac events [18], and TdP is thought to occur with an incidence of less than 1%, likely because it also blocks the slow inward calcium current and does not increase QT dispersion [19]. However, certain clinical risk factors may increase the proarrhythmic potential of this drug. Namely, the risk for amiodarone-induced TdP greatly increases in the setting of electrolyte disturbance, simultaneous treatment with drugs that delay ventricular repolarization, and low-penetrance gene mutations responsible for congenital LQT syndrome [20-23]. It is therefore important for health care practitioners to contemplate the possibility of LQT and the presence of certain clinical risk factors in dealing with acute cases of polymorphic ventricular tachycardia prior to considering amiodarone administration.

As is highlighted by this case, patients need to be monitored for potential drug interactions and alternative drugs should be considered where possible. In the setting of a medication with known risks, vigilance in addressing potentially compounding risk factors is required. As such, diuretics can induce electrolyte depletion, and closer monitoring is highly recommended to avoid hypokalemia and hypomagnesemia, which enhance the risk of LQT [24]. In the case of patients on MMT, the increase in unexpected harm that may occur as a result of this therapy needs to be considered in the context of how to best balance optimization of a patient's pain control while minimizing the increased risk of arrhythmia. Based on the evolving literature, physicians must be wary of the possible drug interactions of MMT and the potential risk for life threatening arrhythmias and act accordingly when concern is warranted.

Conclusion

This case reflects the risk of QT interval prolongation when methadone therapy, polypharmacy and electrolyte imbalances coexist in the same patient. Despite an established association between methadone and LQT, the development of TdP remains difficult to predict and multiple risk factors need to be taken into consideration when treating these patients. Promising alternatives to MMT that appear to have less QT prolonging properties are on the horizon and should be considered in patients with multiple risks for LQT and TdP.

References

1. Digby G, MacHaalany J, Malik P, Methot M, Simpson CS, et al. (2010) Multifactorial QT Interval Prolongation. Cardiol J 17: 184-188.
2. Andrews CM, Krantz MJ, Wedam EF, Macuson MJ, Capacchione JF, et al. (2009) Methadone-induced mortality in the treatment of chronic pain: Role of QT prolongation. Cardiol J 16: 211-217.
3. Joseph H, Stancliff S, Langrod J (2000) Methadone Maintenance Treatment (MMT): A review of Historical and Clinical Issues. Mt Sinai J Med 67: 347-364.
4. Trafton JA, Ramani A (2009) Methadone: A new old drug with promises and pitfalls. Curr Pain Headache Rep 13: 24-30.
5. Fonseca F, Marti-Almor J, Pastor A, Cladellas M, Farré M, et al. (2009) Prevalence of long QTc interval in methadone maintenance patients. Drug Alcohol Depend 99: 327-332.
6. Maremmani I, Pacini M, Cesaroni C, Lovrecic M, Perugi G, et al. (2005) QTc Interval Prolongation in Patients on Long-Term Methadone Maintenance Therapy. Eur Addict Res 11: 44-49.
7. Orman JS, Keating GM (2009) Buprenorphine/Naloxone: A Review of its use in the treatment of opioid dependence. Drugs 69: 577-607.
8. Krantz MJ, Kutinsky IB, Robertson AD, Mehler PS (2003) Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. Pharmacotherapy 23: 802-805.
9. Martell BA, Arnsten JH, Ray B, Gourevitch MN (2003) The impact of methadone induction on cardiac conduction in opiate users. Ann Int Med 139: 154-155.
10. Fanoe S, Hvidt C, Ege P, Jensen GB (2007) Syncope and QT prolongation among patients treated with methadone for heroin dependence in the city of Copenhagen. Heart 93: 1051–1055.
11. Baranchuk A, Simpson CS, Methot M, Gibson K, Strum D (2008) Corrected QT interval prolongation after an overdose of escitalopram, morphine, oxycodone, zopiclone and benzodiazepines. Can J Cardiol 24: 1-3.
12. Digby G, Pérez Riera AR, Barbosa Barros R, de Sousa Belem L, Fong C, et al. (2010) Multifactorial QT Interval Prolongation: The Risk of Polypharmacy. Can J Cardiol 26: 132D.
13. Abramson DW, Quinn DK, Stern TA (2008) Methadone-Associated QTc Prolongation: A Case Report and Review of the Literature. J Clin Psychiatry 10: 470-476.
14. Olgin JE, Zipes DP (2008) Specific arrhythmias: Diagnosis and treatment. In: Libby P, Bonow RO, Mann DL, Zipes DP eds. Braunwald'sheart disease: A textbook of cardiovascular medicine. 8th Ed. W.B. Saunders Company, Philadelphia.

15. Hanon S, Seewalk RM, Yang F, Schweitzer P, Rosman J (2010) Ventricular arrhythmias in patients treated with methadone for opiod dependence. J Interv Card Electrophysiol 28: 19-22.

16. Cruciani RA (2008) Methadone: to ECG or not to ECG… That is still the question. J Pain Symptom Manage 36: 545-552.

17. Bajaj BP, Baig MW, Perrins EJ (1991) Amiodarone induced torsades de pointes: the possible facilitatory role of digoxin. Int J of Cardiol 33: 335-337.

18. Riera AR, Uchida AH, Ferreira C, Ferreira Filho C, et al. (2008) Relationship among amiodarone, new class III antiarrhythmics, miscellaneous agents and acquired long QT syndrome. Cardiol J 15: 209-219.

19. Hohnloser SH, Klingenheben T, Singh BN (1995) Amiodarone-associated proarrhythmic effects. A review with special reference to torsade de pointes tachycardia. Ann Intern Med 122: 553-554.

20. Hohnloser SH, Klingenheben T, Singh BN (1995) Amiodarone-associated proarrhythmic effects. A review with special reference to torsade de pointes tachycardia. Ann Intern Med 121: 529-535.

21. Di Micoli A, Zambruni A, Bracci E, Benazzi B, Zappoli P, et al. (2009) "Torsade de pointes" during amiodarone infusion in a cirrhotic woman with a prolonged QT interval. Digest Liver Dis 41: 535-538.

22. Priori SG, Napolitano C, Schwartz PJ (1999) Low penetrance in the long-QT syndrome: clinical impact. Circulation 99: 529-533.

23. Moro C, Romero J, Corres Peiretti MA (1986) Amiodarone and hypokalemia. A dangerous combination. Int J Cardiol 13: 365-368.

24. Johri AM, Baranchuk A, Simpson CS, Abdollah H, Redfearn DP (2009) ECG Manifestation of Multiple Electrolyte Imbalance: Peaked T wave to P wave ("Tee-Pee Sign"). Ann Noninvasive Electrocardiol 14: 211-214.