Original Article

Measurement of QTc in Patients Receiving Chronic Methadone Therapy

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Abstract
Recent reports suggest that methadone may prolong the QTc interval and cause torsades de pointes. This study was conducted to evaluate the prevalence of QTc prolongation during oral methadone therapy and identify factors associated with prolongation. Patients receiving oral methadone as treatment for chronic pain or addiction were eligible for the study. One hundred four patients who were receiving ≥ 20 mg methadone per day for ≥ 2 weeks underwent electrocardiograms to measure QTc interval duration. Sixty-three (61%) patients were male and 63 (61%) were receiving methadone maintenance for opioid addiction. The mean (± SD) age was 45.3 ± 9.4 years. The median (range) methadone dose was 110 mg/day (20-1200 mg/day); median (range) number of months on methadone was 12.5 months (1-444 months). The median (range) QTc interval was 428 msec (396-494 msec). Thirty-three percent had QTc prolongation (males 40%, females 20%; P = *0.03). No patient had a QTc longer than 500 msec. Significant dose response was observed in males on methadone <12 months (*rho = *0.60,* P = *0.02). Our study suggests that methadone may prolong the QTc interval in specific subpopulations but poses little risk of serious prolongation.* J Pain Symptom Manage 2005;29:385–391.

Key Words
QTc prolongation, cardiac toxicity, methadone, opioids, MMTP, pain management

Introduction

Methadone is widely used in the management of addiction and chronic pain.[1] In the United States, about 180,000 patients on methadone maintenance take a single daily oral dose, usually <100 mg/day.[2,3] Oral and parenteral formulations are used as analgesics, often at much higher doses.[4]

Although methadone is generally considered to be safe, adverse effects may occur because of a long and variable half-life, unexpectedly high potency, and drug-drug interactions.[1] Recently, concerns have arisen about the potential for QTc (QT corrected for heart rate) prolongation, which may predispose patients to life-threatening torsades de pointes.[4–6] Data are

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very limited, however, and major references disagree about the need to designate this drug as a risk factor for torsades de pointes.[7] One source lists methadone as a drug generally accepted by authorities to have a risk of torsades de pointes.[8,9] In contrast, another source lists methadone as improbable as a cause of QT prolongation based on a survey of expert opinion.[10] Further studies are needed to define the prevalence and severity of QTc prolongation, and identify predisposing factors.

Materials and Methods

Procedure

The study was approved by the Institutional Review Board at Beth Israel Medical Center, New York, NY and patients provided written consent. Adult patients receiving oral methadone ≥ 20 mg/day for more than two weeks were recruited between August and November 2003 from inpatient medical, psychiatric, and hospice units, and an outpatient pain practice. Patients were excluded if they had congenital long QT syndrome, implanted pacemaker, atrial fibrillation or wide QRS complex on prior electrocardiograms (ECGs). Patients were queried about medical history and methadone treatment. Serum level of electrolytes known to affect the QTc duration (potassium, magnesium, calcium) were measured.[11]

A 12-lead ECG was obtained with a MAC 5000 machine (GE Medical Systems, Milwaukee, Wisconsin). Recent guidelines for measuring QT interval were applied.[10] The QT interval was measured manually by the same investigator (RS), under the supervision of a board-certified cardiologist (PS). The interval was corrected for heart rate using the Bazett formula (QTc = QT/Sqrt [RR]).[12] QTc prolongation was defined as intervals longer than 430 msec for males and 450 msec for females.[13,14]

Data Analysis

Normally-distributed data (e.g., age) are presented as mean ± SD, skewed data (e.g., QTc) as median (range), and categorical data (e.g., gender) as frequency (percent). The bootstrap method was used to estimate the 95% confidence limit around median QTc.[15] The Spearman rho correlation was used to evaluate relationships between QTc and other continuous variables while the Mann-Whitney test was used to estimate associations with dichotomous variables. Pearson correlations were used to estimate regression lines between the natural log of methadone dose and QTc. For QTc prolongation (yes/no), the Mann-Whitney tests were used to evaluate associations with continuous predictors and chi-square tests were used for categorical predictors. A generalized linear model was used to evaluate interaction effects on QTc interval involving methadone dose and other risk factors.[16] A gamma distribution was assumed to underlie the skewed distribution of QTc interval duration. Logistic regression was used to test for dose interactions with QTc prolongation. To compare the magnitude of effect sizes, Cohen's d was calculated for risk factors.[17]

