ORIGINAL ARTICLE

Fluctuating QTc interval in an asymptomatic patient treated with methadone for chronic pain

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ABSTRACT

Prolongation of the QT interval associated with ventricular arrhythmias has been the most common cause of the restriction or withdrawal of drugs from the market in the past 10 years. Methadone, a synthetic opioid that is increasingly used for the management of chronic pain, has recently been implicated in the development of the prolonged QT syndrome. We present a case report of a patient who developed a prolonged QT while being treated with oral methadone for a chronic pain syndrome. Of particular interest in this patient is the fluctuation of the QT interval at a stable dose of methadone, suggesting that a single normal electrocardiogram (ECG) does not guarantee that the patient is not at risk of ventricular arrhythmias. After reviewing the current literature, we suggest that there is no dose of methadone that may be considered to be completely safe. Other risk factors for prolonged QT interval such as underlying cardiac abnormalities, electrolyte disturbances, and concurrent medications should be sought, and all patients should be monitored with serial ECGs even when methadone doses remain stable.

Key words: methadone, prolonged QT interval, chronic pain syndrome, electrocardiogram

INTRODUCTION

The prolongation of the QT interval associated with polymorphic ventricular tachycardia or the potentially fatal arrhythmia torsade de pointes has been the most common cause of the restriction or withdrawal of drugs from the market in the past 10 years.[1] Methadone is a synthetic opioid that is being increasingly used as an effective and inexpensive therapy for chronic pain.[2] Several recently published case series have implicated high-dose methadone in the development of the prolonged QT syndrome and torsade de pointes.[3-5] This effect is mediated through blockage of the ionic current through cardiac potassium channels composed of subunits expressed by the human ether-a-go-go (HERG) gene.[1] A "rate-corrected" QTc interval of > 500 msec is generally accepted as predictive of an increased risk for torsade de pointes.[4] A linear correlation between the log-dose of methadone and QTc interval was shown in a series of patients receiving intravenous methadone for chronic cancer pain.[6] The absolute daily dose at which QTc interval prolongation was seen varied widely between patients, however, depending in part on concurrent pharmacotherapy. No clear definition has yet emerged in the literature regarding what defines a high daily dose of methadone; estimates vary from > 60 mg per day[3] to 275 to 500 mg per day.[5] We present a case report of QTc fluctuation in an asymptomatic patient treated with 180 mg per day oral methadone for a chronic neuropathic pain syndrome.

CASE DISCUSSION

The patient, a 50-year-old woman, presented to a chronic pain clinic with a 20-year history of right knee pain. She had undergone several orthopedic procedures, which had left her with continual right knee and calf pain, as well as bilateral hip pain. The patient had been diagnosed with complex regional pain syndrome type I due to the presence of typical signs and symptoms including pain, allodynia, and trophic changes in the right limb. Before her presentation to our clinic, she had been treated for four years with epidural sympathetic blocks and intravenous lidocaine, which had provided moderate pain relief. Her medications on presentation included slow-release morphine 75 mg tid, oxycocet tablets for breakthrough pain (four to six per day), and gabapentin 1,200 mg qid. Her medical history was significant for osteoarthritis and migraines. There was no history of cardiac disease. Because she complained of inadequate pain relief on long-acting morphine, she was started on methadone, which was gradually titrated to 20 mg tid, or 60 mg per 24 hours. A preoperative electrocardiogram (ECG) performed after eight months of

Table 1. Drugs that interfere with methadone metabolism	
CYP3A4 inducers (decrease levels/effects)	**CYP3A4 inhibitors (increase levels/effects)**
Aminoglutethimide	Azole antifungals
Carbamazepine	Ciprofloxacin
Phenobarbitol	Clarithromycin
Phenytoin	Diclofenac
Rifamycins	Doxycycline
Nafcillin	Erythromycin
Nevirapine	Isoniazid
	Nefazodone
	Nicardipine
	Propofol
	Protease inhibitors
	Quinidine
	Verapamil
	Selective serotonin reuptake inhibitors

methadone treatment at this dose did not display a prolonged QTc. She was referred for a trial of spinal cord stimulation, which failed. Subsequently, her methadone dose was titrated upward over a period of five months to 80 mg tid, or 240 mg per 24 hours. Her other medications remained unchanged.

Because of recent reports in the literature suggesting the risk of QT prolongation in patients on high-dose methadone, the patient underwent a surveillance ECG. The QTc interval (as calculated by the Bazett formula: QTc interval = QT interval/vR-R interval) was found to be 569 msec. Laboratory investigations, including serum electrolytes, magnesium, and calcium, were normal. The patient's dose of methadone was reduced to 60 mg tid, or 180 mg per 24 hours. An ECG performed after three months at this dose showed normalization of the QTc to 407 msec. Despite the fact that the patient remained on a stable dose of methadone, further ECGs showed her QTc interval to be widely variable. Six weeks later, a third ECG, with no change of medication, showed the interval had lengthened to 567 msec. Due to poor pain control, the patient requested that her methadone dose be maintained despite the risk of arrhythmia. A fourth ECG performed three weeks later showed the QTc had again normalized.

DISCUSSION

The ability of methadone to prolong the QT interval, especially during upward titration of the drug, has been demonstrated in several case series.[3-6] None of the reports that we found during our search of the literature examined changes in the QT interval over time in patients on a maintenance dose of methadone. The potential for fluctuation of the QT interval in this situation is therefore unknown. The case we present suggests that there may be significant variation of the QT interval under conditions of stable dosing. This is particularly relevant in the chronic pain population as these patients may be maintained on methadone for long periods of time.

