High-dose methadone and QTc prolongation: Strategies to optimize safety

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INTRODUCTION

Methadone is an effective treatment for opioid dependence and chronic pain and, until recently, was viewed as a medication without cardiac properties. However, high-dose methadone has been linked to prolongation of the rate-corrected QT interval (QTc) and torsade de pointes (TdP). TdP is a form of polymorphic ventricular tachycardia that requires the presence of underlying QTc prolongation. QTc changes in the electrocardiogram (ECG) are often subtle and may be difficult to discern when U-waves are present. The risk of arrhythmia is related to the magnitude of the QTc change from baseline. Clinicians should be cognizant of methadone's potential cardiovascular effects and weigh the benefit-to-risk ratio for each patient, given the individual predisposition for arrhythmia. This manuscript describes a case of presyncope in a patient receiving methadone and highlights cardiac considerations surrounding methadone therapy.

Educational objectives:

1. Describe the QTc-prolonging effects of methadone.

2. Recognize how medications affecting hepatic cytochrome P-450 3A4 enzymes can alter methadone effects.

3. Weigh the benefits of high-dose methadone against the risks of possible TdP.

Key questions:

1. Does high-dose methadone confer additional risk of arrhythmia?

2. Is routine ECG warranted in methadone-treated patients?

3. What degree of QTc prolongation implies definitive risk of arrhythmia?

4. What concomitant medications should raise concern in methadone-maintained patients?

CASE PRESENTATION

Mrs. Y is a 42-year-old African-American woman with hypertension, Type II diabetes mellitus, and human immunodeficiency virus (HIV), who receives 300 mg of methadone daily for chronic pain and opioid maintenance. She presents with complaints of palpitations and presyncope escalating over the past few weeks. Within the last two days, she has felt her heart racing with "skipped beats" and has experienced marked dizziness on three occasions. However, she denies overt syncope, seizure activity, or postictal confusion.

The etiology of the patient's chronic pain is a crush injury to her hip from a motor vehicle accident four years ago. She has no history of prior drug abuse. After three years of using various physician-prescribed narcotics and nonsteroidal anti-inflammatory agents, she became opiate dependent. One year ago, she was referred to your pain clinic and started on oral methadone to address chronic pain and subsequent opiate addiction. For the past six months her pain has been well controlled, but she has needed progressively higher doses of methadone. She started a regimen of oral lamivudine 150 mg b.i.d., stavudine 40 mg b.i.d., and efavirenz 600 mg per day for HIV suppression several months ago. Other medications include hydrochlorothiazide 25 mg per day and metformin 500 mg b.i.d. Her podiatrist also started her five days ago on itraconazole 200 mg per day for onychomycosis.

On physical examination, blood pressure is 132/80 mm Hg without orthostatic changes, heart rate is 70 beats per min, respiratory rate is 15, and pulse oximetry saturation is 96 percent while breathing room air. Cardiovascular and neurologic examinations are entirely normal.

Table 1. Selected medications associated with QTc interval prolongation

Antiarrhythmic drugs
Amidarone
Disopyramide
Dofetilide
Procainamide
Quinidine
Antihistamines
Terfenadine
Astemizole
Antibiotics
Azithromycin
Clarithromycin
Erythromycin
Pentamidine
Sparfloxacin
Moxifloxacin
Antifungals
Itraconazole
Ketoconazole
Psychotropic drugs
Chlorpromazine
Haloperidol
Thioridazine
Fluoxetine
Other
Ephedra
Chloroquine
Cisapride
Levomethadyl
Organophospates
Cocaine

You perform a 12-lead ECG, which reveals normal sinus rhythm, heart rate of 75 beats per min, and no atrioventricular block or conduction abnormalities. However, the QT interval is 455 msec, and the QTc is 510 msec. You retrieve an electronic copy of her ECG from an emergency room visit for chest pain last year and discover that her baseline QTc at that time was 440 msec. You now suspect that her current symptoms may have been caused by QTc prolongation with transient TdP.

Serum electrolytes reveal normal concentrations of potassium, magnesium, and calcium. You discontinue itraconazole immediately and arrange to see the patient in one week, with instructions that she proceed immediately to the emergency department if symptoms recur. She returns with no further symptoms, and repeat ECG demonstrates that the QTc has decreased to 475 msec.

