Drug-Induced Long QT Syndrome in Injection Drug Users Receiving Methadone

High Frequency in Hospitalized Patients and Risk Factors

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Background: Drug-induced long QT syndrome is a serious adverse drug reaction. Methadone prolongs the QT interval in vitro in a dose-dependent manner. In the inpatient setting, the frequency of QT interval prolongation with methadone treatment, its dose dependence, and the importance of cofactors such as drug-drug interactions remain unknown.

Methods: We performed a systematic, retrospective study comparing active or former intravenous drug users receiving methadone and those not receiving methadone among all patients hospitalized over a 5-year period in a tertiary care hospital. A total of 167 patients receiving methadone fulfilled the inclusion criteria and were compared with a control group of 80 injection drug users not receiving methadone. In addition to methadone dose, 15 demographic, biological, and pharmacological variables were considered as potential risk factors for QT prolongation.

Results: Among 167 methadone maintenance patients, the prevalence of QTc prolongation to 0.50 second$^{1/2}$ or longer was 16.2% compared with 0% in 80 control subjects. Six patients (3.6%) in the methadone group presented torsades de pointes. QTc length was weakly but significantly associated with methadone daily dose (Spearman rank correlation coefficient, 0.20; $P<.01$). Multivariate regression analysis allowed attribution of 31.8% of QTc variability to methadone dose, cytochrome P-450 3A4 drug-drug interactions, hypokalemia, and altered liver function.

Conclusions: QT interval prolongation in methadone maintenance patients hospitalized in a tertiary care center is a frequent finding. Methadone dose, presence of cytochrome P-450 3A4 inhibitors, potassium level, and liver function contribute to QT prolongation. Long QT syndrome can occur with low doses of methadone.

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DRUG-INDUCED LONG QT syndrome (diLQTS) is a rare but serious adverse drug effect occurring with a wide range of medications.[1,2] Prolongation of the QT interval serves as a surrogate marker for the risk of developing torsades de pointes (TdP), a potentially lethal ventricular tachyarrhythmia. Morbidity and mortality associated with diLQTS currently constitute the most frequent cause of drug withdrawal or boxed warning after marketing.[3]

Methadone has been successfully used as a substitute for opioid-dependent persons for several decades. Higher doses have been shown to enhance abstinence from illegal opiates.[4] The use of therapeutic drug monitoring has led to large increases of methadone doses in opioid substitution.[5,6] Methadone binds in vitro to the cardiac ion channel *KCNH2* and prolongs the action potential in a dose-dependent manner.[7] Several recent reports suggest that methadone prolongs the QT interval when used in high doses.[8-11] The prevalence of QT interval prolongation with methadone maintenance treatment remains unclear, although early studies suggest a high prevalence.[12] In a prospective study on outpatients receiving methadone, only a modest increase in QT length was found.[11] Drug-drug interactions seem to be a risk factor for QT prolongation in methadone maintenance patients, as suggested by our previous data.[13,14] The aim of the present study was to evaluate the frequency of QT interval prolongation in methadone maintenance patients hospitalized in a tertiary care setting and to identify associated risk factors.

METHODS

STUDY POPULATION

The study protocol was approved by the institutional review board of the Department of Internal Medicine, Geneva University Hospital, Geneva, Switzerland. We conducted a retrospective study on hospitalized injection drug users in whom an electrocardiographic (ECG) recording had been performed.

CASE ASCERTAINMENT

The initial sample consisted of all active or former injection drug users hospitalized between January 1999 and December 2003 in the services of internal medicine and orthopedic surgery. Cases were identified by searching computerized medical records in the hospital database with keywords such as "methadone," "drug addict," and similar terms, including semantic and syntactic synonyms of these keywords.

We identified 527 patients. For each individual patient, all paper files within the study period were extracted and carefully analyzed. All electrocardiographic recordings available were systematically reviewed. A total of 247 injection drug users with electrocardiographic data were included in the study, whereas 280 were excluded (**Figure 1**). Patients with voluntary methadone intoxication were excluded because the methadone dose could not be reliably obtained. Patients with severe structural heart disease were also excluded (ejection fraction <35%, heart or lung transplantation, cardiorespiratory arrest, or myocardial infarction during the same hospitalization). The sample was then divided according to whether patients received methadone maintenance therapy (n=167) or not (control group, n=80). All individuals in the methadone group were participants in a methadone prescription program. Reasons for admission were not systematically reviewed.

