Methadone (Dolophine, Eli Lilly and Company, Indianapolis, IN) is a synthetic opioid antagonist that is used for analgesia and the treatment of opioid dependence and withdrawal.\(^1\)\(^-\)\(^4\) Methadone occupies the same opioid receptors in the brain as heroin, but its withdrawal is much slower and an addict may be maintained on this drug without a euphoric rush or harsh side effects; this liberates patients from uncontrolled, compulsive, and disruptive behaviors resulting from heroin intoxication and withdrawal.\(^1\) Methadone is effective in eliminating withdrawal symptoms for 24 to 36 hours. Approximately 180,000 Americans receive daily methadone maintenance treatment (MMT), and the program is being shifted to primary care practices to increase treatment accessibility and flexibility.\(^1\)\(^,\)\(^4\)\(^,\)\(^5\)

Although methadone has allowed former drug users to reintegrate into society without the potential undesirable heroin withdrawal symptoms, its use may result in life-threatening cardiopulmonary complications if not carefully prescribed.\(^6\)\(^,\)\(^7\) Because the respiratory effect peaks later and persists longer than its analgesic effect, iatrogenic respiratory depression from unintentional overdose is one of the major hazards associated with methadone treatment initiation or dose titration.\(^2\)\(^,\)\(^8\)

QT prolongation is common in patients with MMT, but it does not lead to any significant consequences
unless the corrected QT (QTc) becomes profoundly prolonged (≥500 msec), exposing patients to developing torsades de pointes (TdP). TdP is an abnormal cardiac rhythm displaying a regular and wide polymorphic QRS complex tachycardia that twists around the isoelectric baseline. TdP is French for “twisting of the points.” If left untreated, this cardiac arrhythmia is potentially fatal because it may degenerate into ventricular fibrillation. Methadone has been in clinical use since the 1960s, but this serious cardiac complication remained unrecognized until 2002. Levacetylmethadol, which is an approved derivative of methadone used for opioid-dependency, was recently removed from the European market because of its association with TdP.

A substantial number of healthcare providers cannot correctly measure the QTc interval or identify medications that may cause QTc prolongation, and few physicians in accredited MMT programs are aware of methadone-induced QTc prolongation (41%) or TdP (24%). Because of the potential fatal outcome of TdP, the large number of patients in the MMT program, and the high incidence of concomitant risk factors for QTc prolongation, clinicians need to be aware of these cardiac complications to make a correct diagnosis and deliver appropriate treatment. This article will present a case of methadone-induced TdP, its incidence and cause, diagnosis, treatment, and guidelines for methadone therapy.

**CASE PRESENTATION**

A 61-year-old man had a history of smoking, diabetes mellitus, hypertension, anemia, posttraumatic stress disorder, and anxiety. He was a previous heroin user and had been receiving maintenance methadone of 110 mg/day. He presented to the emergency department after 2 episodes of dizziness and near-syncope. The first episode occurred the night before hospital admission and lasted less than 1 minute without chest pain, shortness of breath, shaking movements, neurologic deficits, or bladder incontinence. The next day, he had a similar episode without loss of consciousness. However, he had bladder incontinence and was therefore brought to the emergency department by his son. Medications included glyburide 5 mg daily, hydrochlorothiazide 25 mg daily, lisinopril 20 mg daily, and metformin 1000 mg twice per day.

The physical examination revealed an irregular pulse, a grade 2/6 holosystolic murmur, and few scattered rhonchi. Laboratory studies revealed anemia (hemoglobin/hematocrit = 8.1/26.2), hypokalemia (2.5 meq/L), and hypomagnesemia (1.5 mg/dL). The electrocardiogram (ECG) showed normal sinus rhythm with atrial bigeminy and a QTc interval of 626 msec (Figure 1). The patient was admitted to a telemetry unit. Later that evening, he developed chest pain and palpitations associated with TdP (Figure 2). Potassium and magnesium were administered intravenously to correct hypokalemia and hypomagnesemia. TdP resolved, and a decrease in QTc prolongation was observed on a subsequent ECG (538 msec). Methadone was initially substituted with a taper of long-acting morphine sulfate, and buprenorphine (Suboxone, Reckitt Benckiser Pharmaceuticals Inc, Richmond, VA) was initiated within a few days after discontinuation of all opioid medications. Because of severe left ventricular dysfunction (ejection fraction of 35%), metoprolol extended release was begun and the lisinopril dose was increased to a maximally tolerated dose. The patient was subsequently referred for additional cardiac evaluation and treatment. His ECG 5 months later was otherwise normal except for borderline QTc prolongation (443 msec) (Figure 3).

