Methadone-associated Q-T interval prolongation and torsades de pointes

JOHN STRINGER, CHRISTOPHER WELSH, AND ANTHONY TOMMASELLO

Purpose. The association of methadone with Q-T interval prolongation and torsades de pointes (TdP) is reviewed, and recommendations for preventing Q-T interval prolongation in methadone users are provided.

Summary. Abnormalities in voltage-gated potassium channels have been shown to lead to prolonged action potentials that are expressed as long Q-T intervals, and methadone has been found to interact with the voltage-gated potassium channels of the myocardium. While cardiac arrhythmias in methadone users have been reported for several decades, specific reports of methadone-associated Q-T interval prolongation and TdP did not appear in the literature until the early part of the 21st century. Because not every patient experiences Q-T interval prolongation with methadone, recent research has elucidated risk factors that predispose patients to this adverse effect, including female sex, hypokalemia, high-dose methadone, drug interactions, underlying cardiac conditions, unrecognized congenital long Q-T interval syndrome, and predisposing DNA polymorphisms.

The health risks associated with a prolonged Q-T interval are unclear. Although individuals with a prolonged Q-T interval are often asymptomatic, some may develop palpitations, syncope, seizures, or cardiac arrest. Q-T interval prolongation can also lead to the potentially
fatal reentrant arrhythmia known as torsades de pointes (TdP). However, the mere presence of Q-T interval prolongation may not lead to TdP. Some medications, such as amiodarone, are commonly associated with a prolonged Q-T interval but rarely with TdP. Conversely, TdP can occur in the individuals with a Q-T interval within the normal range.

The most common (and studied) causes of TdP are congenital abnormalities and drug-induced Q-T interval prolongation. Methadone is a synthetic opioid associated with prolonged Q-T intervals and TdP. This article reviews the available literature on methadone-associated Q-T interval prolongation and TdP and provides recommendations on the prevention of these adverse effects.

Risk factors associated with Q-T interval prolongation and TdP

Current research to better assess the risk factors associated with Q-T prolongation and TdP is under way. Roden compiled a list of factors that may increase the likelihood of a patient developing Q-T interval prolongation and subsequent progression to TdP, such as female sex, hypokalemia, a history of drug interactions, underlying cardiac conditions, unrecognized congenital long Q-T syndrome (LQTS), and predisposing DNA polymorphisms. While these risk factors have not been studied in patients receiving methadone, they should be taken into consideration when treating this specific population.

Sex. Women appear to have a much greater risk of developing drug-induced TdP. Makkar and colleagues conducted a literature review and found about 70% of the reported cases of TdP caused by cardiovascular medications involved women, irrespective of other risk factors. The reasons for this disparity are not entirely clear; however, women tend to have a slightly longer Q-T interval than do men.

Hypokalemia. The role of hypokalemia in Q-T interval prolongation and TdP is better understood, but the mechanism is not completely known. Yang and Roden found that the potassium-channel blockers quinidine and dofetilide are more likely to cause Q-T interval prolongation and TdP when potassium levels are low. Ehret et al. found that potassium levels were significantly lower (3.5 meq/L versus 3.9 meq/L, p < 0.01) in methadone-treated patients with Q-Tc intervals of ≥500 msec.

Drug interactions. In one study, many patients treated with methadone who experienced Q-T interval changes were also receiving treatment with medications that inhibited the metabolism of methadone. This is significant because the binding of methadone to the hERG channel and its subsequent inhibition are dependent on the plasma levels of methadone. Since methadone is metabolized through the cytochrome P-450 (CYP) isoenzyme 3A4, 2B6, and 2C19 pathways, concurrent use of drugs that block these pathways may increase plasma methadone levels. Methadone is also extensively protein bound (85–90%); therefore, the concurrent use of other protein-binding drugs may also increase plasma methadone levels.

Concurrent use of multiple drugs known to prolong the Q-T interval may also increase the risk of Q-T interval prolongation and TdP. The risk of taking methadone with such medications has not been studied directly; however, the addition of another compound that could block the hERG channels may increase an individual’s risk for developing Q-T interval prolongation and TdP.