ECG ASSESSMENT

The QT interval was analyzed on all 12 derivations of each electrocardiogram and corrected for heart rate according to the Bazett formula (QTc).[15] The longest QTc of each patient was used for subsequent analysis. It was recorded within 3 days from hospital admission in approximately 75% of patients. QT length was analyzed as follows: the intersection of a tangent along the descending limb of the T wave with the isoelectric line was used as measurement technique.[16-18] All U waves with at least 50% of the T-wave amplitude were not counted into the QT interval. If a wave following the T wave merged with the end of the T wave, the position of the notch between the waves was used for measurement.

ASSESSMENT OF COVARIABLES

From electronic patient records and nursing charts, we systematically extracted all medications administered during 24 hours preceding the ECG. When patients admitted drug abuse, these substances were also recorded. Laboratory parameters included prothrombin level and factor V level (reflecting hepatic function), electrolyte levels, and renal function calculated from plasma creatinine levels according to Gault et al.[19] Prothrombin levels, measured as a percentage, are predominantly used in Europe and correspond to prothrombin time. The blood sample in closest temporal proximity to the ECG was selected. Laboratory values were not considered if the time interval between the ECG and the blood sample exceeded 1 week (prothrombin and/or factor V level) or 24 hours (other laboratory parameters). No routine toxicologic screening was available.

We computed pharmacokinetic interaction scores for different cytochrome P-450 (CYP) enzymes and for each patient using data on prescribed medications. The following CYP enzymes were analyzed: CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. On the basis of enzymatic and pharmacokinetic data generated in vitro or collected in vivo, quantitative models were used to predict the impact of each comedication on enzyme activity.[20] Inhibitors and inducers of a given cytochrome were scored as follows: weak inhibitor, +1.5 points; strong inhibitor, +2 points;

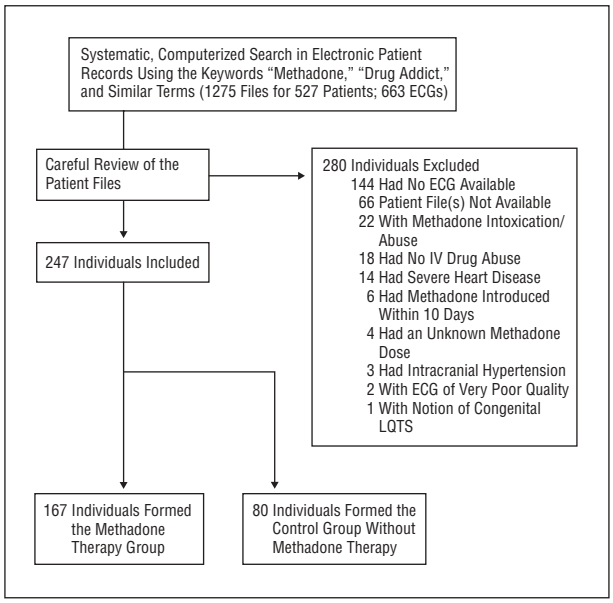

Figure 1. Flowchart of patient identification and inclusion. ECG indicates electrocardiogram; IV, intravenous; and LQTS, long QT syndrome.

weak inducer, –1.5 points; and strong inducer, –2 points. For each patient and each individual cytochrome, a global interaction score was obtained by summing the contributions of the patient's different comedications.

A pharmacodynamic interaction score was also computed for each patient, based on the information in the QT drug database maintained by the University of Arizona Health Sciences Center, Tucson.[21] Substances classified as "drugs with risk of torsades de pointes" were scored 2 points, and those classified as "drugs with possible risk of torsades de pointes" were scored 1 point. The contributions of the different medications were summed for each individual patient.

STATISTICAL ANALYSIS

The Spearman rank correlation coefficient (r_S) was used to test the association between QTc and methadone daily dose. The Mann-Whitney test, χ^2 test, and Wilcoxon test were used for comparing independent and paired samples, respectively. To investigate predictors for QT interval prolongation, multivariate linear models on log-transformed QTc values were used. Methadone daily dose was considered in quartiles (≤50 mg/d, n=44; 51-100 mg/d, n=56; 101-150 mg/d, n=31; and >150 mg/d, n=36). Other potential predictors included sex, age, weight, potassium level, creatinine clearance, prothrombin level, presence of human immunodeficiency virus (HIV), hepatitis B and C infection, the pharmacodynamic interaction score, and the pharmacokinetic interaction scores. Statistical analysis was performed with SPSS version 11 software (SPSS Inc, Chicago, Ill). The significance level was set at $P<.05$ (2-tailed tests).

