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Methadone-induced mortality in the treatment of chronic pain: Role of QT prolongation

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The greatest evil is physical pain
[St Augustine, Soliloquies I, 21]

Abstract

Methadone is increasingly prescribed for chronic pain, yet the associated mortality appears to be rising disproportionately relative to other opioid analgesics. We review the available evidence on methadone-associated mortality, and explore potential pharmacokinetic and pharmacodynamic explanations for its greater apparent lethality. While methadone shares properties of central nervous system and respiratory depression with other opioids, methadone is unique as a potent blocker of the delayed rectifier potassium ion channel (IKr). This results in QT-prolongation and torsade de pointes (TdP) in susceptible individuals. In some individuals with low serum protein binding of methadone, the extent of blockade is roughly comparable to that of sotalol, a potent QT-prolonging drug. Predicting an individual's propensity for methadone-induced TdP is difficult at present given the inherent limitations of the QT interval as a risk-stratifier combined with the multifactorial nature of the arrhythmia. Consensus recommendations have recently been published to mitigate the risk of TdP until further studies better define the arrhythmia risk factors for methadone. Studies are needed to provide insights into the clinical covariates most likely to result in methadone-associated arrhythmia and to assess the feasibility of current risk mitigation strategies. (Cardiol J 2009; 16, 3: 210–217)

Key words: methadone, analgesics, opioid, sudden cardiac death, long QT syndrome, torsade de pointes

Introduction

Chronic pain is one of the most common clinical problems encountered in modern medicine [1]. When pain is acute, the causes are typically apparent and the treatment is simple and straightforward. But when pain becomes entrenched, the pain signals can 'hijack' the nervous system for weeks, months or even years, approaching permanence for certain patients. Various treatments are often attempted prior to referral to a chronic pain practitioner. Therapies attempted may include medication, acupuncture, local electrical stimulation, brain stimulation, psychotherapy, relaxation, biofeedback, behavior modification and various other complementary and alternative therapies. As the cycle of

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pain continues, the neurologic pathways become more reinforced and threaten a patient's chance of returning to his or her pain-free baseline. Over the last ten years, physicians have increasingly recognized the need for opioid-based regimens to combat severe chronic pain [2], yet this has inadvertently led to both increased use and mortality attributed to prescribed opioids.

The use of methadone for chronic pain

Methadone use for the treatment of chronic pain has increased dramatically since 1997 [3] across the United States, in part due to its low cost, long half-life and added effectiveness in modulating pain. Chronic opioid use results in both tolerance to its anti-nociceptive effects as well as heightened sensitivity to pain. These undesirable effects are multifactorial, involving downregulation and desensitization of opiate receptors, an effect that appears dependent on the stimulation of the glutaminergic NMDA receptor [4]. Not only is methadone a μ-opiate receptor agonist (ten times more potent than morphine), it is also an NMDA receptor antagonist, and appears significantly less prone to induction of post-opioid hyperalgesia [5]. Methadone appears therefore to be particularly well-suited to treating chronic pain that has a neuropathic component [6]. Common side effects of methadone are typical for opioids and include constipation, dizziness, drowsiness, itching, nausea, urine retention, and vomiting. Yet with methadone there appears to be less constipation and a reduced level of tolerance to its analgesic effects compared with other opioids [7]. Signs of overdose include shallow breathing, extreme fatigue, dizziness, somnolence, and mental confusion [8].

Methadone and opioid-related mortality

Methadone and opioid associated mortality rates are increasing across the United States. In 2005, drug poisoning surpassed hand guns as a cause of death. While total poisonings increased by 66% from 1997 to 2005, methadone-related deaths increased by 468% [9]. In West Virginia, opioids were involved in 93% of all unintentional fatal poisonings in 2006, and methadone was found in 40% of cases, despite being significantly less frequently prescribed [10]. Approximately 250,000 patients receive methadone through opioid dependency programs [11] and > 700,000 for chronic pain [12]. In Utah, prescriptions for methadone rose by 727% from 1997 to 2004, yet non-suicide methadone related deaths rose by 1770% in same period [13]. While approximately ten times the number of prescriptions are written for hydrocodone and oxycodone compared to methadone, and ten times as many Americans report abusing these agents compared to methadone, the total number of deaths in 2005 was only 12% higher for these compounds than methadone [9]. In 2002, less than 6% of the total morphine equivalents prescribed in the US were attributed to methadone [14], but 24% of the opioid-related deaths involved methadone.

