

ORIGINAL RESEARCH ARTICLES

Effects of Methadone on QT-Interval Dispersion

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Study Objective. To evaluate the effects of methadone on QT-interval dispersion.

Design. Single-center, prospective, cohort study.

Setting. Methadone maintenance treatment facility.

Patients. One hundred eighteen patients who were newly admitted to the facility.

Intervention. Twelve-lead electrocardiograms (ECGs) were performed in patients at both baseline and 6 months after the start of methadone therapy.

Measurements and Main Results. The ECGs were manually interpreted, and investigators were blinded to time interval and methadone dose. At least eight discernible ECG leads were required for study inclusion. Mean differences between baseline and follow-up rate-corrected QT (QTc) interval and QT dispersion were compared. Multivariate associations between clinical characteristics and magnitude of change in QT dispersion were assessed using linear regression. Mean \pm SD baseline QT dispersion was 32.9 ± 12 msec, which increased to 42.4 ± 15 msec ($+9.5 \pm 18.6$ msec, $p < 0.0001$) after 6 months of therapy. The QTc increased by a similar magnitude ($+14.1$ msec, $p < 0.0001$). No QT dispersion value exceeded 100 msec. The only variable associated with a greater increase in QT dispersion was antidepressant therapy (20 vs 8.5 msec, $p = 0.04$).

Conclusion. Methadone modestly increased both QTc interval and QT dispersion. Increased QT dispersion reflects heterogeneous cardiac repolarization and occurs with nonantiarrhythmic agents, such as synthetic opioids. However, the magnitude of this effect appears to be substantially less with methadone than with antiarrhythmic drugs.

Key Words: methadone, QT prolongation, QT dispersion.
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Methadone, a long-acting synthetic opioid indicated for treatment of opioid addiction and chronic pain, is generally regarded as safe and effective. However, a rise in methadone-related deaths has been reported in the United States forensic literature.^{1,2} Although in most cases the mechanism of death appears related to overdose, torsade de pointes associated with high-dose methadone therapy has been described in case series.^{3–5} Moreover, levacetylmethadol, a methadone derivative, was withdrawn from the European market after being associated with torsade de pointes.⁴

Initial data suggest that daily methadone is associated with a 12-msec increase in the rate-corrected QT (QTc) interval.⁶ However, the effects of methadone on QT-interval dispersion are not known. QT dispersion measures interlead variation between QT intervals on the surface electrocardiogram (ECG). It reflects abnormal cardiac repolarization, and may yield additional prognostic information regarding arrhythmia risk beyond that provided by the standard QTc interval.⁷

Nonantiarrhythmic drugs have been implicated in the development of torsade de pointes, but

prospective data quantifying their effects on cardiac repolarization are frequently lacking. Therefore, we evaluated the long-term effects of oral methadone on QT dispersion, a marker of arrhythmia risk with both antiarrhythmic and nonantiarrhythmic agents. We also assessed the effects of concomitant drug therapies and comorbidities on the magnitude of change in QT dispersion.

Methods

Patients

From December 2001–January 2003, we recruited consecutive patients who were admitted to a methadone maintenance treatment facility. Criteria for admission to the facility were opioid addiction for at least 1 year, age older than 18 years, and at least one previous attempt with supervised ambulatory detoxification. Patients were excluded if they self-reported methadone intake in the 2 weeks before admission. Informed consent was obtained from each patient. The study protocol was approved by the human subjects committees at the Albert Einstein Medical College and the University of Colorado Health Sciences Center.

Overall, 233 patients agreed to participate in the study. Of these patients, 149 had ECGs performed at both baseline (methadone naïve) and 6 months after the start of methadone

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administration and titration. Principal reasons for dropping out of the study were discontinuation of methadone treatment, incarceration, transfer to another facility, and refusal to participate. Of the 149 participating patients, 118 had an interpretable ECG at both baseline and 6 months. An interpretable ECG was defined as a 12-lead tracing with at least eight discernible leads.

Methadone 30 mg/day was started, with progressive increases in dosage based on self-reported heroin use, clinical assessment of opioid withdrawal symptoms, and evidence of illicit opioid use detected by urine toxicology. Serum electrolyte levels were measured for all patients (Bendiner and Schlesinger Medical Laboratories, Inc., New York, NY) at the time of enrollment in the study. Hypokalemia was defined as a serum potassium level less than 3.5 mEq/L. Use of drugs, alcohol, and illicit substances (e.g., cocaine) known to affect cardiac repolarization or alter methadone metabolism was tabulated for all patients.