RESULTS

PATIENT CHARACTERISTICS

The present study included 247 active or former injection drug users for whom at least 1 ECG was available. The total sample consisted of 167 methadone maintenance patients and 80 patients not receiving methadone, who served as a control group. The 2 groups did not statistically differ with

Table 1. Demographic and Electrocardiographic Characteristics of the Methadone and Control Groups

Characteristic	Methadone Group (n = 167)	Control Group (n = 80)	*P* Value*
Age, median (range), y	37 (18-60)	36 (20-58)	.39
Female sex, No (%)	57 (34)	28 (35)	>.99
QTc			<.001
Median (range), s$^{1/2}$	0.44 (0.36-0.75)	0.43 (0.36-0.49)	
≥0.50 s$^{1/2}$, No. (%)	27 (16.2)	0	
≥0.46 s$^{1/2}$, No. (%)	50 (29.9)	8 (10.0)	
Methadone, median (range), mg/d	100 (4-600)	NA	NA
Viral infections, No. (%)			
HIV	67 (40)	19 (28) (n = 69)	.09
HBV	44 (26)	11 (16) (n = 69)	.12
HCV	124 (74)	56 (79) (n = 71)	.55

Abbreviations: HBV, hepatitis B virus, HCV, hepatitis C virus; HIV, human immunodeficiency virus; n, number of patients for which data was available; NA, not applicable.

*P values for differences between groups were calculated with the Mann-Whitney test for continuous variables and the χ^2 test for categorical variables. Statistics refer to the entire group of patients, unless otherwise indicated.

respect to age and sex (**Table 1**). The median age was 37 years (range, 18-60 years), and the majority of patients were male (66%). Among methadone maintenance patients, the methadone daily dose ranged from 4 mg/d to 600 mg/d. Only 5 patients were treated with doses larger than 300 mg/d. Infection rates with HIV and hepatitis B and C were not significantly different between the 2 groups. Eight individuals in the methadone group and 12 individuals in the control group presented a history of structural heart disease without significant functional consequences (previous endocarditis and other). None of these individuals presented a QTc prolongation of 0.50 second$^{1/2}$ or longer.

The most frequently encountered drug inhibitors of CYP enzymes were fluoxetine (12.2% [n = 6] of patients treated), clarithromycin (6.1% [n = 3] of patients treated), fluconazole (6.1% [n = 3] of patients treated), and valproate (6.1% [n = 3] of patients treated) among the 49 patients with a QTc of 0.46 second$^{1/2}$ or longer; and olanzapine (7.7% [n = 9] of patients treated), fluoxetine (4.3% [n = 5] of patients treated), and ritonavir (3.4% [n = 4] of patients treated) among the 117 patients with a normal QT length. The pharmacodynamic interaction score was not significantly different between patients with a prolonged and normal QT.

QT INTERVAL PROLONGATION, TdP, AND CORRELATION OF QTc WITH METHADONE DAILY DOSE

Of the 167 patients receiving methadone, 27 (16.2%) presented with a QTc of 0.50 second$^{1/2}$ or longer on at least 1 ECG (example in **Figure 2**). All 80 patients in the control group had a QTc shorter than 0.50 second$^{1/2}$. Considering QTc values of 0.46 second$^{1/2}$ or longer, 50 patients (29.9%) in the methadone group and 8 patients (10.0%) in the control group fulfilled this criterion (see **Figure 3A** for the frequency distribution of QTc values). The difference of QTc length between methadone and control groups was highly significant (Mann-Whitney test, $P<.001$).

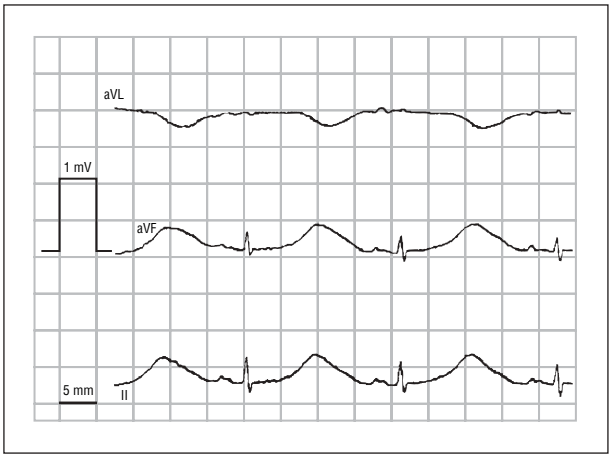

Figure 2. QT interval prolongation in a 39-year-old patient receiving methadone maintenance therapy, 85 mg/d. The QTc is 0.70 second$^{1/2}$. This patient subsequently developed torsades de pointes. Paper speed is 25 mm/s.