During a four year prospective study evaluating patients who had sudden cardiac death in and around Portland, Oregon, it was shown that 72 of 178 sudden deaths had methadone in their blood. Of those with methadone in the therapeutic range, 77% had no cardiac abnormalities found at autopsy, and only one had an additional opioid (oxycodone). Their conclusion was, given the significantly lower prevalence of structural heart disease in the methadone group, that even at therapeutic levels, methadone was a likely cause of sudden death [15]. These data suggest strongly that methadone is significantly more toxic than other opioids, but does not definitively suggest that the nature of its toxicity is cardiac in origin.

Pharmacokinetic properties

Methadone has unusual pharmacokinetic properties that contribute to unintentional toxicity. Methadone's elimination half-life (8–130 h) is longer than its duration of analgesic action (4–8 h) [8, 16]. This discrepancy can require up to four times daily dosing for chronic pain and can result in significant systemic accumulation of the drug. Methadone is metabolized by hepatic cytochromes CYP3A4 and CYP2D6, and many common medications (e.g. ciprofloxacin, fluconazole, fluoxetine) can inhibit its metabolism, causing elevated serum levels and unanticipated side effects [17]. Approximately 90% of the drug remains protein-bound but a six fold variance between subjects has been described [18].

In-vitro cardiac repolarization properties

Unlike other available opioids, methadone is a particularly potent blocker of the IKr channel, and 10 μM of methadone will cause a 50% reduction in the current. Of currently used opioids, only methadone's clinical serum levels (Cmax) are close to the IC50 for the human Ether-à-go-go Related Gene (hERG) potassium channel current (IhERG) [19]. Interestingly, methadone and the potent IKr blocker terfenadine are molecularly similar in that they

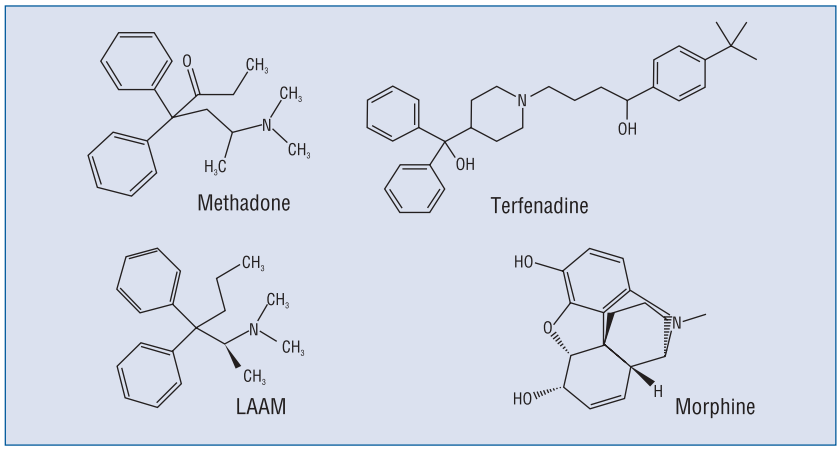

Figure 1. Comparison of the chemical structure of methadone with LAAM and terfenadine, two other known potent blockers of the hERG-related channel, IKr. Note that they share a bi-phenyl ring structure, while morphine, a weak hERG blocker does not.

Table 1. Relationship between QTc and torsade de pointes (TdP) with d-Sotalol [20].

On-therapy QTc	Incidence of TdP	Change baseine [ms]	Incidence of TdP
< 500	1.3% (1787)	< 65	1.6% (1516)
500–525	3.4% (236)	65–80	3.2% (158)
525–550	5.6% (125)	80–100	4.1% (146)
> 550	10.8% (157)	100–130	5.2% (115)
Number of patients assessed		> 130	7.1% (99)

contain a bi-phenyl structure (Fig. 1), while morphine does not.