CLINICAL QUESTIONS

What causes QTc prolongation, and what represents an unacceptable increase?

QTc prolongation is most commonly associated with drugs and electrolyte disorders, primarily hypokalemia and hypomagnesemia.[1-3] Additional etiologies include congenital long-QT syndrome, subendocardial ischemia, and central nervous system insult.[4,5]

It is generally accepted that women have a slightly longer QTc interval than men, with a prolonged QTc interval defined as > 470 msec and > 450 msec, respectively.[3,6] Although there is disagreement over the exact risk QTc prolongation confers,[3,5-8] it is generally accepted that measurements over 500 msec indicate a significant risk for the development of TdP and increases of 40 msec over baseline merit clinical concern.[3,5-9]

How might methadone cause QTc prolongation?

Methadone and its derivative, levomethadyl acetate (LAAM),[10,11] have been demonstrated to prolong the QTc interval and may predispose susceptible patients to ventricular arrhythmias such as TdP.[12-23] A potential mechanism of arrhythmia may be blockade of the cardiac ether-a-go-go-related gene (HERG) potassium current.[5,26] Blockade of this cardiac ion channel leads to delayed repolarization, which manifests as QTc interval prolongation on the surface 12-lead ECG.[25,26]

Is methadone–associated QTc prolongation dose dependent?

For some medications (e.g., sotalol), there is a clear relationship between dose and plasma levels and the magnitude of QTc interval prolongation.[1,5] For methadone, the relationship is less clear; however, one

prospective study[18] demonstrated a modest impact of oral methadone therapy on the QTc interval. In this study, patients were initiated on oral methadone, 30 mg daily, and increased in 10-mg increments according to self-reported opiate use, presence of opiate withdrawal symptoms, and urine toxicology results. At six months, the median daily methadone dose was 80 mg (interquartile range, 60 to 100 mg; range, 20 to 180 mg). At 12 months, the median daily methadone dose was 90 mg (interquartile range, 60 to 120 mg; range, 20 to 200 mg). This study demonstrated mean QTc increases of 12.4 ± 23 msec at six months, 10.7 ± 30 msec at 12 months, and that mean QTc change from baseline to 12 months correlated with trough (r = +0.37, p = 0.008) and peak (r = +0.32, p = 0.03) serum methadone concentrations.[18]

Also, a retrospective linear regression analysis of 17 methadone-treated patients who developed TdP demonstrated a dose-dependent relationship between methadone and the absolute QTc interval (r = +0.51, p = 0.03).[23] Daily methadone dose ranged from 65 mg to 1,000 mg, with a mean daily methadone dose of 397 ± 283 mg per day. These data suggest that escalating doses of methadone are likely to modestly increase the risk of QTc interval prolongation. No predefined cutpoint for a dose-QTc relationship can be readily identified to predict arrhythmia risk due to the modest effects of methadone on QTc and the wide individual variation.

How might other medications interact with methadone to increase the likelihood of QTc prolongation?

Methadone is metabolized by the hepatic cytochrome P-450 3A4 enzyme and does not possess active metabolites.[27,28] Medications that inhibit or induce CYP3A4 may alter plasma methadone levels dramatically,[14,16,27,29] increasing a patient's propensity for arrhythmia.[1,7,14,16] Such medication interactions are especially important for HIV patients, as many HIV treatments have P-450 effects.[12,27,29-31]

Also, there are a multitude of US Food and Drug Administration (FDA)-approved medications and herbal preparations that cause QTc prolongation on their own.[3,14,32] Medications associated with a prolonged QTc interval far outnumber those that have been proven to cause TdP.[32] Selected medications associated with QTc prolongation are shown in Table 1. However, it is notable that the majority of patients receiving QTc-prolonging drugs manifest no adverse cardiac sequelae.[3,5,8,32]

What medications may have caused this patient's prolonged QTc interval?