**INCIDENCE**

Oral methadone significantly increases the QTc interval, and more than 80% of patients in MMT programs have some degree of QTc prolongation. However, profound QTc prolongation is less common, and its reported incidence in the literatures varies from 2.4% to 16.7%. Data on methadone-induced TdP are limited, and prior publications presented a small series of patients or individual case reports. Twenty-two percent of all Food and Drug Administration (FDA) Adverse Event Reporting System cases of TdP between January 2004 and December 2007 were associated with methadone; this was second only to amiodarone-related TdP. The true incidence of methadone-induced TdP is unknown. One study reported an incidence of 3%, but another study found a higher incidence (3.6%).

**CAUSE**

The QT interval represents ventricular depolarization and repolarization. Methadone acts by inhibiting rectifier potassium ion flux IKr, which leads to an increased action potential duration and a prolonged QTc interval. It has been reported that increases in QTc interval are dose dependent. Most of the fatal cases of TdP in the FDA MedWatch system involved patients taking more than 100 mg/day of methadone. Two studies of 5 and 17 patients with methadone-induced TdP reported even higher daily methadone doses (268 ± 190 and 397 ± 283 mg daily) than normally recommended for MMT (60-120 mg/day). Only 6 patients (27.3%) in these 2 series received methadone within the recommended ranges.

Although QTc prolongation occurs more frequently in patients taking high daily doses or those with recently increased dosages, other factors may
contribute to methadone-induced QTc prolongation. Methadone is mainly metabolized by the isoenzyme cytochrome P3A4 of the hepatic cytochrome-P450 (CYP450) system, and its serum level may be influenced by a variety of CYP450 inhibitors, such as antibacterial or antiviral drugs. Other contributing factors include concomitant administration of other QTc-prolonging substances (eg, alcohol, cocaine, benzodiazepines, and certain antibiotics), electrolyte abnormalities (eg, hypokalemia, hypocalcemia, and hypomagnesemia), hepatic failure, and preexisting heart disease. However, a multilinear regression in one study found that methadone dosing was the only predictor of QTc interval in patients with TdP.

The above-mentioned predisposing factors for QTc prolongation are also expected to predispose patients to TdP. In addition, congenital long-QT syndrome may also contribute to developing this serious arrhythmia. Approximately 2% of the population has an abnormal human cardiac ether α-go-go gene, which encodes $I_{Kr}$. This genetic abnormality makes these patients more susceptible to methadone-induced QTc prolongation and TdP. Female preponderance has been reported, although the data on underlying structural heart disease remain inconclusive. Drug-induced TdP rarely develops in patients whose heart rate is more than 110 bpm, which indicates a protective effect of tachycardia against TdP. Methadone also has negative chronotropic effects through calcium channel blocking and anticholinesterase properties, which leads to a bradycardia that may also contribute to the development of TdP.

**Diagnosis**

Most patients with methadone-induced QTc prolongation remain asymptomatic, and the diagnosis depends on the documentation of a long QTc. The QT interval is measured from the beginning of Q wave to the end of T wave on the ECG (Figure 4). This interval is affected by heart rate and needs to be corrected accordingly. Multiple acceptable formulas have been described, such as Bazett’s correction, Fridericia’s correction, and Framingham correction. Bazett’s correction is the most commonly used, in which the QTc interval is calculated by dividing measured QT interval in milliseconds by the square root of the R-R interval in seconds. Normal QTc intervals are ≤ 430 msec for men and ≤ 450 msec for women; definite QTc prolongations are defined as > 450 msec for men and > 470 msec for women. There is no reliable criterion to
identify the amount of QTc prolongation that will lead to TdP. However, it is generally accepted that QTc intervals ≥ 500 msec will predispose patients to developing this arrhythmia. Presenting symptoms of TdP include palpitations, dizziness, syncope, or full cardiopulmonary arrest because of its potential deterioration to fatal arrhythmia.