Mechanism of torsade de pointes

A QTc greater than 500 ms is thought to indicate a threshold of increased danger for torsade de pointes (TdP). In the long-QT syndrome registry, those with a QTc > 500 ms had a four fold greater risk of sudden death compared to a QTc of 450 ms. The QTc is the rate corrected QT interval calculated by QT/√RR. In the sotalol package insert, a QTc between 500 and 525 ms was associated with a 3.4% incidence of TdP (Table 1) [20]. The Antzelevich laboratory has provided a powerful paradigm for understanding the mechanism by which QTc interval prolongation promotes the induction of reentrant tachyarrhythmias in the absence of structural heart disease. Their elegant work has demonstrated intrinsic heterogeneity of repolarization across the layers of the ventricle such that the cells of the middle ('M') layer have the longest action potentials while the epicardium has the shortest. The morphology of the T wave is determined by this difference between the repolarization of the M and epicardial layers of the heart. This heterogeneous electrophysiology of the myocardial layers results in transmural dispersion of repolarization (TDR) which can promote the induction of reentry [21]. There are two components of the delayed rectifier potassium current, the IKr (rapid) and IKs (slow). These play a dominant role in the repolarization of the action potential and are important determinants of its duration [22]. Due to the presence of decreased repolarizing IKs current and increased depolarizing late INa and sodium-calcium exchange currents in M cells, the midmyocardial layer is particularly susceptible to drugs that block IKr, resulting in a greater delay of repolarization compared to the epicardial layer and increased TDR. If TDR is large enough and a premature depolarization occurs, the midmyocardial layer may still be refractory to depolarization and thus block the impulse, causing it to travel in parallel fashion until excitable tissue is found [23]. Once found, a re-entrant circuit is established causing a rotor-like pattern of depolarization which processes through the ventricle, giving the characteristic polymorphic pattern of TdP on the surface electrocardiogram (ECG). Drugs which block IKr but also reduce inward currents, such as ranolazine, verapamil, and

amiodarone, may increase the QTc interval but do not increase TDR. This provides a possible explanation for the paucity of reports associating these drugs with TdP. It is not known whether methadone increases TDR; early reports attribute calcium channel blocking actions to methadone, which might counterbalance the drug's effect on IKr [24, 25].

Clearly the mechanism by which drug-induced QTc prolongation leads to TdP is complex and multifactorial. Typically it requires the presence of a hERG blocking drug and some other undesirable co-factor. The most powerful predisposing co-factor is the presence of an unsuspected hERG mutation (0.1–1% of population), the gene that encodes formation of the IKr channel on cardiomyocites. This mutation may result in a dysfunctional protein increasing the sensitivity of the channel to blockade by drugs. A pre-existing QTc > 450 ms has been associated with a significantly increased risk of sudden cardiac death as well as an increased risk of TdP. In a meta-analysis of 1288 patients who received the QTc interval–prolonging drug sotalol, an increased pretreatment QTc interval was the strongest predictor of arrhythmia (mean QTc interval of 455 ms in those experiencing TdP *vs*. 428 ms), which occurred in 2% of the overall cohort [26]. A study of the antiarrhythmic drug dofetilide found a doubled risk of sudden death if the pretreatment QTc interval exceeded the upper quartile value of 479 ms, highlighting the importance of pretreatment ECG screening for identifying susceptible patients [27]. Other risk factors for TdP include hypokalemia, hypomagnesemia, female gender, inhibition of drug metabolism, cardiac ischemia, congestive heart failure, bradycardia, liver disease (e.g. cirrhosis), and anorexia nervosa [25, 28, 29].