Hemodialysis. Nakamura and colleagues investigated Q-T interval changes in patients receiving hemodialysis and found that those patients with past cardiovascular complications had longer Q-T intervals than individuals not receiving hemodialysis and that this interval increased acutely after the procedure. The authors noted that a prolonged Q-T interval after hemodialysis is not an expected physiological response; the reason for this is unknown.

Variations in glucose levels. Zhang and colleagues studied the significance and possible effect of glucose changes on hERG channels. They found that through the inhibition of proper voltage flow, both hypoglycemia and hyperglycemia can cause Q-T interval changes. In hypoglycemic states, the changes in voltage flow are partially due to the underproduction of adenosine triphosphate. In hyperglycemic states, the changes are most likely due to the production of reactive oxygen species. Therefore, fluctuations in glucose levels outside of the normal range can result in cardiac rhythm changes, but not everyone who has these fluctuations will develop the rhythm changes.

Congenital LQTS. Having a genetic predisposition for arrhythmia may significantly increase the chances of a patient receiving methadone to experience Q-T interval prolongation. Several mechanisms have been proposed for the physiological basis of TdP predisposition. One possibility is congenital LQTS.

LQTS was first reported in 1957 by Jervell and Lange-Nielsen. They reported on six siblings who suffered from LQTS and congenital deafness. Of the six children, four died of sudden cardiac death. This type of LQTS (Jervell and Lange-Nielsen syndrome) is inherited through an autosomal recessive pattern. Years later, another form of congenital
LQTS was identified (Romano-Ward syndrome) that followed an autosomal dominant pattern and was not associated with deafness.6,16,17 Although most cases can be traced through familial lineage, approximately one in four patients with congenital LQTS have no familial history of the disorder.13 Both types of LQTS have been traced to mutations in at least three genes (possibly seven or more genotypes17) that produce an alteration in the cellular ion-transport mechanism.14 Individuals with congenital LQTS often experience signs and symptoms early in life. Some may develop syncope or arrhythmia during physically or emotionally stressful times, but many individuals experience sudden cardiac arrest before any other symptoms.2

Priori and colleagues19 found that some individuals have a hERG mutation without the phenotypic expression of a prolonged Q-T interval under normal conditions. Each of these individuals had family members with symptomatic congenital LQTS. Those individuals with low penetrance may be more prone to drug-induced Q-T interval changes and TdP compared with patients without the hERG mutation.

Since congenital LQTS is a relatively rare condition, a conclusive link between the disease and the risk of methadone-induced and other types of drug-induced Q-T interval prolongation has not been made. Some researchers have found that a percentage of patients with acquired, drug-induced Q-T interval prolongations have detectable mutations in hERG channels.7,20

Genetic variation alone does not reliably predict the occurrence of drug-induced Q-T interval prolongation. “Repolarization reserve” has been offered as another possible explanation.7 A healthy heart has several redundant mechanisms to counteract congenital or acquired abnormalities. In terms of ion flow, variations of ion channels may act to maintain proper function. The two components necessary in the proper flow of current in the heart are variations of I Kr: the rapidly activating component (I Ks) and the slowly activating component (I Kr). These channels display different functional characteristics and different responses to drugs. The structure of I Kr allows for interactions with a wide range of drug molecules, and this is believed to be the most probable reason that drugs affect the Q-T interval.5 However, I Ks may be able to compensate for lost current flow if I Kr is blocked. This would explain why the occurrence of Q-T interval prolongation and TdP may require more than just the addition of a single drug.

Literature review

Despite a report in 1973 showing that methadone might affect cardiac function,31 specific reports of methadone-associated Q-T interval prolongation and TdP did not appear in the literature until the early part of the 21st century.22–40 These case reports have included patients receiving methadone for the treatment of opioid addiction and of chronic pain.41 Hussain and Ewer42 reported the case of a possible arrhythmia in an infant born to a mother on methadone treatment. Their research did not establish a causal relationship between methadone use and TdP. In a later publication, Krantz et al.11 further analyzed the same data and determined that methadone use was the only variable predictive of Q-Tc interval increases and that the increases were dose dependent.

