Case Files of the Drexel University Medical Toxicology Fellowship: Methadone-Induced QTc Prolongation

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CASE PRESENTATION

A 22-year-old man, on long-term methadone maintenance (125 mg daily), with a history of intermittent heroin abuse, came to the Emergency Department (ED) after ingesting 250 mg of methadone. He was lethargic on presentation. Vital signs were: temperature 36.2 °C; respiratory rate 10/min; heart rate 50/min; blood pressure 104/62 mmHg; and room air oxygen saturation 99%. A rapid beside glucose determination was 90 mg/dl. His physical examination was significant for lethargy, "pinpoint" pupils and bradycardia, but was otherwise normal. No "track marks" or other stigmata of parenteral drug abuse were found. The cardiac monitor demonstrated sinus bradycardia. Toxicology was consulted. Clinically, this patient demonstrated a toxidrome consistent with opioid intoxication. An IV was established and a 12-lead EKG was performed, demonstrating sinus bradycardia (HR: 51/min) with a markedly prolonged QTc (516 ms). A total of 0.6 mg intravenous naloxone, 0.2 mg every 5 minutes, was given with restoration of a normal mental status. A CBC of differential, basic metabolic panel, and serum calcium and magnesium levels were normal. A urine drug screen (UDS) was positive for methadone, benzodiazepine, and cocaine metabolite(s).

Defining a Prolonged QTc

The QT interval of the electrocardiogram (EKG) is measured from the beginning of the QRS complex to the end of the T wave. The QT interval is commonly corrected to reflect its inverse relationship to the heart rate. Bazett's formula is one of the commonly used formulas for QTc measurement, where QTc = QT interval (ms)/square root of the RR interval (s) [1]. For women, a QTc interval in considered prolonged when the interval is greater than 450 ms to 470 ms; for men, a QTc interval is considered prolonged when the interval is greater than 430 ms to 450 ms [1–3].

What medications are known to cause QT prolongation?

Table 1 provides a list of known medications that cause QT Prolongation [4].

What is methadone?

Methadone is a lipophilic synthetic opioid, and it is a standard detoxification treatment for opioid addiction. Methadone is an μ opiate-receptor agonist that has pharmacologic actions similar to morphine. The bioavailability of methadone after oral ingestion is between 36 to 100%. It reaches peak plasma concentrations between 1 to 7.5 hours post-ingestion. The half-life varies widely between 8 to 59 hours. It is metabolized by the liver via N-demethylation by several P-450 isozymes (CYP3A4, CYP2B6, and CYP2C19) to form an inactive metabolite (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene [EDDP]) that is excreted in the urine [5].

What factors affect methadone clearance?

Since methadone is cleared via the liverhepatic dysfunction, congestive heart failure, and numerous medications alter serum clearance. Concomitant use of P-450 inducers, including phenytoin, phenobarbital and carbamazepine, enhance methadone clearance and may increase the incidence of opiate withdrawal. On the other hand, P-450 inhibitors, including antifungals and macrolide antibiotics, increase the serum methadone level by decreasing serum clearance, resulting in the potential increase in methadone toxicity [5].

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Table 1: QT Prolongation Drugs [4]

Albuterol	Fenfluramine	Ondansetron
Alfuzosin	Flecainide	Paroxetine
Amantadine	Fluconazole	Pentamidine
Amiodarone	Fluoxetine	Phentermine
Amitriptyline	Foscarnet	Phenylephrine
Amoxapine	Fosphenytoin	Phenylpropanolamine
Amphetamine/ dextroamphetamine	Galantamine	Pimozide
Arsenic trioxide	Gatifloxacin	Procainamide
Atomoxetine	Gemifloxacin	Protriptyline
Azithromycin	Granisetron	Pseudoephedrine
Bepridil	Halofantrine	Quetiapine
Chloral hydrate	Haloperidol	Quinidine
Chloropromazine	Ibutilide	Ranolazine
Chloroquine	Imipramine	Risperidone
Ciprofloxacin	Indapamide	Ritodrine
Cisapride	Isoproterenol	Roxithromycin
Citalopram	Isradipine	Salmeterol
Clarithromycin	Itraconazole	Sertraline
Clomipramine	Ketoconazole	Sibutramine
Clozapine	Levalbuterol	Solifenacin
Cocaine	Levofloxacin	Sotalol
Desipramine	Levomethadyl	Sparfloxacin
Dexmethylphenidate	Lithium	Tacrolimus
Dextroamphetamine	Mesoridazine	Tamoxifen
Disopyramide	Metaproterenol	Telithromycin
Dobutamine	Methadone	Terbutaline
Dofetilide	Methylphenidate	Thioridazine
Dolasetron	Mexiletine	Tizanidine
Domperidone	Midodrine	Tolterodine
Dopamine	Moexipril/HCTZ	Trimethoprim-Sulfa
Doxepin	Moxifloxacin	Trimipramine
Droperidol	Nicardipine	Vardenafil
Ephedrine	Norepinephrine	Venlafaxine
Epinephrine	Nortriptyline	Voriconazole
Erythromycin	Octreotide	Ziprasidone
Felbamate	Ofloxacin	