Figure 3B shows the correlation between QTc values and methadone daily dose. A higher daily dose was weakly, but significantly associated with QTc prolongation (r_s=0.20; $P<.01$). The lowest daily dose of methadone at which QTc prolongation to 0.46 second$^{1/2}$ or longer occurred was 20 mg/d. The lowest daily dose associated with a QTc of 0.50 second$^{1/2}$ or longer was 30 mg/d. Heart rate was not correlated with methadone dose (r_s=0.04; P=.58).

Torsades de pointes was documented in 6 patients (3.6%) in the methadone group, as indicated in Figure 3B. Of the 6 patients with TdP, 5 (83.3%) were male and 3 (50.0) were bradycardic immediately prior to TdP. The methadone dose among patients with documented TdP ranged from 40 to 200 mg/d, and the QTc length on the ECG preceding TdP ranged from 0.43 second$^{1/2}$ to 0.75 second$^{1/2}$. In 2 cases, TdP was preceded by ventricular bigeminy. One patient presented bigeminy without documented TdP. Given the small number of patients with documented TdP, clinical predictors are difficult to identify. The only significant difference between the TdP and non-TdP groups was a higher number of patients with comedication use in the former group (median numbers, 9 vs 4; Mann-Whitney test, P=.01).

In 17 patients from the methadone group, a measurement of QT length was also available without methadone use, after opioid rotation or discontinuation. Thirteen patients had a QTc of 0.47 or longer while receiving methadone. **Figure 4** shows individual QT lengths for these 13 individuals, with methadone treatment and after opioid rotation or discontinuation. The median methadone dose was 100 mg/d (range, 20-370 mg/d), and the median QTc length with and after methadone withdrawal was 0.53 and 0.44 second$^{1/2}$, respectively (Wilcoxon test, P=.002).

FACTORS ASSOCIATED WITH QT PROLONGATION

In a first step, we compared methadone maintenance patients presenting with a QTc of 0.50 second$^{1/2}$ or longer and those with a shorter QT with respect to demographic characteristics, biochemical parameters, comorbid conditions, and pharmacokinetic interaction