We estimated that a minimal sample of 85 patients would allow for 80% power to detect a correlation r = 0.30 between methadone dose and QTc. By comparison, a previous study found a correlation for methadone dose-QTc of at least 0.54. [4] A significance level of 0.05 was assumed for all statistical comparisons. SPSS 11.5 (SPSS, Inc, Chicago, IL) was used for all univariate analyses and SAS 9.0 (SAS Institute Inc., Cary, NC) was used for the bootstrap estimation and the generalized linear modeling.

Results

Of 110 consenting patients, six were excluded from the data analysis; two were treated with methadone for less than two weeks, two lacked laboratory data, one engaged in recent illicit methadone use, and one had an unreadable ECG. Sixty-one percent ($n = 63$) of the final sample originated from the methadone maintenance program, 82% ($n = 85$) were white, and 61% ($n = 63$) were male (Table 1). Mean (± SD) age was 45.3 ± 9.4 years. Median methadone dose was 110 mg/day (range 20-1200 mg/day). Median treatment duration was 12.5 months (range 1 month – 37 years). Seven patients (7 %) had a previous history of structural heart disease.

Twenty-five (24%) patients were currently taking drugs (apart from methadone) which have been cited as possibly associated with QTc prolongation[10] and 26 (25%) were taking drugs which are listed as being associated with torsades de pointes[8] (Table 2). Thirty patients (29%) were taking drugs which may increase

Table 1
Background Characteristics of the Patients

Characteristic	Result (n = 104) n (%)
Males	63 (61)
Age	45.3 ± 9.4[a]
Race	
White	85 (82)
Black	14 (14)
Other	5 (5 %)
Treatment	
Maintenance	63 (61)
Pain Control	27 (26)
Both	14 (14)
Methadone Dose (mg/day)	110 (20, 1200)[b]
Duration of Methadone Treatment (Months)	12.5 (1, 444)
Structural Heart Disease[c]	7 (7)

[a]Mean ± SD (range).
[b]Median (range).
[c]Structural heart disease: history of congestive heart failure, coronary artery disease, or myocardial infarction.

methadone serum concentration via pharmacokinetic interactions.[18,19]

Table 3 presents the serum electrolyte and ECG characteristics of the study sample. One patient with a magnesium level of 1.5 mg/dl showed an abnormally low electrolyte level. Twenty-two patients (21%) had pulse rates ≤60 bpm and four (4%) had pulse rates ≥100 bpm. Median QTc was 428 msec (range 396-494 msec). The bootstrap 95% confidence limit was (424, 435). Thirty-three patients (32%) had QTc prolongation.

Table 2
Drugs Taken by Methadone Patients

Characteristic	Result (n = 104) n (%)
Drugs with Risk for QTc prolongation[a]	
No likely risk	79 (76)
Possible in high risk patients	23 (22)[b]
Very probable	2 (2)[c]
Drugs with Risk for TdP[d]	
No likely risk	78 (75)
Avoid in patients with congenital QTcP	12 (12)[e]
May be associated	13 (13)[f]
Generally accepted to have risk	1 (1)[g]
Drugs interacting with methadone[h]	30 (29)[i]
Anti-depressant drugs	36 (35)
Anti-anxiety drugs	24 (23)
Anti-retroviral drugs	18 (17)
Anti-microbial drugs	19 (18)