Methadone's association with QTc prolongation

In assessing the *in vivo* evidence for QTc prolongation due to methadone there are 26 case reports or series documenting QTc prolongation [30––56]. In addition, a number of cohort studies suggest important effects of methadone on the QTc interval. For example, Maremmani et al. [42] showed 83% of methadone-treated patients had a more prolonged QTc interval than the reference values for persons of the same sex and age. No correlation emerged between QTc values and methadone dosages. In a Swiss cohort, 16% demonstrated a QTc > 500 ms, and six of their patients (3.6%) developed TdP. In that study, the QTc correlated with methadone dose [31]. In a study from Copenhagen among 393 methadone treated patients (dose > 100 mg), 32% had a QTc > 440 ms, and 8 patients exhibited a QTc > 500. They found the QTc increased by ~0.140 ms for each 1 mg increase in daily methadone dose. Additionally, odds for reporting any syncope were 1.2 (95% CI 1.1–1.4) times higher when the methadone dose was increased by 50 mg. This study included 43 buprenorphine-treated patients, and 0% of these had QTc > 440 ms [33].

A prospective randomized controlled trial has only reinforced these data [53]. Levomethadyl acetate, methadone (high and low dose) and buprenorphine were compared in a cohort of 220 opioid-addicted individuals with a normal pre-drug QTc during a 17-week study. Levomethadyl acetate (LAAM) is a opioid derived from methadone that was recently removed from the market [57]. Due to ethical concerns of using a placebo in a population who were judged to need medical therapy, the 'control' arm was randomized to 20 mg of methadone; however this group was not included in the QT analysis due to an 80% attrition rate. Using stringent QTc criteria defining a prolonged QTc as > 470 ms for men and > 490 ms for women, the odds ratio (OR) for QTc prolongation on methadone was 14.4 compared to buprenorphine (CI 1.9––109.5, p = 0.01). Overall, 12% of the methadone group and only 2% of the buprenorphine group exhibited an increase from baseline QTc exceeding 60 ms or more, resulting in an OR 8.4 (95% CI 1.9––36.4, p < 0.004). On average they had a 34 ms increase in the QTc, three times the amount of the buprenorphine group (11.3 ms, p = NS, Fig. 3A).

An unexpected finding was progressive QTc prolongation in the subgroup who were maintained on a fixed dose of methadone (Fig. 3B). Importantly, six of 52 (11.5%) in the methadone group and 0% in buprenorphine group had a QTc > 500 ms [53, 58].

Methadone's association with torsade de pointes

There are 15 case reports or case series reporting TdP with methadone [31, 32, 34, 35, 37, 39–41, 45, 46, 48–50, 55, 56]. Krantz et al. [39] first reported 17 episodes of TdP associated with very high dose methadone, mean 397 ± 283 mg. The Food and Drug Administration MedWatch system documents 43 cases of TdP associated with methadone; 8% were fatal and most involved doses of methadone exceeding 100 mg/day [46]. One recent series from the Massachusetts General Hospital conducted between 1999 and 2007 followed eight patients