Efavirenz, a non-nucleoside reverse transcriptase inhibitor, may have induced P-450 metabolism of her methadone,[30] which therefore required escalation of

Table 2. P450-methadone interactions
Decreases plasma methadone concentration via hepatic P450 induction
Phenobarbital
Carbamazapine
Phenytoin
Ethanol
Rifampin
Dexamethasone
Efavirenz
Griseofulvin
Nevirapine
Rifabutin
Increases plasma methadone concentration via hepatic P450 inhibition
Cimetidine
Ciprofloxacin
Clarithromycin
Diltiazem
Erythromycin
Amitriptyline
Fluvoxamine
Fluoxetine
Grapefruit juice
Itraconazole
Ketoconazole
Nifedipine
Omeprazole
Protease inhibitors
Verapamil
Adapted with permission from Krantz MJ, Mehler S: Treating opioid dependence. Growing implications for primary care (Table 2). *Arch Intern Med*. 2004; 164: 277-288.

Table 3. Clinical indications for electrocardiogram in patients receiving methadone
Prior history of long-QT syndrome or torsade de pointes
Family history of long-QT syndrome or early sudden cardiac death
Structural heart disease
Cardiac arrhythmia and heart block (second- or third-degree AV block)
Anorexia nervosa
Frequent electrolyte depletion (potassium, calcium, magnesium)
Human immunodeficiency virus-infected patients on multiple-antiretroviral therapy
Active cocaine abuse
Methadone dosages greater than 150 mg per day
Initiation of a P-450 inhibitor
Initiation of medications associated with QTc prolongation
Presyncopal or syncope symptoms
Unexplained tonic-clonic seizures with anormal electroencephalogram

methadone dosage. The dose increase, in turn, may have increased the QTc interval from baseline 440 msec to 475 msec.

Once itraconazole was started, there could have been a dual effect: first, itraconazole can increase QTc on its own[32]; second, it inhibits P-450, thereby increasing methadone plasma levels.[27] Either of the two, or a combination, may have caused an increase in QTc to 510 msec and induced self-terminating TdP. A list of medications that may induce or inhibit the metabolism of methadone are depicted in Table 2.

Given the patient's persistently abnormal QTc interval, should her methadone dose be decreased?

The patient's symptoms have resolved, but the physician is faced with an abnormal QTc interval of 475 msec. Treatment options include the following: one, her methadone could be decreased until her QTc returns to baseline; two, her HIV medications could be changed to a regimen that does not include P-450 inhibitors, such as abacavir/didanosine/lamvudine[32]; three, she could be taken off methadone, placed on long-acting morphine or other narcotics, and eventually switched to buprenorphine (a synthetic opioid FDA approved for addiction, which appears to have minimal to no impact on QTc interval in vivo[19]);. four, she could be kept on her present medications, as her symptoms have resolved, but to avoid any QTc prolonging agents or P-450 interactions.

Should methadone initiation be preceded by a screening electrocardiogram?

For most heroin addicts presenting in acute opioid withdrawal, screening ECG is probably unwarranted and extremely impractical. However, a screening ECG is indicated if there are other pertinent risk factors for QTc prolongation, such as drug-drug interactions or long-standing cocaine abuse, which may lead to significant left ventricular systolic dysfunction or accelerated coronary artery disease. ECG screening should be considered when methadone dosages exceed 150 mg. Screening may also be considered in patients with multiple risk factors for QTc prolongation—a family history of long-QT syndrome or early sudden cardiac death, a history of electrolyte depletion, and on initiation of a P450 inhibitor (Table 3).

Are other tests of clinical value?

Echocardiography is not indicated unless a patient presents with a history consistent with structural heart disease such as congestive heart failure or myocardial infarction. A 24-hour Holter monitor could provide useful information but only if the symptoms are frequent enough to be captured with brief monitoring. In cases in which syncope owing to TdP is suspected, immediate hospitalization with ECG monitoring is warranted. If asymptomatic QTc prolongation is detected by a 12-lead ECG, then a Holter monitor would not likely change treatment decisions.

Plasma levels of methadone may be of academic interest but probably will not change treatment decisions. Genetic testing for congenital long-QT syndrome is expensive and not widely available. At present, it should be performed only if a congenital disorder is suggested by the family history or as part of a research initiative.

What are some limitations and challenges in identifying risk for arrhythmia?