[a]Listed by Al-Khatib as drugs associated with QTc prolongation.[10]
[b]4 patients took amitriptyline, 1 clarithromycin, 9 olanzapine, 1 risperidone, 8 sertraline, and 6 venlafaxine.
[c]2 patients took sotalol.
[d]Listed by torsades.org as drugs with risk for torsades de pointes.[8]
[e]Eleven patients took albuterol, 1 moxifloxacin, 2 methylphenidate.
[f]One patient took azithromycin, 1 took levofloxacin, 1 took quetiapine, 1 took risperidone, 1 took salmeterol, 1 took tizanidine, 6 venlafaxine.
[g]One patient took clarithromycin.
[h]inhibitors of CYP3A4.[18,19]
[i]Two patients took ciprofloxacin, 1 clarithromycin, 4 diazepam, 4 fluconazole, 4 fluoxetine, 3 omeprazole, 9 paroxetine, 8 sertraline, 1 verapamil.

Table 3
Serum Electrolytes and ECG Results

Characteristic	Result (n = 104)
Sodium	139.4 ± 2.9[a]
Potasssium	4.3 ± 0.42
Calcium	9.1 ± 0.42
Magnesium	1.9 ± 0.20
Heart Rate (bpm)[b]	70.9 ± 13.3
Bradycardia[c]	22 (21 %)[d]
Tachycardia[e]	4 (4 %)
QTc (msec)[f]	428 (396, 494)[g]
QTcP[h]	33 (32 %)

[a]Mean ± SD (range)
[b]bpm: beats/minute.
[c]Bradycardia: heart rate < 60 bpm.
[d]Number of patients (%).
[e]Tachycardia: heart rate > 100 bpm.
[f]msec: milliseconds
[g]Median (range).
[h]QTc Prolongation: QTc duration >430 msec for males, >450 msec for females.

All possible univariate associations between QTc and each of the other factors listed in Tables 1-3 were examined. Only calcium level showed a modest but significant negative correlation with QTc (rho = -0.22, P = 0.02). Table 4 shows the results for factors typically accepted as placing patients at risk for QTc prolongation or torsades de pointes in addition to the results for methadone dose and treatment duration. No effect size is greater than 0.50 (medium effect size) and those for methadone dose and treatment duration are close to being equal to zero.

To further explore the relationship between methadone and QTc, multivariate analyses were done to evaluate potential interaction effects among relevant variables. A significant two-way interaction was found for dose and treatment duration; specifically, QTc was related to both higher methadone dose and shorter methadone treatment duration (P = 0.04, d = 0.40). Upon further exploration, this interaction was found to be primarily due to a dose × duration interaction for males (dose × duration × sex interaction P = 0.049, d = 0.40). Analyzing the interaction for the sexes separately identified a highly significant dose × duration interaction for males (P = 0.0009, d = 0.86) but not for females (P = 0.85, d = 0.05). The dose × duration interaction for

Table 4
Univariate Analysis of Risk Factors for QTc Prolongation

Risk Factor	Result	*P*-value	Effect Size
Gender			
Male	428 (399, 492)[a]	0.95	0.01[b]
Female	427 (396, 494)		
Age	−0.04[c]	0.68	0.08
Bradycardia			
No	429 (396, 494)	0.57	0.11
Yes	423 (407, 468)		
Potassium	−0.04	0.72	0.08
Magnesium	0.05	0.64	0.10
Calcium	−0.22	0.02	0.46
Drugs with Risk for QTcP			
No Likely Risk	428 (396, 494)	0.46	0.18
Possible in High Risk Patients	425 (404, 475)		
Very Probable	441 (436, 446)		
Drugs with Risk for TdP			
No Likely Risk	428 (399, 494)	0.29	0.22
Avoid in Patients with Congenital QTcP	435 (407, 466)		
May be Associated	414 (396, 466)		
Generally Accepted to have Risk	458 (NA)		
Methadone Dose	−0.01	0.89	0.03
Duration of Methadone Treatment	.01	0.94	0.02

[a]Median (range) of QTc duration (msec).
[b]Cohen's d.
[c]Spearman's rho.

males was still significant even after controlling for calcium ($P = 0.0026$, d = 0.78), while calcium was not significant.