Is the misuse of methadone becoming more common?

Methadone has become a popular street drug with a high potential for abuse. Between 2004 and 2005, the Drug Abuse Warning Network (DAWN), a public health surveillance system that monitors drug-related ED visits for the nation and for selected metropolitan areas, reported a 29% increase of ED visits related to the non-medical use of methadone [6]. There were 75 methadone-related fatalities reported in the Annual Report of the American Association of Poison Control Centers (AAPCC) in 2004 and 69 fatalities in 2005 [7]. Death in a majority of these cases was a result of intentional suicide, intentional abuse, or intentional misuse.

How does methadone cause QTc prolongation?

During normal myocardial repolarization, potassium ions exit the cells through potassium channels. There are I_{Kr} (rapid component) and I_{Ks} (slow component) channels. The human ether-a-go-go-related gene (HERG) encodes the I_{Kr} channel protein. Methadone blocks the human ether-a-go-go-related gene K^+ current (I_{HERG}), diminishing the potassium efflux that triggers repolarization. When repolarization is delayed, the QT interval is prolonged [8,9].

It has been suggested that the two, phenyl groups in methadone are responsible for the inhibitory effects on HERG. Even though the EDDP metabolite also contains two phenyl groups, it is a weaker inhibitor of HERG, perhaps related to its additional cyclic structure and positive charge [8].

When was methadone-induced QTc prolongation first recognized?

In 1973, Lipski and colleagues attempted to investigate the cause(s) of sudden death syndrome in heroin users. They performed EKGs on 75 asymptomatic patients admitted to a methadone maintenance program. In Group I, 34 patients received parenteral heroin and an EKG was performed prior to methadone administration. Group II consisted of 41 patients, on methadone for different durations, who concomitantly used other drugs, including barbiturates, heroin, cocaine, and alcohol. The investigators reported QTc prolongation in 19% of the patients in Group I and 34% of the patients in Group II. They reported that "the most striking electrocardiogram" was a case of sudden death in a 31-year-old, long-term addict who was taking 100 mg/day of methadone. This patient's EKG showed a QTc of 480 ms, and the toxicological report was positive for methadone only [10]. However, methadone-induced QTc prolongation was not truly appreciated until 2002 when Krantz and colleagues reported Torsades de Pointes in patients receiving high-dose methadone [11,12]. They reported a retrospective case series of 17 patients reported to have had Torsades de Pointes. These patients took 65 mg to 1000 mg of methadone daily for less than 1 month to greater than 12 months. Their QTc intervals ranged from 522 ms to 785 ms [11].

Is QTc prolongation from methadone dose dependent?

Factors including hypokalemia, concomitant use of CYP3A4 inhibitors, hepatic dysfunction, and higher maintenance doses of methadone were found to prolong the QTc in methadone maintenance patients [13]. Martell and colleagues reported that

Table 2: Drugs with Risk of Torsades de Pointes [20]

Amidarone	Domperidone[a]	Pentamidine
Arsenic trioxide	Droperidol	Pimozide
Bepridil	Erythromycin	Procainamide
Chloroquine	Halofantrine	Quinidine
Chlorpromazine	Haloperidol	Sotalol
Cisapride	Ibutilide	Sparfloxacin
Clarithromycin	Levomethadyl	Thioridazine
Disopyramide	Mesoridazine	
Dofetilide	Methadone	

[a]Not available in the United States

Table 3: Drugs with Risk of Torsades de Pointes [21]

Alfuzosin	Granisetron	Ranolazine
Amantadine	Indapamide	Risperidone
Azithromycin	Isradipine	Roxithromycin[a]
Chloral hydrate	Levofloxacin	Tacrolimus
Clozapine	Lithium	Tamoxifen
Dolasetron	Moexipril/HCTZ	Telithromycin
Felbamate	Moxifloxacin	Tizanidine
Flecainide	Nicardipine	Vardenafil
Foscarnet	Octreotide	Venlafaine
Fosphenytoin	Ofloxacin	Voriconazole
Gatifloxacin	Ondansetron	Zipradidone
Gemifloxacin	Quetiapine	