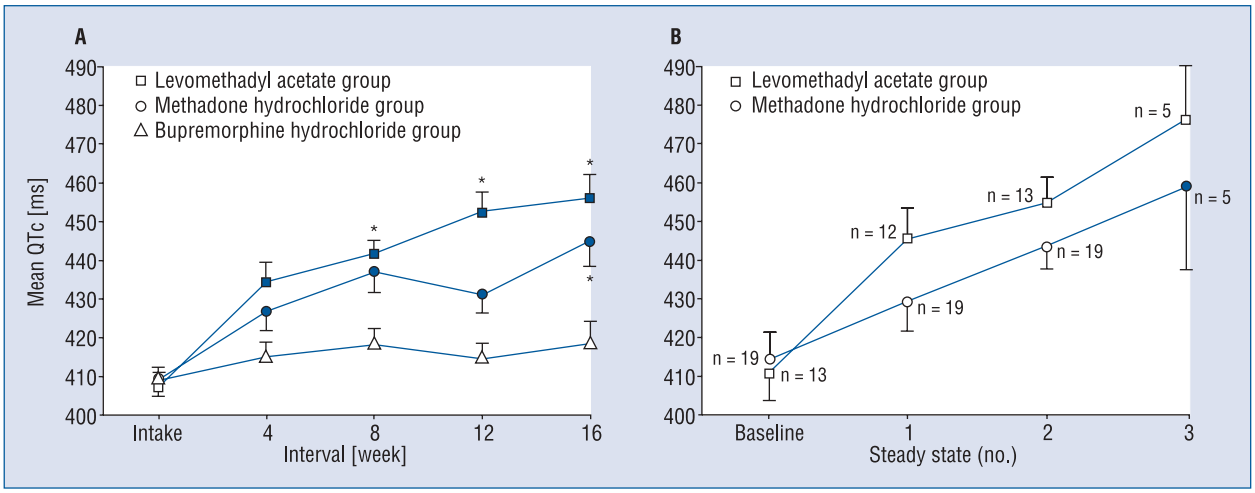

Figure 2. Comparison of the mean rate of Bazett's corrected QT interval (error bars indicate confidence intervals). **A.** Comparison in the three study groups during the trial. Filled symbols indicate significant Tukey *post hoc* comparisons between treatment weeks and week 0 ($p < 0.05$). Asterisks indicate significant Tukey *post hoc* comparisons to buprenorphine hydrochloride group at that treatment week ($p < 0.05$); **B.** Comparison in the levomethadyl acetate and methadone hydrochloride groups receiving a fixed dose of the study drug for at least two 4-week intervals. Filled symbol indicates a statistically significant difference compared with the first steady state period ($p < 0.05$).

with a history of TdP while enrolled in a methadone maintenance program after re-challenge with methadone following implantation of a defibrillator. All but one had preserved left ventricular function on transthoracic echo (ejection fraction mean 61 ± ± 1.1%), and none had evidence of coronary artery disease by myocardial perfusion scintigraphy or left heart catheterization. All of the patients had prolonged QTc intervals (mean 613 ± 71 ms) while taking methadone. One subject died due to undetermined causes, and three of the remaining seven had multiple recurrent defibrillations for TdP during a mean follow-up period of 27 months [45]. Of the six subjects who had ECGs prior to methadone, three had QTc ≥ 450 ms, which further supports the utility of baseline ECG screening to measure the QTc interval prior to initiating therapy with this agent.

Additional risk factors for mortality in methadone treatment

Several studies have found an increased incidence of mortality during first 14 days of therapy [59]. Additionally, subjects found at autopsy to have methadone in their blood frequently did not have prescriptions for that compound, suggesting it had been 'diverted' from someone else and may represent a first exposure to the drug [10]. This apparent early increase in mortality may represent respiratory suppression in a naïve individual, but experience with QTc prolonging drugs (such as quinidine) also identifies the early treatment period as a time of high risk for TdP [60]. Data from canine myocytes exposed to dofetilide suggest that exposure to IKr blockers induces a compensatory increase in IKs within 24 hours; early tolerance to QTc prolongation may develop relatively rapidly [61]. Benzodiazepines are frequently found in the blood of someone who suffers a methadone-related death. While combining benzodiazepines with methadone may simply increase respiratory depression, an alternative explanation may be that some benzodiazepines block IKs [62], and may further reduce repolarization reserve and trigger a greater QTc prolongation [63].

Other contributory toxic effects of methadone include its association with sleep apnea. Sleep apnea itself is associated with bradycardia [64] and significant QTc prolongation [65], both independently associated with TdP [28, 29]. Wang found that 30% of those on methadone had central sleep apnea *vs*. 0% in body mass index matched controls. The methadone group also had significantly higher waking $PaCO_2$, consistent with depressed ventilatory drive [66]. How methadone compares to other opioids with respect to sleep apnea is not described in the literature and further studies are needed. Nonetheless, sleep apnea has been shown to cause QTc prolongation in subjects in the absence of QTc--prolonging drugs [65], and so these two mechanisms may be synergistic in their tendency to promote sudden death during methadone therapy.

Table 2. 2009 Consensus Recommendations for Physicians Prescribing Methadone [67].