The pattern of interaction for the males is illustrated in Fig. 1, which shows the relationships between methadone dose and QTc in males and females according to treatment duration. Males who had been receiving methadone for less than 12 months had a strongly positive relationship between dose and QTc (Spearman rho = 0.60, $P = 0.01$, d = 1.5). This correlation remained significant even after adjusting for multiple comparisons (Bonferroni corrected *P*-value = 0.03). None of the other groups show any significant dose relationship.

Similar relationships were found in analyses that evaluated the presence or absence of QTc prolongation. Male sex was associated with a higher rate of QTc prolongation (40% vs. 20%, $P = 0.03$). There was also a significant dose × duration × sex interaction ($P = 0.03$), with the dose × duration interaction being in males ($P = 0.03$) but not in females ($P = 0.26$). QTc prolongation was associated with higher doses only among male patients who had been treated with methadone for ≤12 months.

Discussion

In a mixed sample of 104 methadone-treated patients, 32% had QTc prolongation but none had a QTc duration beyond the value (500 msecs) considered a definite risk for torsades de pointes.[10,11,13] Although a large percent of patients presented with QTc prolongation, the lack of serious prolongation in a sample of patients taking as much as 1200 mg daily is reassuring and suggests that the general risk of seriously prolonged QTc and torsades de pointes may be low in these patients.

The data further suggest that the relationship between dose and cardiac effects may be complex and related to sex and duration of treatment. In contrast to previous studies of drug-induced QTc prolongation, which found females more at risk,[20] our data indicate that the risk of methadone-induced QTc prolongation may be greater for males, especially soon after treatment is initiated. The lack of dose-dependent cardiac effects for male patients on methadone for twelve months or more raises the possibility that tolerance to any possible cardiac effects of methadone in males may develop over time.

At least three previous studies have reported methadone-induced QTc prolongation. One widely-cited report simply looked at 17 patients taking between 65 and 1000 mg of methadone daily who developed torsades de pointes and concluded that seriously prolonged QTc interval is possible during methadone treatment.[5]