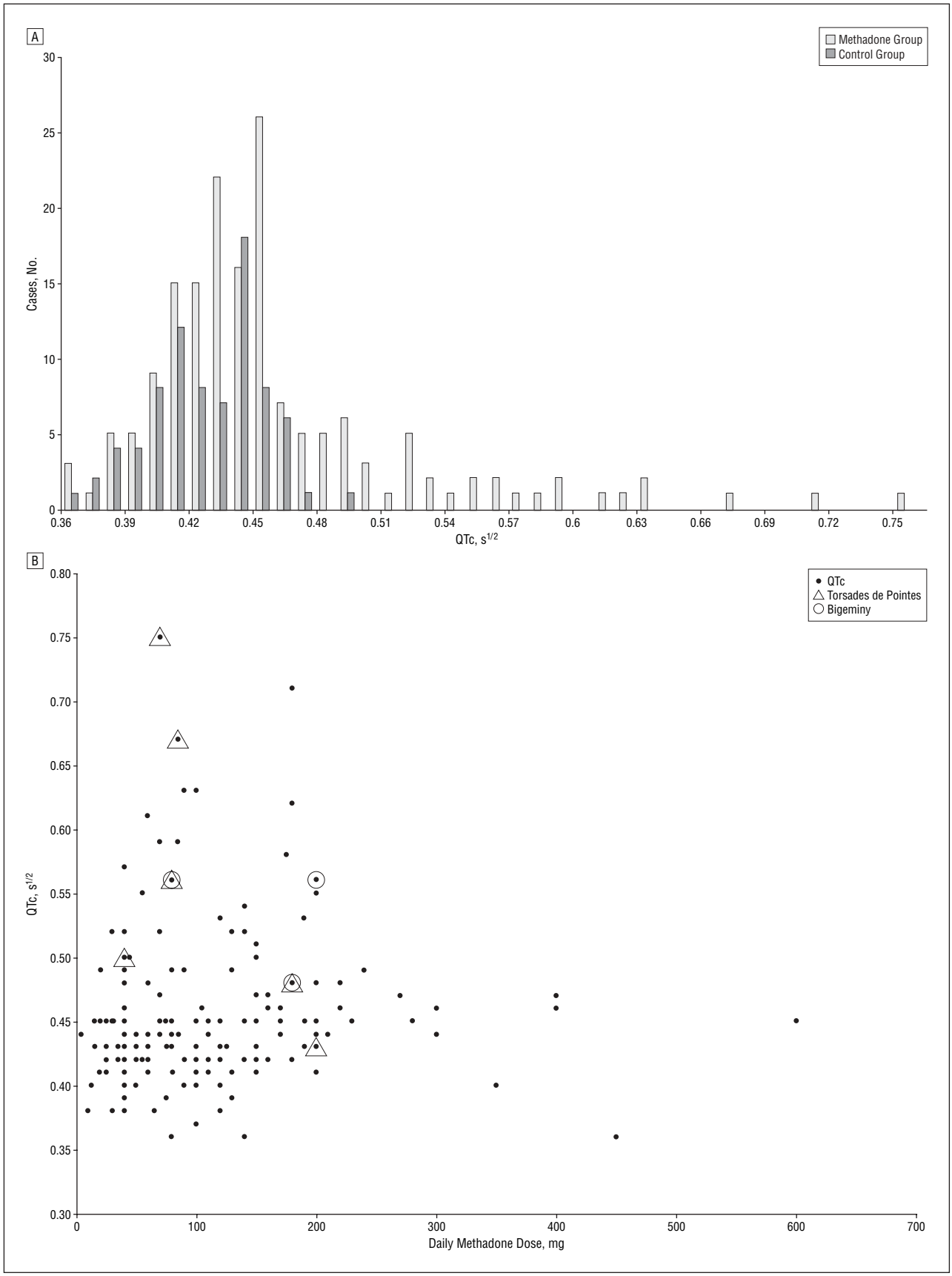

Figure 3. Distribution of QTc values in methadone and control groups (A) and correlation of QTc with the daily dose of methadone (B). In the methadone group, 16.2% of patients presented a QTc of 0.50 second$^{1/2}$ or longer, whereas the longest QTc in the control group was 0.49 second$^{1/2}$. QTc and methadone daily dose were weakly but significantly correlated (Spearman correlation coefficient, 0.20; $P<.01$). Other observations on the electrocardiogram are depicted: 6 patients presented with torsades de pointes and 3 with bigeminy.

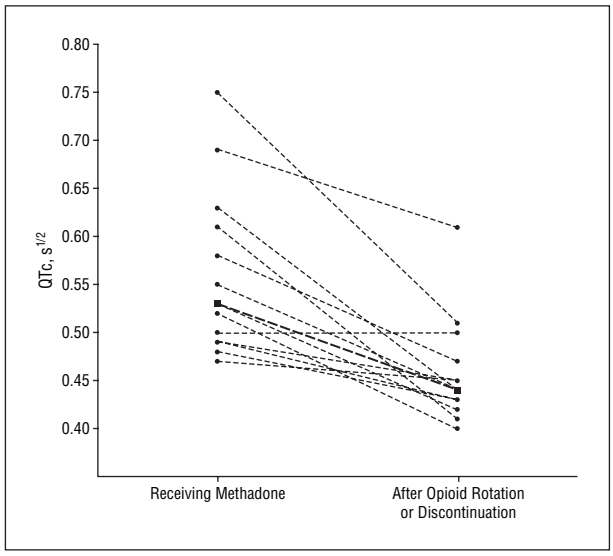

Figure 4. QTc values with and without methadone use in 13 patients. QTc values are displayed for each patient receiving methadone treatment and after opioid rotation or discontinuation (Wilcoxon test, *P*=.002). The bold dashed line represents the median values.

scores derived from comedication data (**Table 2**). Only the potassium level was significantly lower in patients with a QTc of 0.50 second$^{1/2}$ of longer (median values, 3.5 vs 3.9 mEq/L; $P<.01$).

In a second step, the combined influence of different predictors on QT length was investigated with multivariate linear models. In addition to methadone daily dose, 3 variables were identified as significant predictors of QTc length (**Table 3**). QT prolongation was associated with a higher methadone daily dose, lower potassium level, lower prothrombin level, and comedication use with higher inhibition potential at CYP3A4. Two significant interaction terms in the model indicated that the influence of lower potassium levels was increased at lower prothrombin levels and in the presence of higher CYP3A4 interaction scores. The model including the 4 predictors and their interactions accounted for 31.8% of QTc variability.