Recommendations	
1 (Disclosure)	Clinicians should inform patients of arrhythmia risk when they prescribe methadone.
2 (Clinical history)	Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.
3 (Screening)	Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and then a follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/d. or if patients have unexplained syncope or seizures.
4 (Risk stratification)	If the QTc interval is greater than 450 ms but less than 500 ms, discuss potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.
5 (Drug interactions)	Clinicians should be aware of interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone.

Recommendations to clinicians

A committee consisting of cardiologists, pain specialists, and opioid addiction specialists recently published a scientific consensus statement with recommendations for managing patients initiating or continuing methadone therapy (see Table 2) [67]. In brief, the recommendations are similar to those in place for dofetilide or other potent QTc-prolonging drugs [68], and include counseling patients about the risks of TdP, examination of a pre-drug ECG to identify those with QTc of 450 or greater, a repeat ECG at one month, and yearly ECGs or whenever the dose exceeds 100 mg. Patients with QTc > 500 ms should be evaluated for dose reduction or alternative therapy. Based on the evolving literature in this area, it is reasonable to limit the use of benzodiazepines or drugs (such as fluoxetine) which inhibit the CYP3A4 hepatic enzyme. In one prospective cohort study, methadone was associated with increased QTc interval dispersion, a marker of arrhythmia risk [67]. In this study, the presence of anti-depressant therapy was an independent predictor of QTc prolongation among methadone-maintained patients after multivariate adjustment.

Future directions

Methadone is an important cause of sudden death in the US. QTc prolongation associated with methadone has been clearly established, but TdP remains difficult to predict. A potential future alternative therapy, not yet available in the US, is the non-racemic (R) methadone formulation. It appears to exhibit less hERG channel blockade than standard (R,S) methadone and could prove a safe therapeutic alternative [30, 69].

Methadone (R,S) may also be a good candidate drug for evaluating new modalities for risk stratification because it is typically given to patients without structural heart disease or other conditions that can delay or de-stabilize cardiac repolarization independently. Measuring QTc variability on 24 hour digital Holter has recently become feasible and may be a useful modality to examine the contribution of inadequate repolarization reserve in pre-drug subjects. Hinterseer et al. [70] recently found that subjects who experienced drug induced TdP have increased beat-to-beat QTc variability even in the off-drug state. Other novel approaches to repolarization instability, such as T wave alternans by the modified moving average method and T wave variability can be assessed using high frequency digital Holters, and future studies of QTc-prolonging agents are likely to benefit from these techniques [71].

Conclusions

Methadone and other opioids are being widely prescribed for chronic pain, yet methadone-associated mortality is rising out of proportion to its prescriptions. This increase in deaths likely in part reflects unrecognized arrhythmia, though accidental overdose given methadone's potency and complex pharmacokinetics are also important alternative or synergistic mechanisms. Unlike other opioids, methadone is a potent hERG blocker carrying an undeniable proarrhythmic effect. Buprenorphine and extended release morphine have significantly fewer QTc-prolonging consequences and appear to have less morbidity in terms of TdP and

sudden cardiac death. Oxycodone has recently been shown to be a weak hERG channel blocker (IC50 171 μM compared to 10 μM for methadone), but no significant QTc prolongation was noted in the cohort study. Nevertheless, further study is needed before oxycodone can be recommended as an appropriate alternative to methadone in subjects with QTc prolongation or TdP [72]. Further research must identify the critical co-variants and risk factors contributing to methadone-associated mortality, such as the prevalence of susceptible hERG mutations, variability in opioid respiratory depression, interaction with pre-existing sleep apnea and potential for effective treatment of obstructive sleep apnea, and the role of other compounds with synergistic effects. Until newer and better risk-stratifying strategies are developed, we recommend the use of screening 12-lead ECGs among patients treated with methadone to improve the safety of this important agent [67]. Clinicians need to be aware that an increasing number of their patients will be exposed to methadone, and exercise significant caution when adding additional drugs to their regimens that may interfere with its metabolism or provoke additional QTc prolongation. Finally, the evaluation of unexplained syncope or cardiac arrest needs to include the appropriate toxicologic screening to rule out the presence of methadone, a compound responsible for an increasing number of unexplained deaths.

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