QTc prolongation remains a specialized area of cardiology in which there is significant disagreement over the validity of ECG machine measurements, formulas for the "corrected" QT interval, the role of QT dispersion, the influence of genetic markers, and what actual risk for arrhythmia a prolonged QTc represents.[1,3,4,6-7,33-37]

Due to automated ECG inaccuracy in measuring the QTc intervals, manual confirmation with calipers is often required. QTc is calculated by the following formula: QTc = QT interval (in msec) divided by the square root of the preceding RR interval (in sec).[8,38] It is often preferable to measure the QTc interval in limb leads; however, precordial interpretation is acceptable if the termination of the T-wave is better discerned.[7] Readers should recognize the effects of bradycardia, position, time of day, and food intake on QTc interval variability.[8,39,40] If there is uncertainty regarding the presence of significant QTc prolongation, it may be prudent to repeat the ECG and/or have the tracing interpreted by a cardiologist.

What is the rationale for continuing to administer methadone in cases in which QTc prolongation could occur?

Methadone is an opioid agonist with a longer duration of action than morphine, making it effective for opioid dependence and chronic pain management.[28,41-43]

In opioid-dependent patients, the benefits of methadone (particularly when combined with psychosocial services) include reducing illicit drug use, crime, HIV/hepatitis risk, and death, and improving employment and social adjustment.[44-50] Higher doses of methadone are associated with decreased opioid use and improved treatment retention, as shown in randomized clinical trials[51-53] and in retrospective analyses of outcome in clinical populations.[54-57] Even temporary dose increases can lead to decreases in illicit drug use and improvement in social functioning.[58]

In patients with chronic pain, methadone presents a therapeutic alternative to other narcotics, as it is well-absorbed orally, has a long half-life, and provides analgesia similar to that of morphine (via affinity to μ-receptors) without detrimental euphoria.[59,60] Methadone appears to possess other ancillary properties that enhance analgesic efficacy. In particular, it has been demonstrated to have antagonist activity at the N-methyl-D-aspartate receptor in animal studies.[27,61] This antagonist activity may decrease both pain and development of tolerance to the analgesic effects of methadone.[62-64] Thus, the higher doses of methadone that may increase risk of arrhythmia may also be more effective for opioid maintenance and alleviation of chronic pain.

DISCUSSION

This case review illustrates that methadone prolongs the QTc interval in some, but not all, patients. QTc prolongation is associated with an increased risk of ventricular arrhythmias such as TdP. QTc changes may occur over a wide range of doses but are more likely to occur at higher dose. Because the metabolism of methadone can be altered by other drugs via multiple hepatic P-450 pathways, complex medication interactions may occur. Sorting out the etiology of a medication-induced QTc change or arrhythmia may present a significant clinical challenge.

Routine ECG screening for methadone induction is not indicated unless risk factors for QTc prolongation/arrhythmia are present. However, as methadone's cardiac properties are not always predictable, and can even occur in individuals without predisposing risk factors, patients should be monitored for symptomatic manifestations of arrhythmia (i.e., syncope, presyncope). ECG is indicated for patients with structural heart disease and among patients receiving QTc prolonging drugs, and when methadone doses exceed 150 mg per day. Any QTc interval over 500 msec confers a significant risk for the development of TdP. Increases of 40 msec also merit clinical concern. Decreasing methadone dosages or drug discontinuation has been shown to result in normalization of QTc prolongation.[19,20,22] This may, however, lead to other unfavorable results: for patients with opioid dependence, undertreatment may lead to relapse to intravenous heroin use and its associated morbidity. For patients with chronic pain, undertreatment may cause unacceptable pain and loss of function. On the other hand, knowingly keeping a patient on medications or dosages of medication that pose potential cardiovascular risk is unacceptable from a safety perspective.

Treatment decisions to optimize safety must weigh the patient's benefits (e.g., alleviation of pain, abstinence from illicit opioids, decreased risk of HIV/hepatitis C) against their risk profile for arrhythmia. Clearly, a patient with structural heart disease or concurrent cocaine abuse presents a higher risk compared to a patient without such risk factors. Just as many QTc-prolonging drugs are given safely, methadone can be dispensed effectively in high dosages, as long as the potential for QTc prolongation is recognized.

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