According to the model (Table 3), if prothrombin level decreases and comedication use includes CYP3A4 inhibitors, the effect of hypokaliemia on QT prolongation is expected to be amplified. For a typical patient with a potassium level at 3.6 mEq/L, a prothrombin level at 100%, a methadone daily dose of 50 mg or less, and no comedication likely to interact with CYP3A4, the model predicted a QTc of 0.41 second$^{1/2}$. When each factor is considered alone, neither reduced potassium level (3 mEq/L), nor reduced prothrombin level (60%), nor a CYP3A4 interaction score of 2 would be accompanied with a QTc of 0.50 second$^{1/2}$ or longer. However, the combined effect of these 3 factors would lead to a QTc value of 0.55 second$^{1/2}$ even if the methadone daily dose remains 50 mg or less. In contrast, an increase of methadone daily dose to greater than 150 mg would lead to a QTc value of only 0.45 second$^{1/2}$, in the absence of any change of the other 3 predictors. In this quantitative model, methadone dose thus appears to exert a weaker effect on QT length compared with the other predictors acting synergistically. **Figure 5** further illustrates the extent of QT length variation expected from the combined influence of potassium level, prothrombin level (80% vs 20%), methadone daily dose (≤50 vs >150 mg), and comedication use (CYP3A4 inhibition score, 0 vs 2).

COMMENT

In a population of active and former injection drug users hospitalized in a tertiary care center, we observed a high frequency of long QT syndrome associated with methadone therapy and suggest that methadone dose, use of CYP3A4 inhibitors, low potassium level, and hepatic dysfunction all contribute to diLQTS. In the group of patients using methadone substitution therapy, we found a high number of individuals (n=27; 16.2%) with a QTc of 0.50 second$^{1/2}$ or longer, compared with none in the control group without methadone use. A QTc of 0.50 second$^{1/2}$ is generally considered as a threshold for risk of developing TdP,[1,22] and TdP is rarely associated with QTc values of less than 0.50 second$^{1/2}$.[23] Bradycardia, T-wave morphologic changes, and other factors can increase the risk of TdP for any given abnormal QTc duration.

We observed a significant dose-effect of methadone on QT interval prolongation. Importantly, QT interval prolongation as well as TdP also occurred with relatively low doses of methadone: 30 mg/d was the lowest prescribed dose in patients with a QTc of 0.50 seconds$^{1/2}$ or longer, and TdP occurred with doses of methadone as low as 40 mg/d. Although no clear dose threshold for methadone was identified, QTc prolongations to 0.50 second$^{1/2}$ or more were less common at methadone doses below 40 mg (1 of 27 cases of QT prolongation to 0.50 second$^{1/2}$ or longer). Episodes of TdP were less common at doses below 70 mg/d (1 of 6 cases with TdP).

Using a multivariate linear model, we identified 3 additional significant covariables of QT interval prolongation: use of CYP3A4 inhibitors, decreased prothrombin level indicating diminished liver function, and hypokalemia. The data suggest that these 3 variables act synergistically with methadone dose to prolong QT. The final model explained 31.8% of QTc variability.

The importance of pharmacokinetic interactions in diLQTS has been demonstrated in a large study on patients treated with erythromycin.[24] We have previously reported cases of drug-drug interactions involving methadone use associated with diLQTS.[13,14] To our knowledge, no large study suggesting the involvement of CYP3A4 inhibition in methadone-induced long QT syndrome had been reported previously. The major hepatic enzyme involved in the *N*-demethylation of methadone is CYP3A4.[25] Inhibition of CYP3A4 has been shown to markedly increase plasma concentrations of a congener of methadone.[26] The predictive value of prothrombin level in our model is also most likely due to a pharmacokinetic effect because severe liver disease has been reported to decrease methadone clearance.[25] Pharmacodynamic interactions were evaluated, and no additional risk for QT interval prolongation could be demonstrated. However, medications known to prolong the QT interval were infrequent in our patient population, and a correlation might be masked by the effect of CYP3A4 inhibitors be-

Table 2. Characteristics of Patients With and Without QT Interval Prolongation of 0.50 Second½ or Longer