ECG Analysis

Methadone was dispensed under direct supervision from 9 A.M.–2 P.M.; ECGs were recorded within 1–2 hours of administration. A single interpreter, blinded to both the methadone dose and the time of ECG reading, analyzed all tracings. Both the baseline and 6-month ECGs were recorded at a paper speed of 25 mm/second with conventional amplification (1 mV = 10 mm) using a single machine (GE Healthcare Systems, Milwaukee, WI). The QT intervals were manually measured without magnification and recorded in milliseconds (msec) approximated to the nearest 10 msec. Measurements immediately after atrial or ventricular premature contractions were avoided.

The QT interval was defined as the time between the first deflection from the isoelectric PR interval and the visual return of the T wave to the T-P segment. The QTc was then calculated using Bazett's formula: $QTc \text{ (in msec)} = QT \text{ interval (in msec)} / \sqrt{\text{preceding R-R interval (in sec)}}$.⁸ The QT intervals were measured in a standard limb lead, preferably lead II. If this was not interpretable, the QT interval was measured in whichever lead provided the most definitive measurement; U waves were incorporated only if they were large enough to appear in a limb lead and merge with the T wave. Otherwise the interval was measured at the nadir of the trough between the T and U

waves.⁹ The QT dispersion was calculated as the difference between the maximal and minimal QT intervals.

Statistical Analysis

The mean differences between baseline and follow-up heart rate, QRS duration, QTc interval, and QT dispersion were tested for statistical significance using a paired *t* test for normally distributed data. The proportion of patients with QTc intervals exceeding the upper limit of the normal range at baseline and 6 months was compared using the Fisher exact test. Univariate associations with both baseline QT dispersion and QTc interval, and with the changes in these parameters from baseline to follow-up, were tested using Pearson correlation coefficients for continuous independent variables and the Student *t* test for categoric independent variables. Multivariate associations with the magnitude of the change in QT dispersion or QTc interval were tested using linear regression models. Analysis was performed using SAS, release 8.1 (SAS Institute Inc., Cary, NC).

Results

Baseline clinical and electrocardiographic characteristics of the patients reflected a young population with active substance abuse disorder (Table 1). All patients self-reported heroin use at baseline. Alcohol and cocaine abuse was common, but use of prescription drugs known to affect cardiac conduction was infrequent. Few patients reported a history of cardiovascular disease or had electrocardiographic evidence of structural heart disease. Nearly all patients were active smokers.

Mean \pm SD QT dispersion was 32.9 ± 12 msec (range 10–70 msec) at baseline and 42.4 ± 15 msec (range 10–80 msec) after 6 months of methadone therapy, with a mean increase of 9.5 ± 18.6 msec ($p < 0.0001$; Table 2). Mean heart rate increased from 65 to 69 beats/minute ($+4$ beats/min, $p = 0.0005$). The QRS interval

Table 1. Baseline Clinical and Electrocardiographic Characteristics of 118 Study Patients^a

Characteristic	Value
Age, mean \pm SD (yrs)	43 \pm 8
	No. (%)
Male	73 (62)
Substance abuse with known cardiovascular effects	
Current tobacco use	114 (97)
Cocaine	53 (45)
Alcohol (> 10 drinks/wk)	14 (12)
Prescription drugs taken that affect methadone metabolism	
Antiretroviral agents	9 (8)
Isoniazid	6 (5)
Use of prescription drugs that affect cardiac conduction	
Antidepressants	12 (10)
Diuretics	5 (4)
Calcium channel blockers	3 (3)
β -Blockers	4 (3)
Phenytoin	4 (3)
Comorbid conditions	
Hepatitis C seropositivity	52 (44)
HIV seropositivity	21 (18)
Cardiovascular disease	14 (12)
Hypokalemia (potassium level < 3.5 mEq/L)	2 (2)
ECG characteristics	
Prolonged QTc (> 430 msec in men, > 450 msec in women)	19 (16)
Sinus bradycardia (heart rate < 55 beats/min)	17 (14)
Left or right ventricular hypertrophy	14 (12)
Nonspecific ST- and T-wave changes	5 (4)
Prominent U waves	1 (1)
Previous myocardial infarction	1 (1)

HIV = human immunodeficiency virus; QTc = rate-corrected QT interval; ECG = electrocardiogram.