Kornick and associates45 conducted a study comparing the Q-Tc intervals of 47 patients receiving i.v. methadone for treatment of cancer pain. Q-T intervals were measured while patients were on and off their methadone infusion. The authors found a mean ± S.D. increase of 41.7 ± 7.8 msec in Q-Tc interval (using Bazett’s formula) among patients while on methadone (p = 0.0001). They compared this
increase to the mean ± S.D. increase in Q-Tc interval of patients receiving i.v. morphine (9 ± 6.1 msec, p = 0.15). A significant trend of increasing Q-Tc interval with increasing log-dose of methadone was also found (p < 0.0001). On the other hand, no minimum “safe” dose of methadone was found, as significant Q-Tc interval prolongation was seen in patients receiving a methadone dosage of 0.4 mg/hr. Q-Tc interval prolongation was significantly correlated with above-normal total bilirubin levels. No cases of TdP were reported in the study.

In the same article, the authors sought to evaluate the relative contribution of chlorobutanol (a preservative found in the only parenteral methadone formulation available in the United States) to Q-Tc interval prolongation. Using a patch-clamp recording technique, various concentrations of methadone and chlorobutanol were applied to human embryonic kidney cells and the cardiac hERG potassium currents were measured. Chlorobutanol alone was found to block cardiac hERG potassium currents, and a synergistic, as opposed to additive, blockade can occur when methadone and chlorobutanol are present together.

Martell et al. Martell and colleagues published a retrospective study of 132 patients (66% male, 68% Hispanic) on methadone maintenance treatment for heroin dependence. Baseline ECGs were performed before methadone induction. Patients were stabilized on a methadone dosage of 30 –150 mg daily, and ECGs were performed at two months. The mean Q-Tc interval increase from baseline to follow-up was 10.8 msec (p < 0.001), with a mean ± S.D. follow-up Q-Tc interval of 428 ± 21 msec. No patient had an increase of greater than 40 msec. Patients receiving methadone dosages exceeding 110 mg daily had the greatest prolongations. No episodes of TdP were observed or reported, though 61 patients (32%) were no longer in treatment at the two-month follow-up.

Pearson and Woosley. In 2005, Pearson and Woosley published a review of methadone-related adverse events reported to the Food and Drug Administration (FDA). Between 1969 and 2002, 5503 reports had been filed, 59 of which were related to Q-T interval prolongation or TdP. Of these, 28 resulted in hospitalization and 5 resulted in death. Interestingly, 56 of the cases were reported in the last two years of the review. The authors proposed several explanations for this, including the fact that the arrhythmias can be confirmed only through ECG monitoring, which was not routinely conducted in the earlier years of methadone treatment. They also found that the abnormal cardiac rhythm events reported occurred over a large range of doses.

Ehret and associates examined ECG changes in a retrospective study of 527 former heroin users. Of these, 280 were excluded for not having adequate records available, for abusing methadone, or for having severe heart disease. The remaining 247 individuals were separated into two groups: methadone maintenance patients (n = 167) and patients not receiving any pharmacotherapy (n = 80). Twenty-seven patients in the methadone maintenance group had a Q-Tc interval of 500 msec or longer compared with no patients in the control group (p < 0.001). The relationship between dose and Q-T interval was weakly associated, but a higher daily methadone dose was associated with significantly greater Q-Tc interval prolongation (p < 0.01). In this study, the lowest methadone dosage found to increase the Q-Tc interval above 500 msec was 30 mg per day. In the methadone-treated group, 6 patients experienced TdP. These patients were taking 40–200 mg per day and had a Q-Tc interval of 430–750 msec. Of note, 2 of the patients who experienced TdP had Q-Tc intervals within the normal range.

Maremmani et al. Maremmani and associates conducted a study with 83 patients addicted to heroin on methadone maintenance for at least six months. At the time of ECG recording, all patients had urine toxicology negative for opioids, cocaine, and amphetamines, and none were taking other medications associated with Q-Tc interval prolongation. Eighty-three percent of the patients had Q-Tc interval prolongation greater than the reference value for persons of the same sex and age, though only 2 patients had Q-Tc intervals exceeding 500 msec. No baseline ECGs or plasma methadone levels were obtained. The mean daily dose of methadone was 87 mg (range, 10–600 mg daily), but no correlation was found between dose and Q-Tc interval prolongation.