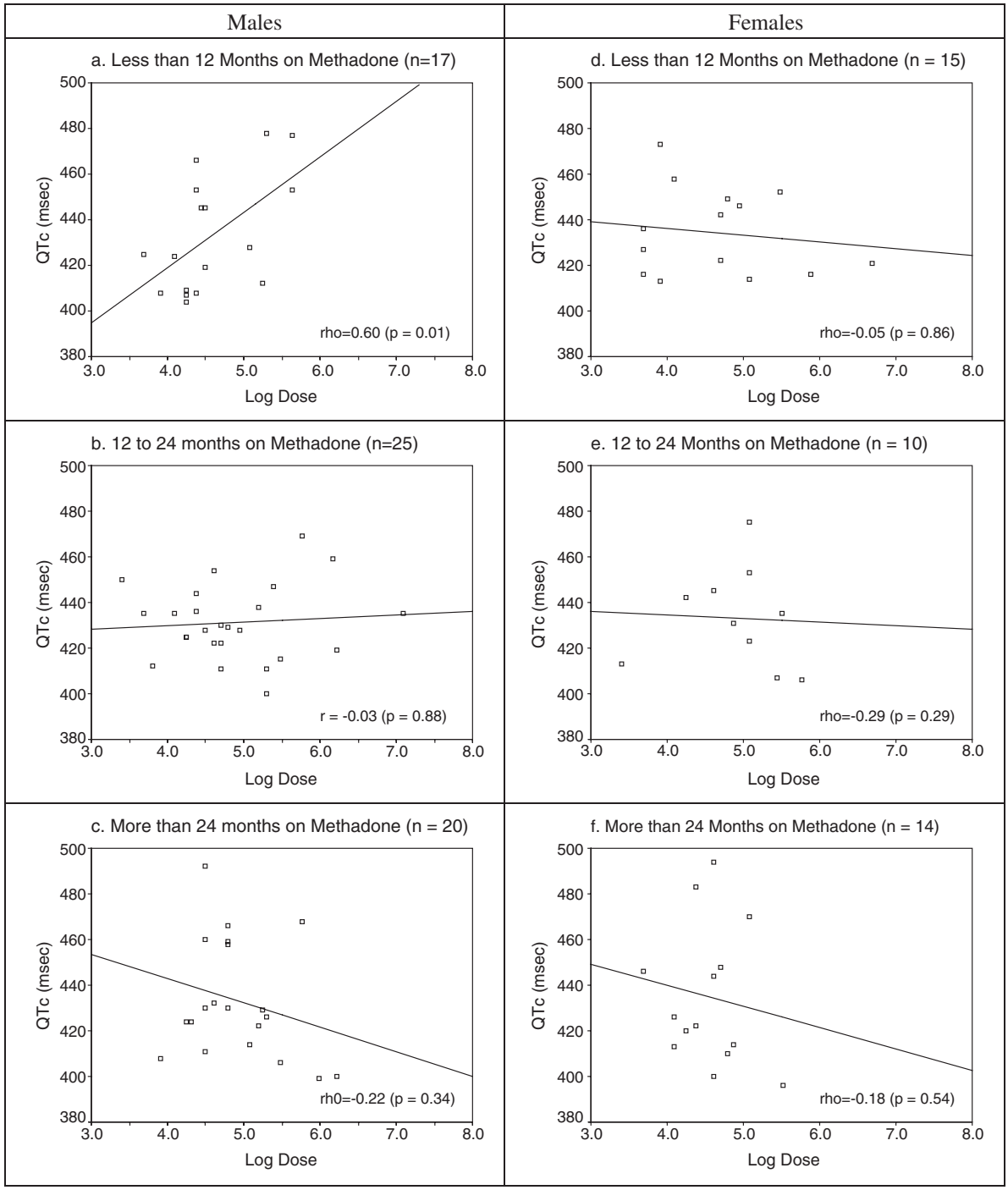

Fig. 1. Scatterplots with regression lines for QTc as a function of log dose and months on methadone for males and females. Regression lines are based on Pearson correlation between QTc and log dose and vary slightly from Spearman rho results.

The design of this study does not allow for determination of either the prevalence of QTc prolongation in patients taking methadone or the possible causal role of methadone. Moreover, seven of the patients in the study were hypokalemic and this may have been the actual predisposing factor in these patients, rather than methadone.

Another study looked retrospectively at 190 patients treated with intravenous methadone and 301 treated with intravenous morphine over the course of 20 months.[4] In the 47 methadone patients who underwent at least one ECG while receiving methadone, mean QTc duration increased significantly by 42 msecs when compared to an ECG done off-methadone. In contrast, the QTc duration increased only by 9 msec for the 35 patients treated with morphine who also had at least one ECG.[4] Similar to our findings, this study identified a dose-dependent prolongation of QTc with higher doses of methadone. There were no significant sex differences. The significant disproportion of patients in the two treatment groups who received ECGs while receiving methadone (47/190 patients) or morphine (35/301) ($P = 0.0002$) may be considered either additional support for methadone patients being at greater risk or may indicate possible selection bias.

Finally, a prospective study of 132 methadone maintenance patients looked at QTc before the initiation of treatment and after two months of follow-up.[6] Overall mean QTc increased significantly from 418 to 428 msec but there were no instances of torsades de pointes in patients receiving up to 150 mg of methadone per day. There were no significant sex differences, although males increased by 13 msec while females increased by 6 msec. These results agree with the absence of serious QTc prolongation observed in our study, as well as the possibility of a dose-dependent effect in male patients on methadone for less than one year. There remains the question of whether QTc prolongation lasted substantially beyond the two month follow-up of the methadone maintenance patients.

Given the limited and exploratory nature of our study, no conclusions can be drawn about the risk of prolongation related to other variables, such as structural heart disease, or the dose or duration of use of medications known to prolong QTc duration or increase methadone serum levels. Further studies are needed to address these potential risk factors, as well as to confirm the importance of sex and treatment duration on the cardiac effects of methadone. Although absence of QTc prolongation above 500 msec is reassuring, our data suggest that methadone may prolong QTc in males within one year of start of treatment.

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