**TREATMENT**

In the presence of QTc prolongation, methadone dose should be adjusted or switched to an alternative drug and the ECG should be repeated. Methadone is recommended to be promptly substituted by another drug if the patient’s QTc is ≥ 500 msec, and the patient should also be referred to a cardiologist. In patients with nonsustained TdP, electrolyte abnormalities need to be promptly corrected, and methadone and other concomitant CYP450 inhibitors or QT prolonging drugs need to be discontinued. Intravenous potassium repletion to 4.5 to 5.0 mM/L may be necessary to terminate methadone-induced TdP associated with hypokalemia, and magnesium administration is reasonable for those with QTc prolongation even if the serum magnesium level is normal. Although intravenous lidocaine may be effective, emergency direct cardioversion is necessary for sustained TdP and cardiac pacing or isoproterenol Isuprel (Hospira, Inc, Lake Forest, IL) administration is recommended for recurrent TdP associated with bradycardia. Internal cardioverter-defibrillators may be lifesaving in those who continue to require methadone treatment after their initial episodes of TdP (eg, intractable dependence) and is recommended in those with severe underlying left ventricular dysfunction (ejection fraction ≤ 30%) with or without drug withdrawal. An immediate referral to a cardiologist for additional clinical evaluation and management is mandatory for all patients who develop methadone-induced TdP.

**GUIDELINES FOR METHADONE THERAPY**

Before initiating methadone therapy, a detailed history and physical examination are important; particular attention should be given to any symptoms or family history suggestive of heart disease or syncope. Medication review needs to account for any concurrent drugs that may cause QTc prolongation. The Maudsley prescribing guidelines advise the clinician to avoid prescribing methadone, especially in high doses, to patients who are taking CYP450 inhibitor or QTc prolongation drugs. Any underlying physiologic or pathologic risk factors for QTc prolongation need to be corrected before starting methadone. Patients with chronic electrolyte abnormalities, such as hypokalemia, hypomagnesemia, and hypocalcaemia, should also be excluded from methadone treatment. A detailed cardiovascular examination is important to uncover any underlying structural heart disease. The recommendations on pretreatment and follow-up ECGs remain inconclusive. Although a recent
expert panel recommends pretreatment and more frequent follow-up ECGs, other authors maintain that it is not necessary or cost-effective to obtain ECGs for all patients before methadone initiation.\textsuperscript{11,39-41} They also suggest that initial screening ECG and biyearly follow-up ECGs should only be performed in patients on very high doses of methadone and those with underlying risk factors for QTc prolongation or TdP.\textsuperscript{35,40,42}

A multidisciplinary panel was recently formed to establish safety guidelines for prescribing methadone.\textsuperscript{41} The panel was composed of experts on the cardiac effects of methadone, representatives from the FDA, and members of 3 national organizations devoted to drug abuse, addiction, and treatment. This panel systemically reviewed literature on methadone and heart disease (including QTc prolongation and TdP) from 1966 to 2008. Five recommendations were proposed: (1) disclosing arrhythmia risk of methadone therapy to the patient; (2) assessing for a history of structural heart disease, arrhythmia, and syncope; (3) screening for QTc prolongation, including pretreatment ECG, ECG at 30-day follow-up and annually, ECG before prescribing high-dose methadone (>100 mg), and ECG with history of unexplained syncope or seizure while taking methadone; (4) risk stratifying—discussing risk and benefits of frequent ECG monitoring at mild QTc prolongation < 500 msec, eliminating contributing factors, and considering a reduced dose or alternative therapy for profound QTc prolongation ≥ 500 msec; and (5) being aware of interactions between methadone and CYP450 inhibitors or QT prolongation drugs.

**DISCUSSION**

It is generally agreed that there is enough evidence to suggest that methadone may cause TdP in patients who also have coexisting risk factors for QT prolongation/TdP or in those receiving very high doses of methadone.\textsuperscript{6} The case presentation demonstrated several clinical features associated with methadone-induced TdP. The patient was taking a relatively high dose of methadone and had symptoms of dizziness and near syncope, which should arouse a strong suspicion for methadone-induced TdP. In particular, he also had profound QTc prolongation, hypokalemia, and hypomagnesemia. In this case, electrolyte corrections should have been initiated in the emergency department before admitting the patient to a telemetry unit. When he developed TdP, corrections of electrolyte abnormalities with intravenous potassium and magnesium aborted the TdP and led to mild shortening of QTc interval, which still remained profoundly prolonged until methadone was substituted with buprenorphine. Even though this patient had no symptoms suggestive of cardiac disease, he had multiple coronary artery disease risk factors and was subsequently found to have severe left ventricular dysfunction that required further evaluation.

**CONCLUSIONS**

To prevent possible fatal outcome from methadone-induced TdP, healthcare providers need to be aware of this potential life-threatening adverse effect of methadone treatment and should be diligent in identifying patients who are at risk of developing TdP. The providers need to obtain careful medication and drug-use histories, screen for risk factors associated with QT prolongation, counsel patients regarding potential drug interactions, and measure the QT interval before and during methadone treatment, especially in high-risk patients.

**REFERENCES**

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