Wedman et al. Wedman and associates conducted a follow-up study of 220 patients with opioid dependence to evaluate the changes in Q-Tc intervals of patients previously enrolled in a randomized, blinded study of methadone, levomethadyl, and buprenorphine. Patients’ ECG data were analyzed, and Q-Tc threshold values of 470 and 490 msec were selected for men and women, respectively. Controlling for the use of other medications, hypokalemia, and renal insufficiency, the investigators found that 28% of patients in the levomethadyl group, 23% of patients in the methadone group, and none in the buprenorphine group exceeded this threshold during the 16-week study (p < 0.001). Twenty-one percent of the levomethadyl-treated patients and 12% of the methadone-treated patients had a Q-Tc interval increase from baseline of >60 msec at some point in the study. This difference was significant when compared with buprenorphine (p < 0.001). There was no significant difference observed in the Q-Tc interval of patients receiving methadone versus levomethadyl when using Bazett’s formula. However, the researchers
found a progressive prolongation in the Q-Tc interval of patients receiving methadone even when their dose remained stable \( (p = 0.01) \). This trend was not significant among patients treated with levomethadyl. They found no significant difference in interval prolongation between men and women.

**Fanoe et al.** Fanoe and colleagues\(^5^0\) reported on the effects of methadone and buprenorphine on Q-Tc interval in 450 heroin-addicted patients. The authors obtained ECGs approximately 24 hours after the last dose of methadone and found a significant association between Q-Tc interval and methadone dose in both sexes. The association existed regardless of the correction formula used \( (p < 0.001) \). There was no association between Q-Tc interval and buprenorphine dose. Overall, 32% of patients treated with methadone had a Q-Tc interval greater than 440 msec. There was no significant association between Q-Tc interval and age or length of time in treatment. The investigators also asked the patients about histories of syncope over the prior year and found that a higher percentage of patients receiving higher doses of methadone reported more episodes of syncope. Syncope was also found to be related to longer Q-Tc intervals. Limitations of the study included lack of baseline ECGs and information regarding other concurrent medications.

**Peles et al.** Peles and associates\(^5^1\) published the results of a study of 138 patients \( (71\% \text{ male}) \) on methadone maintenance for heroin dependence for a mean of 4.4 years \( (\text{range}, \, 0.3–10.7 \text{ years}) \). ECGs were performed and serum methadone levels were measured for all patients approximately 24 hours after their last methadone dose. The mean ± S.D. methadone dosage was 170.9 ± 50.3 mg daily \( (\text{range}, \, 40–290 \text{ mg daily}) \), with 80.4% of patients receiving greater than 120 mg daily. The mean ± serum methadone concentration was 708.2 ± 363.1 ng/mL \( (\text{range}, \, 110–2350 \text{ ng/mL}) \). The mean ± S.D. Q-Tc interval was 418.3 ± 32.8 msec \( (\text{range}, \, 330–520 \text{ msec}) \). During the month before the study, 29.7% of the patients had urine toxicology positive for opiates and 22.5% had toxicology positive for cocaine. Neither the methadone dose nor the serum methadone concentration correlated with Q-Tc interval. Of the 3 patients who had Q-Tc intervals greater than 500 msec, 2 had died by the time of the two-year follow-up, though neither death was attributed to cardiac causes. None of the 19 patients with Q-Tc intervals of 450–500 msec had any cardiac problems.

**Chugh et al.** Chugh and associates\(^2^\) conducted a prospective evaluation of all patients who had sudden cardiac death and were assessed by a medical examiner. Case subjects included those with therapeutic blood methadone concentrations \( (<1 \text{ mg/L}) \) on postmortem toxicological evaluation, and controls included subjects who did not take methadone. Cases in which higher methadone levels were present were presumed to be overdoses and excluded, as were cases in which recreational drug use was determined to be the cause of death. A total of 22 patients with sudden cardiac death and therapeutic methadone levels were identified and compared with 106 patients in the control group. After autopsy, it was determined that a structural cardiac abnormality that could have caused sudden cardiac death \( (\text{coronary artery disease, severe left ventricular hypertrophy, hypertrophic cardiomyopathy}) \) was present in only 23% of the patients, compared with 60% of patients in the control group \( (p = 0.002) \). Use of other medications \( (\text{benzodiazepines, antidepressants, anticonvulsants, anxiolytics, muscle relaxants}) \) was similar in both groups. Although it was not possible to determine how many of the individuals had died from respiratory depression unrelated to a cardiac event, the authors concluded that the results of the study supported the presence of a cardiac risk associated with therapeutic levels of methadone.