remained virtually unchanged, decreasing from 92.8 to 92.6 msec (-0.2 msec, $p = 0.76$), whereas the QTc interval increased from 415.3 to 429.4 msec ($+14.1$ msec, $p < 0.0001$). The QTc intervals ranged from 367–483 msec at baseline, which increased to 376–533 msec at 6 months. The number of patients in whom the QTc interval exceeded the upper limit of normal (430 msec for

Table 2. Baseline and 6-Month Electrocardiographic Data

Variable	Baseline	At 6 Months	Change	p Value
Heart rate (beats/min)	65	69	+4	0.0005
QRS duration (msec)	92.8	92.6	-0.2	0.76
QTc (msec)	415.3	429.4	+14.1	<0.0001
Patients with increased QTc ^a (%)	14	31	+18	0.2
QT dispersion (msec)	32.9	42.4	+9.5	<0.0001

^aDefined as > 430 msec in men and > 450 msec in women.

men, 450 msec for women) increased from 16 (14%) to 36 (31%) at study completion ($p=0.2$).

Baseline clinical variables tested for association with QT dispersion were age, sex, taking drugs that affect cardiac repolarization or methadone metabolism, self-reported cardiovascular disease, use of cocaine at baseline, and infection with human immunodeficiency virus or hepatitis C. Of these variables, the only one associated with the magnitude of QT dispersion at baseline was self-reported cardiovascular disease (42.1 vs 31.7 msec, $p<0.01$). At 6 months, however, none of these variables remained significantly associated with absolute QT dispersion.

The same clinical variables were then tested for association with the magnitude of change in QT dispersion over 6 months. Only concurrent antidepressant therapy was associated with a greater increase in QT dispersion (20 vs 8.5 msec, $p=0.04$). Mean \pm SD methadone daily dose after 6 months of therapy was 80 ± 32 mg (range 20–180 mg). However, the dose at 6 months was not associated with the magnitude of change in QT dispersion ($r = -0.08$, $p=0.4$), nor did self-reported cocaine abuse correlate with the change in QT dispersion ($r = +0.09$, $p=0.3$). No episodes of torsade de pointes, cardiac arrhythmia, or sudden death were documented during the study.

Discussion

This study demonstrates that in a cohort of patients relatively free of structural heart disease, methadone induction and maintenance result in a modest but statistically significant increase in QT dispersion similar in magnitude to the observed increase in QTc interval. To our knowledge, the effect of methadone or any other opioid on QT dispersion has not been reported.

Both QT dispersion and QTc are increased in a variety of disease states, such as myocardial ischemia,^{10, 11} hypertrophic cardiomyopathy,^{12–14} chronic heart failure,^{15, 16} and anorexia nervosa.¹⁷ The increase is greatest in patients with congenital long QT syndrome.^{18–20}

Like most noninvasive measures used to predict arrhythmia risk, QTc and QT dispersion have inherent limitations. The QTc interval is generally a poor predictor of arrhythmia risk in any given patient. In addition, the normal range is often difficult to define, although QTc intervals of less than 430 msec in men and less than 450 msec in women are widely accepted as normal.²¹ Increases in QTc greater than 30 msec, or absolute QTc values exceeding 500 msec, are

most predictive of development of drug-induced torsade de pointes.²² Similarly, the standard distribution for QT dispersion is not well defined, although 30–60 msec is generally considered normal.^{23, 24} Estimates vary widely, however, and measurements in healthy subjects as low as 11 msec and as high as 71 msec have been reported.^{10, 25} This variability is often the result of difficulty discerning the exact termination of the T wave.²⁶

Another limitation of this study is the inaccuracy of Bazett's formula⁸ at extremes of heart rate. However, this method remains the most widely used in clinical practice for correcting the rate of the QT interval.

Despite these limitations, markedly elevated QT dispersion values (e.g., > 100 msec) are generally accepted as indicative of high arrhythmia risk and invariably occur in patients with structural heart disease or those receiving potent antiarrhythmic drugs.²⁷ However, some studies suggest that even a small relative increase in QT dispersion may be an important predictor of future arrhythmia, particularly on a population basis. For instance, a subgroup analysis from a trial involving patients at high risk of coronary artery disease indicated that an increase in QT dispersion of only 10 msec elevated the risk of death or nonfatal myocardial infarction by 13%.²⁸

Both antiarrhythmic and nonantiarrhythmic drugs affect the QTc interval and QT dispersion (Table 3).^{29–39} Antiarrhythmic drug classes Ia (quinidine and disopyramide)^{29, 40, 41} and Ic (propafenone)⁴² have been shown to increase QT dispersion. In one study, three of 26 patients with quinidine-associated torsade de pointes had increases in QT dispersion of more than 50% from baseline.²⁹

The effect of sotalol on QT dispersion appears to be more complex. Although this agent significantly increases QTc, it appears to have less impact on QT dispersion.^{29, 30} In one study, however, patients who experienced torsade de pointes during sotalol administration had significant increases in QT dispersion after therapy.⁴³ Amiodarone, one of the safest antiarrhythmic agents, prolongs the QTc interval but decreases QT dispersion.^{30–32} This may explain the very low risk of torsade de pointes attributable to amiodarone.