In a study of 17 patients who developed torsade de pointes on high-dose methadone, Krantz et al., using multiple linear regression analysis, found that only the daily methadone dose was predictive of the QTc interval.[4] The average daily dose of methadone in these patients was 397 ± 283 mg. The duration of methadone therapy ranged from less than one month to greater than one year. The authors note that the methadone dose of six patients had been increased just before the development of cardiac arrhythmias.[3] This suggests that upward titration of the dosage may represent a period of increased risk for prolongation of the QT interval.

Further supporting the claim that methadone treatment may place patients at risk for cardiac arrhythmias, a study of 190 patients receiving intravenous methadone for cancer pain demonstrated a dose-dependent relationship between methadone log-dose and QTc prolongation.[6] In this study, there was not a particular dose below which QTc prolongation was not seen. The authors therefore suggested that no dose of intravenous methadone could be considered safe, and that all patients undergoing this therapy should receive prospective ECG monitoring. A confounding factor in this study was that the intravenous methadone was formulated with chlorobutanol, an additive that also prolongs the QTc.

Table 2. Drugs that may prolong the QT interval				
Antiarrhythmic drugs	**Antimicrobial drugs**	**Antihistamines**	**Psychotropic drugs**	**Other drugs**
Quinidine	Erythromycin, azithromycin	Terfenidine	Thioridazine	Vasodilators—prenylamine
Procainamide	Clarithromycin	Astemizole	Phenothiazines	Diurectics—via electrolyte change
Diisopyramide	Trimethoprim-sulfamethoxazole		Butyrophenones	Motility drugs—cisapride, domperidone
Amiodarone	Pentamidine		Tricyclic or tetracyclic antidepressants	Droperidol
Sotalol	Some fluoroquinolones		Haloperidol	Probucol
Ibutilide	Other—spiramycin, chloroquine, halofantrine, mefloquin		Selective serotonin reuptake inhibitors	Cocaine
Bepridil			Risperdone	Terodiline
			Methadone	Papaverine
				Chloral hydrate
				Arsenic trioxide
				Cesium chloride

The duration of methadone therapy before ECG changes was not stated, although it was likely of short duration given that the drug was used in the context of patient-controlled analgesia (PCA) in an inpatient setting. Certainly, the daily dose of methadone for these patients could have been quite variable because it was being administered by PCA.

In contrast to these reports, two recent papers challenge the risk posed to patients by methadone use. Cruciani et al. studied 104 patients on more than 200 mg daily of oral methadone for chronic pain and narcotic addiction.[7] They found that 33 percent developed QTc prolongation, but none over 500 msec. Risk factors for lengthening of the QTc interval were male gender and duration of therapy less than 12 months. The authors concluded that, although methadone does increase the QTc interval, it does not increase the risk of torsade de pointes. A similar conclusion was reached by Martell et al.[8] In a letter to the editor published in the *Annals of Internal Medicine*, they reviewed the ECGs of 132 patients that were performed two months after initiation of methadone maintenance treatment for heroin addiction. The patients were on a stable methadone dose at the time of the ECG. The authors found that none of the patients experienced a QTc interval increase greater than 400 msec, and none had a QTc interval greater than 500 msec. Taken together, these articles suggest that there is less of a risk of QT prolongation when patients are on a stable maintenance dose of methadone.

Fluctuations in the effect of methadone on the QT interval may owe partially to the substantial variation in metabolism of the drug. Inturrisi et al. found that the interindividual variation in elimination half-life and clearance of methadone from the blood was fourfold and fivefold, respectively.[9] Methadone is metabolized in the liver by the type I cytochrome P450 (CYP450) group of enzymes. The CYP3A4 enzyme is the main CYP450 subtype enzyme mediating N-demethylation of methadone. The activity of this enzyme can vary by as much as 50-fold in the adult population, explaining some of the unpredictability in methadone's metabolism, effects, and side effects.[10] This enzyme is also subject to induction and inhibition by a large number of other drugs (Table 1). Of particular concern in patients taking methadone

are the inhibitors of CYP3A4, which increase the drug's bioavailability and may lead to overdose.[10]

The risk of prolonged QTc and the development of torsade de pointes should be carefully considered in chronic pain patients on methadone. Assessment of risk factors should be performed before prescribing the drug, and a baseline ECG is necessary to establish any underlying conduction abnormalities. Clinicians prescribing methadone should maintain a high index of suspicion, especially if patients are on multiple drugs that may prolong the QTc (Table 2), or if new drugs are added to their regimen. Further studies are required to explore the relationship between methadone dose and risk of QTc prolongation. Hayes et al. recently suggested that an ECG, serum electrolytes, and magnesium should be ordered on all patients taking oral methadone in doses exceeding 240 mg per day.[11] The recently released College of Physicians and Surgeons of Ontario (CPSO) consensus guidelines on the use of methadone for chronic pain advise a surveillance ECG in patients receiving doses greater than 200 mg per day.[12] However, our patient displayed a clinically significant prolongation of the QTc interval at a total daily dose of 180 mg per day of methadone. Several reports indicate that a particular danger period for the development of cardiac arrhythmias is during upward titration of the drug.[3] This case report demonstrates that the QTc interval may be variable even at a stable dose of methadone. We suggest that ECG monitoring should be conducted regularly to rule out prolonged QTc in patients on long-term methadone, as a single ECG is not sufficient to dismiss this risk. Conversely, a prolonged QTc found during surveillance may normalize as levels of methadone stabilize over time. Prolongation of the QT interval to > 500 msec should prompt a reevaluation of the risks and benefits of methadone treatment, consideration of alternatives, and a search for additional predisposing factors such as hypokalemia or other drugs. In addition, we follow the CPSO guidelines, which recommend a cardiology consult for all patients found to have a prolonged QTc interval.[12]

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