**Mechanism behind changes in Q-T interval**

The reason for the variability in Q-T intervals among patients treated with methadone is not completely clear. Ehret and associates\(^5^6\) believed that some other factors might have contributing roles, as they found that long Q-T intervals seemed to be associated with the use of CYP3A4 inhibitors, low potassium concentrations, and abnormal hepatic function. They concluded that the occurrence of ECG changes is more likely in patients receiving methadone, and other physiological factors are likely to contribute to the manifestation of abnormal cardiac function.

The chiral nature of the methadone molecule may also be important in understanding Q-T interval prolongation associated with methadone. In addition to CYP3A4, methadone is metabolized by CYP2B6 and CYP2D6.\(^5^3-5^5\) Stereoselectivity of CYP2B6 toward S-methadone has been demonstrated in vitro\(^5^6\) and in vivo.\(^5^7,5^8\) It appears as though slow metabolizers of CYP2B6 who possess a *6/*6 genotype have difficulty metabolizing S-methadone but not R-methadone. Eap and associates\(^5^8\) recently demonstrated that S-methadone blocks the hERG channel more potently than does R-methadone and that slow metabolizers of CYP2B6 with a *6/*6 genotype were more likely to have a prolonged Q-Tc interval than did patients without the *6/*6 genotype \( (\text{extensive metabolizers}) \). This is likely clinically significant, as approximately 6% of Caucasians and African Americans possess the *6/*6 genotype.\(^5^7,5^8\)

**Q-T interval changes caused by other opioids**

The adverse events of methadone
followed a history similar to that of levoacetylmethadol, a structural derivative of methadone. Levoacetylmethadol was approved in 1993 for the treatment of opioid dependence. It was developed and studied as an alternative to methadone because it was longer acting than methadone and required less-frequent administration. Originally, it was found to be as safe as methadone. In 2001, reports of adverse cardiac effects associated with high doses of levoacetylmethadol began to surface, and levoacetylmethadol production was subsequently curtailed. Some researchers still believe that levoacetylmethadol is safe when administered in accordance with guidelines (e.g., routine ECG monitoring, proper dose selection) and that it should be reconsidered as an option for treatment.

Aside from levoacetylmethadol and methadone, no other opioid or opioid-related compounds have been associated with adverse effects on Q-T intervals when used at therapeutic levels. Katchman and associates found that codeine, buprenorphine, and fentanyl can block potassium ion channels, but these drugs reach lower plasma concentrations than levoacetylmethadol and methadone. Therefore, codeine, buprenorphine, and fentanyl may be less likely to cause noticeable Q-T interval prolongation. Propoxyphene, which is structurally similar to methadone, has been noted to prolong Q-T intervals in acute overdose cases, but this effect seems to be related to interactions with sodium channels.

Recommendations

There are no current, widely accepted recommendations for the prevention and treatment of methadone-induced Q-T interval prolongation. In November 2006, FDA issued an alert that highlighted the potential for “serious cardiac conduction effects” and provided broad recommendations to “carefully weigh methadone’s risks with its potential benefits before prescribing it.” As with all clinical situations, the risks of a given intervention must be carefully weighed against the alternatives. Given the high mortality rates seen in untreated illicit opioid users and the clear efficacy of methadone in treating opioid addiction, the risk of methadone use, even in a patient with other risk factors for Q-T interval prolongation, may outweigh the alternative of no pharmacologic treatment. All patients should be evaluated for the presence of risk factors for Q-T interval prolongation before methadone initiation. Risk factors should be stratified into modifiable and nonmodifiable factors, and attempts should be made to modify those factors that can be changed. If the decision is made to use methadone, every attempt should be made to use the lowest dose necessary.