Like most nonantiarrhythmic drugs, the effect of methadone on cardiac repolarization appears to be mediated through blockade of the human ether-a-go-go (HERG) potassium channel.⁴⁴ This channel reflects the rapid component of the

Table 3. Comparative Repolarization Effects of Selected Antiarrhythmic and Nonantiarrhythmic Drugs

Agent	Population Studied	QT Change (msec)	
		QTc	Dispersion
Antiarrhythmic agents			
Quinidine	25 patients with persistent atrial fibrillation ²⁹	+48	+10
Sotalol	25 patients with persistent atrial fibrillation ²⁹	+58	+4
	26 patients with ventricular arrhythmias ³⁰	+50	-6
Amiodarone	47 patients with ventricular arrhythmias ³¹	+29	+3
	52 patients with ventricular arrhythmias ³²	+25	+3
	26 patients with ventricular arrhythmias ³⁰	+50	-30
Nonantiarrhythmic agents			
Methadone	118 patients without structural heart disease ^a	+14.1	+9.5
Terfenadine	28 control patients ³³	+6	NA
	28 patients with coronary artery disease ³³	+12	NA
Moxifloxacin	2650 control patients ³⁴	+6	NA
Cisapride	51 patients with gastrointestinal disease ³⁵	+13	-1
Metabolife 365 (ephedra-containing compound)	15 subjects without structural heart disease ³⁶	+27.2	+21.4
Grapefruit juice	10 subjects without structural heart disease ³⁷	+12	NA
Thioridazine	9 subjects without structural heart disease ³⁸	+22	-12
Intravenous erythromycin	49 patients with and without coronary artery disease ^{39, b}	+51	+46

QTc = rate-corrected QT interval; NA = information not available.

^aOur study.

^bRetrospective electrocardiogram study; selection bias may have magnified repolarization effects.

delayed rectifier potassium current. A mutation in the HERG channel is responsible for a subtype of the prolonged QT syndrome,⁴⁵ and the QT-prolonging effect of a broad range of antiarrhythmic and nonantiarrhythmic drugs is mediated through HERG channel blockade.⁴⁶

Because of the known experimental effect of methadone on cardiac repolarization, we sought to explore its effect on QT dispersion, a measure of repolarization variability. In our cohort, methadone therapy led to significant increases in QTc and QT dispersion. Such increases could plausibly contribute to a predilection for torsade de pointes in susceptible patients. The magnitude of the change in repolarization with methadone was similar to that associated with other nonantiarrhythmic drugs, but less than that associated with most antiarrhythmic agents (Table 3).²⁹⁻³⁹ Therefore, antiarrhythmic drugs that prolong the QT interval represent the high end of a spectrum of risk; torsade de pointes consistently develops in more than 1% of patients who receive these agents (except amiodarone).⁴⁷ By contrast, nonantiarrhythmic drugs, such as methadone, appear to result in clinically less significant cardiac repolarization effects.

We suggest that clinicians treating patients with methadone be aware of the cardiac repolarization effects of this drug, particularly when prescribing it for patients receiving other

QT-prolonging agents, such as antidepressants. Nonetheless, the modest effects of methadone on cardiac repolarization must be considered in the context of the substantial morbidity associated with untreated heroin addiction and the lack of effective pharmacologic alternatives approved by the Food and Drug Administration for treating opioid-dependent patients. Our preliminary data suggest that buprenorphine may be a reasonable alternative to methadone for patients who develop torsade de pointes.⁴⁸ However, methadone's more favorable cost profile and its efficacy in patients experiencing active opioid withdrawal suggest that this niche drug will likely remain a first-line agent in the treatment of heroin addiction.

Conclusion

Methadone modestly increases both QTc interval and QT dispersion. Increased QT dispersion reflects heterogeneous cardiac repolarization and occurs with nonantiarrhythmic agents, such as synthetic opioids. However, the magnitude of this effect appears to be substantially less with methadone than with antiarrhythmic drugs.

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