Characteristic	Methadone Group: QTc ≥0.50 s½ Group (n = 27)	Methadone Group: QTc <0.50½ Group (n = 140)	*P* Value*
Age, median (range), y	39 (20 to 53)	37 (18 to 60)	.07
Female sex, No. (%)	8 (30)	49 (35)	.75
QT			NA
QTc, median (range), s½	0.55 (0.50 to 0.75)	0.43 (0.36 to 0.49)	
QT, median (range), s	0.52 (0.36 to 0.72)	0.38 (0.28 to 0.55)	
Methadone dose, median (range), mg/d	90 (30 to 200)	100 (4 to 600)	.59
Viral infections, No. (%)			
HIV	10 (37)	57 (41)	.89
HBV	5 (19)	39 (28)	.44
HCV	20 (74)	104 (74)	>.99
Electrolytes			
Potassium, median (range), mEq/L	3.5 (2.3 to 4.6) (n = 26)	3.9 (2.4 to 6.9) (n = 129)	.004
Magnesium, median (range), mg/dL	2.07 (1.34 to 2.97) (n = 10)	1.97 (0.88 to 3.65) (n = 24)	.95
Calcium, median (range), mg/dL	9.32 (7.84 to 6.11) (n = 14)	9.32 (6.76 to 10.76) (n = 37)	.98
Creatinine clearance	(n = 23)	(n = 120)	
Median (range), mL/min	103 (34 to 188)	102 (5 to 314)	.92
<20 mL/min, No.	0	5	
Factor V	(n = 8)	(n = 10)	
Median (range), %	55 (33 to 92)	91 (36 to 100)	. . .
<50%, No.	3	3	
Prothrombin level	(n = 26)	(n = 120)	
Median (range), %	79 (36 to 100)	88 (24 to 100)	.19
<50%, No.	7	11	
Comedications, median (range), No,	4 (1 to 11) (n = 26)	4 (0 to 14) (n = 140)	.45
CYP inhibitors + inducers†	(n = 26)	(n = 140)	
3A4 score			
Range	−2 to 5	−2 to 4	.82
≥2, No.	4	23	
2D6 score, range	0 to 4	−2 to 7	.28
2C9 score, range	0 to 7	−2 to 7	.67
2C19 score, range	0 to 4	−2 to 7	.95
1A2 score, range	0 to 3	−2 to 4	.70
Comedication with other QT prolonging drugs	(n = 26)	(n = 140)	
PD score,† range	0 to 2	0 to 4	.45

Abbreviations: CYP, cytochrome P-450; HBV, hepatitis B virus, HCV, hepatitis C virus; HIV, human immunodeficiency virus; n, number of patients for which data were available; NA, not applicable; PD, pharmacodynamic interaction.

SI conversion factors: To convert magnesium to millimoles per liter, multiply by 0.411; to convert calcium to millimoles per liter, multiply by 0.25; to convert creatinine clearance to milliliters per second, multiply by 0.0167.

*P values for differences between groups were calculated with the Mann-Whitney test for continuous variables and the χ^2 test for categorical variables. Statistics refer to the entire group of patients, unless otherwise indicated. Factor V levels were not compared between the groups because of missing data.

‡For pharmacokinetic interaction scores and PD score, see the "Methods" section.

cause the substance specificities often overlap. Hypokalemia, the fouth factor in our model, is a well-recognized risk factor for QT prolongation.[2]

We did not identify an effect of sex on QT prolongation or TdP as described previously.[2,27] It is interesting to note that sex disparities could not be demonstrated for all individual drugs and there might be specific effects.[27]

Methadone is valued, among other indications, for its beneficial effect on mortality and morbidity in opiate-dependent persons.[28,29] Cost of treatment is low, and no life-threatening adverse drug reaction other than overdose has been reported. This favorable drug profile has led to large increases of the methadone doses used in methadone maintenance therapy, often exceeding the "high doses" (60-100 mg/d) considered in efficacy studies.[4] This trend was driven in part by studies suggesting that individual drug levels are highly variable because of different pharmacokinetic parameters among patients.[5]

Methadone was documented as a possible cause of diLQTS in several case reports, surveillance data, and, notably, one study comparing QT before and after introduction of methadone in an ambulatory setting.[7-10,12,30,31] Until now, QT prolongation attributed to methadone treatment has been modest. In an outpatient setting, Martell et al[10,11] described that only 1.3% of patients presented with a QTc prolongation to longer than 0.50 second½ after introduction of methadone. The divergence with respect to the present results might be attributed to differences in patient characteristics (eg, ambulatory vs inpatient setting). Doses of methadone were higher in our sample, and high numbers of patients with comedication use were frequent. As a consequence, the present results might not be applicable to all methadone maintenance patients but provide important information on hospitalized patients and the cumulative contribution of different risk factors. Data indicate that significant QT prolongation is particularly fre-

Table 3. Multivariate Model for QTc Length in 138 Methadone Maintenance Patients*

Predictor Variables	Regression Coefficient (B)	*P* Value
Methadone dose (4 groups), mg/d		
≤50	−0.0382	.01
51-100	−0.0089	
101-150	−0.0202	
>150	(Reference category)	
K	−0.0769	<.001
PT	−0.0044	<.001
IS	0.119	<.001
K × IS	−0.0290	<.001
K × PT	0.0009	.002

Abbreviations: IS, cytochrome P-450 3A4 (CYP3A4) interaction score; K, potassium level; PT, prothrombin level.