Issues to consider before initiating methadone

A baseline ECG measurement, personal and family history of syncope, and a complete medication history should be obtained before starting a patient on methadone. Given the increasing reports of Q-T interval prolongation with methadone, it might be prudent to obtain a baseline ECG for all patients for whom methadone is being considered. In the acute setting, it is important to remember that cocaine use and electrolyte imbalances may influence the baseline reading. A history of unexplained syncope may indicate the presence of one of the common genetic subtypes (LQT1, LQT2, LQT3) of LQTS. If a patient has a history of unexplained syncope, genetic testing for the common heritable subtypes can be performed to assist in clinical decision-making. A family history of syncope or sudden death may indicate a genetic predisposition to a prolonged Q-T interval. This assessment should include clear episodes of unprovoked sudden death as well as other deaths that may be associated with LQTS (e.g., drowning, sudden infant death syndrome, nonintoxication-related driving fatalities). It should be remembered, however, that because there is also a genetic component to addiction, a family history of sudden death may be attributed to overdose or substance-induced cardiac event. As with the personal history, a positive family history for sudden death may warrant genetic testing for the common heritable subtypes.

A thorough history of current medications must be taken. Special attention should be given to medications that prolong the Q-T interval, lower the level of potassium or other electrolytes (e.g., certain diuretics), inhibit the metabolism of methadone, or are highly protein bound. If a patient is taking any of these medications and the use of methadone is deemed essential, consultation with the patient’s primary care provider is needed.

Issues to consider after initiating methadone

Given the apparent synergistic effects of parenteral methadone and chlorobutanol, oral methadone should be used whenever possible. Once methadone treatment is initiated, patients should be asked to promptly report any symptoms of palpitations, syncope, or near syncope. Patients should also be informed that certain conditions (e.g., vomiting, diarrhea, dehydration) or medications (e.g., diuretics) could lead to hypokalemia and increase their risk of developing a prolonged Q-T interval. They should also be asked to report the addition of any new medications and be evaluated for potential drug interactions that could lead to Q-T interval prolongation.

For patients who develop prolonged Q-T intervals while on methadone, treatment strategies differ..
depending on the indication. For patients receiving methadone for pain, an alternative opioid (i.e., morphine, codeine, or oxycodone) should be used. For those receiving methadone for opioid dependence, an alternative agent, such as buprenorphine–naloxone or naltrexone, should be used. A case of a successful switch from methadone to buprenorphine with resolution of TdP has been described. However, this option may not always be available in the outpatient setting. Federal regulations dictate the use of buprenorphine–naloxone, which make it difficult for the patient to receive this type of treatment. Within an acute hospital setting, patients may be maintained on any opioid, including buprenorphine or buprenorphine–naloxone, as long as they were admitted for a condition other than the opioid addiction. In the outpatient setting, however, buprenorphine–naloxone can only be prescribed by a physician with a specific waiver from the federal government.

ECGs should be periodically monitored in patients with other risk factors for Q-T interval prolongation or in those taking higher dosages of methadone (i.e., >60 mg daily). Serum electrolyte levels should also be monitored if the patient is taking diuretics or has chronic nausea or vomiting. Given the association of cocaine use with Q-T interval prolongation, patients can only be prescribed by a physician with a specific waiver from the federal government.

After the manuscript was accepted for publication, the *Annals of Internal Medicine* released recommendations developed by Krantz and associates for cardiac safety in methadone patients. After conducting a literature review, the authors determined that existing evidence supports the possibility that methadone can induce Q-Tc interval prolongation, warranting cautious prescribing of the drug. The authors developed the following recommendations for physicians who prescribe methadone:

- The patient should be informed of the risk of arrhythmia.
- A thorough history of the patient’s cardiac health (e.g., structural heart disease, arrhythmia, syncope) should be conducted.
- The patient’s medications should be continually evaluated for possible drug interactions.
- A pretreatment ECG should be performed; a follow-up ECG should be performed one month into treatment and annually thereafter. More frequent ECG monitoring is recommended if the patient is taking a daily methadone dose exceeding 100 mg or if the patient experiences unexplained syncope or seizure.
- If the patient has a Q-Tc interval of 450–500 msec, the patient should be monitored more frequently and the patient should be informed of the increased risk. A Q-Tc interval exceeding 500 msec requires a decrease in or discontinuation of methadone or the elimination of potential drug interactions or both.

**References**

12. Nakamura S, Ogata C, Aihara N et al. QTC dispersion in haemodialysis patients with
Methadone-associated Q-T interval prolongation