[a]Not available in the United States

methadone-induced QTc prolongation was dose dependent. In this study, patients were initially started on 30 mg oral methadone, increased to a median daily dose of 80 mg by 6 months, and 90 mg by 12 months. They found that QTc increased by 12.4 ± 23 ms by 6 months and 10.7 ± 30 ms by 12 months [3]. QTc prolongation, however, has been reported with low-dose methadone therapy (14 mg/day) when hepatic metabolism of methadone is affected by other drugs [14]. Ehret and colleagues also reported that QTc prolongation occurred in patients taking methadone, 30 mg/day [13]. Improvement in QTc prolongation was observed when methadone was stopped, suggesting that methadone was causative [14].

In contrast to other studies, Reddy and colleagues reported that daily median methadone doses of 30 mg had no significant effect in QTc prolongation in 56 cancer patients. The mean QTc was 413 ms before and after methadone treatment [16]. No statistically significant QTc prolongation was found in another small prospective case series (n = 8) with mean oral methadone doses of 51 mg/day at 2 weeks, 56 mg/day at 3 months, and 57 mg/day at 9 months. The mean QTc intervals were 420 ms at baseline, 440 ms at 2 weeks, 430 ms at 3 months, and 430 ms at 9 months [17].

The exact dose of methadone required to produce clinically significant QTc prolongation is unknown. However, QTc prolongation is, in our opinion, likely to be dose-related. QTc interval prolongation (>500 ms) is a prominent risk factor for Torsades de Pointes and sudden cardiac death [1]. High dose methadone (>60 mg/day) has been reported to cause Torsades de Pointes [11,18,19].

What other medications cause Torsades de Pointes?

Table 2 and *Table 3* provide a list of known medications that cause Torsades de Pointes [20,21].

Could cocaine be the cause of QTc prolongation in our patient?

Our patient had a positive urine drug screen for cocaine. Cocaine has also been shown to prolong the QTc by the same mechanism as methadone [22]. Magnano and colleagues reported statistically significant QTc prolongation and heart rate elevation in fourteen habitual cocaine users. The subjects smoked 25 mg of cocaine, and the QTc interval increased by 15 ms within 2 minutes and lasted throughout the 12 minute observation period [23]. Gamouras and colleagues reported that QTc prolongation after cocaine use could be delayed for up to 24 to 48 hours [24].

Our patient was bradycardic, so it is unlikely that his QTc prolongation was secondary only to acute cocaine use. Methadone has also been reported to cause bradycardia [25,26]. Because the structure of methadone is similar to verapamil, it is suggested that methadone decreases heart rate by blocking the calcium channels [27]. In addition, bradycardia may increase the chance for Torsades de Pointes by prolonging the QTc interval because the heart rate and QTc are inversely related.

What is the management for methadone overdose and methadone-induced QTc prolongation?

Naloxone may be given as an antidote for methadone overdose, especially for patients presenting with an opioid toxidrome (miosis and decreased blood pressure, heart rate, respiratory rate, and mental status). Patients who overdose on methadone should be admitted to a monitored unit because methadone has a long half-life allowing for delayed and/or recurrent toxicity, even if the initial toxidrome can be reversed with naloxone.

Methadone administration should be stopped or the dosage decreased. Toxicologists should correct underlying electrolyte abnormalities (hypokalemia, hypocalcemia, and hypomagnesemia) and follow Advanced Cardiac Life Support (ACLS) protocol for symptomatic bradycardia, prolonged QTc, and/or Torsades de Pointes.

CASE CONTINUATION

Because of the long half-life of methadone and the prolonged QTc, the patient was admitted to the intensive care unit for close

monitoring. The patient did not receive any methadone during hospitalization, and—except for mild opiate withdrawal— he experienced no untoward events. The QTc returned to normal (425 ms) on hospital day 3.

FINAL NOTE

Methadone can prolong the QTc interval to a degree that predisposes methadone-users to malignant cardiac arrhythmias. Recently, the FDA MedWatch issued a warning titled "Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat" [28]. The exact dose and circumstances of methadone-induced prolonged QTc are not fully defined. Individuals who overdose on methadone, those on high maintenance doses of methadone (>60 mg/day), and those at the initiation of therapy seem at highest risk. EKG evaluation and continuous cardiac monitoring of patients who overdose on methadone is prudent.

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