*The model was written as $\log_{10}(QTc) = \text{intercept} + B_1 \times (\text{dose group}) + B_2 \times K + B_3 \times PT + B_4 \times IS + B_5 \times K \times IS + B_6 \times K \times PT$. The percentage of explained variability (R^2) was 32% (intercept=0.0451). Complete data were available for 138 patients.

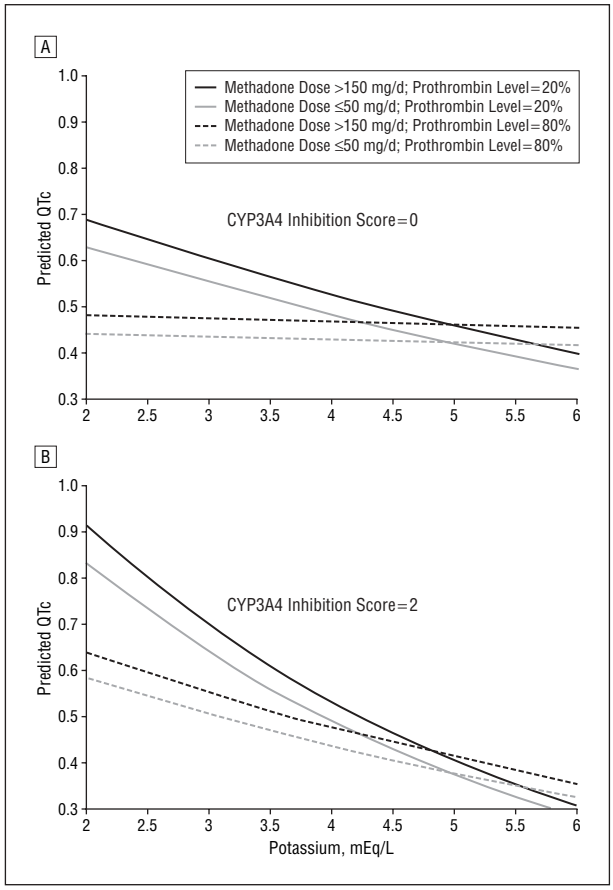

Figure 5. Predictions from a model describing QTc as a function of potassium level, prothrombin level, methadone daily dose, and cytochrome P-450 3A4 (CYP3A4) interaction score based on patient comedication use. The 2 parts illustrate the relationship between QTc and the 4 predictors according to the model in Table 3, in the absence (A) and presence (B) of CYP3A4 inhibitors.

quent when several concomitant factors act simultaneously. The recognition of cardiovascular adverse effects of methadone is particularly important because young patients rarely undergo cardiac monitoring and are susceptible to the use of drugs that interfere with cardiac electrical activation. Among other factors potentially involved in QT prolongation, we were unable to identify a significant association between the presence of HIV infection and QT length,[9,32] but as hospitalized HIV-positive patients often receive a large number of medications, such an effect might have been masked.

Several limitations should be pointed out. We cannot formally exclude a difference in the prevalence of structural heart disease in the methadone and control groups, but available data speak against the presence of such a confounder. Data on other illicit drug use relied on voluntary reporting only. Because we did not exclude the presence of such substances by routine toxicologic screening, a different pattern of substance use in the 2 groups cannot be excluded. This also holds true for additional unreported methadone or alcohol use. The simultaneous consumption of alcohol and cocaine might also lead to QT interval prolongation by the formation of cocaethylene.[33] Finally, the data were collected in 1 institution only. In the present study, we could not assess the relevance of QT prolongation as a surrogate marker of morbidity or mortality.

Our data suggest that among opioid-dependent persons receiving methadone treatment, hospitalized in a tertiary center, QT interval prolongation is a frequent finding, that can be partly explained by the concomitant effect of several factors. We show that drug-drug interactions play a key role in the occurrence of QT interval prolongation. Effective and safe treatment of methadone-induced long QT syndrome exists with the use of opioid rotation.[34] Electrocardiographic control in patients at risk could thus be beneficial as a simple means of screening for QT interval prolongation, especially after introducing a CYP3A4 inhibitor and increasing the methadone dose and in the presence of hypokalemia or diminished liver function.

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