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Risk of QTc prolongation in a cohort of opioid-dependent HIV-infected patients on methadone maintenance therapy

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Key points

1. High prevalence of prolonged QTc interval in opioid-dependent HIV-infected patients on methadone maintenance therapy.

2. HIV patients with chronic hepatitis C-induced cirrhosis, antiretroviral-naive HIV patients and HIV patients receiving higher doses of methadone are at increased risk for prolonged QTc interval.

ABSTRACT

Background: Concern regarding the QTc interval in HIV-infected patients has been growing in recent years, and cases of prolonged QTc interval and Torsades de Pointes have been described in HIV-infected patients on methadone therapy. This study aimed to determine the prevalence and factors associated with long QTc interval in a cohort of opioid-dependent HIV-infected patients on methadone maintenance therapy.

Methods: A cross-sectional study was conducted in opioid-dependent HIV-infected patients on methadone maintenance therapy at a drug abuse outpatient center. Patients with any cardiac disease, drug-positive urine test, electrolyte abnormalities and changes in their antiretroviral therapy or methadone doses in the last two months were excluded. Heart rate and QT interval in lead II were measured using Bazett's formula.

Results: Ninety-one patients were included: 58 (63.7%) were males with a median age of 44.5 years and 68/91 (74.7%) were on antiretroviral therapy. Median methadone dose was 70 (15-250) mg/day and mean QTc interval 438+34 ms. Prolonged QTc interval (>450 ms) was documented in 33/91(36.3%) patients and 3/91 (3.2%) had QTc >500 ms. On multiple linear regression analysis methadone doses (*P* 0.005), chronic hepatitis C-induced cirrhosis (*P* 0.008) and antiretroviral naive therapy (*P* 0.036) were predictive of prolonged QTc.

Conclusions: The prevalence of prolonged QTc interval in opioid-dependent HIV-infected patients on methadone maintenance therapy is high. Risk factors for prolongation of the QTc interval are chronic hepatitis C-induced cirrhosis, higher methadone doses and antiretroviral-naive therapy. Thus, ECG monitoring is required to minimize cardiovascular morbidity and mortality in this specific HIV group.

INTRODUCTION

In recent years, cardiovascular disease has emerged as a major cause of morbidity and mortality in human immunodeficiency virus-(HIV-) infected patients (1, 2).

Prolongation of the QTc interval on the electrocardiogram surface (ECG) indicates an increase in ventricular repolarization time and represents a major risk for polymorphous ventricular tachycardia (Torsades de Pointes) and sudden arrhythmic death (3,4).

The prevalence of prolonged QTc in HIV patients compared with HIV-uninfected subjects has increased (5-7). Acquired QT prolongation is more prevalent than the congenital form in HIV-positive patients and has been associated with HIV-associated autonomic dysfunction (8), hepatitis C infection (7) and several drugs including methadone and highly active antiretroviral therapy (HAART) (5-12).

Methadone maintenance therapy is recommended as a safe and effective treatment for reducing illicit opioid use and promoting longer retention in treatment of opioid-dependent HIV patients. However, cases of prolongation of the QTc interval and Torsades de Pointes in HIV patients receiving high doses of methadone have been reported (13-15). The mechanism underlying this increase is related to the inhibitory action of methadone on the hERG voltage-gated potassium channel encoded by the human ether a-go-go related gene (*hERG*) (16).

Nevertheless, no cohort studies evaluating the QTc interval in opioid-dependent HIV-infected patients on methadone maintenance treatment have been reported. Owing to the large number of HIV patients exposed to methadone (17) and the fact that it is not possible to predict the risk of QT interval prolongation in a given individual, further studies are required to identify the risk factors associated with long QTc interval so as to design prevention strategies and reduce the risk of Torsades de Pointes in this specific group of HIV patients.

Therefore, the aim of this study was to determine the prevalence and factors associated with long QTc interval in a cohort of opioid-dependent HIV-infected patients on methadone maintenance therapy.

METHODS

This cross-sectional study included HIV-infected intravenous drug users who met the criteria for DSM-IV-TR opioid dependence disorder. Patients were controlled at a multidisciplinary drug abuse outpatient center in Barcelona (CAS-Barceloneta) where they received simultaneous treatment for both HIV and opioid dependence.

Subjects were informed and signed a consent form prior to being admitted to the methadone program. More details regarding the work of the CAS-Barceloneta are published elsewhere (18, 19).

Patients with any cardiac disease, drug-positive urine test, serum electrolyte abnormalities and changes in their antiretroviral therapy or methadone doses in the last two months were excluded.

Following routine clinical practice for patients on the methadone maintenance program, a 12-lead ECG at rest was recorded just 24 hours after the last supervised oral methadone administration. All ECGs were recorded using the same device (Agilent®, Model: M17772A; Serial: CND4750784), printed at a paper speed of 25 mm/s, amplified to 10mm/mV and recorded during the morning (between 9 am and 1 pm). Heart rate and QT interval in lead II were measured by a senior consultant specialist in internal medicine. The QT interval was corrected (QTc) by heart rate using Bazett's formula (20).

In addition to the sex-adjusted QTc thresholds, we used a recently updated sex-independent categorical threshold of QTc >450 ms was used for QTc interval

prolongation and QTc >500 ms for significant arrhythmia risk according to the higher risk documented in methadone patients (21, 22).

Patients´ general characteristics and medical history were extracted from a database used in the routine care of these patients.

HAART was composed of one of the following combinations: (1) a boosted protease inhibitor (PI) plus 2 nucleoside reverse-transcriptase inhibitors (NRTIs), (2) a boosted PI monotherapy, (3) a non-NRTI (NNRTI) plus 2 NRTIs, or (4) abacavir in combination with lamivudine and zidovudine or stavudine (3 NRTIs).

Screening for chronic hepatitis C infection was determined by EIAII anti-HCV antibodies HCV (COBAS Core EIA Anti-HCV, Roche Diagnostics) and confirmed by detection of HCV RNA by real-time PCR (COBAS TaqMan HCV assay, Roche Diagnostics). The diagnosis of liver cirrhosis was based on the result of a liver biopsy or by transient elastography.

The extensive set of lists from the Arizona Center for Education and Research on therapeutics was used to identify drugs that prolong the QT interval and/or induce Torsades de Pointes ventricular arrhythmia (23).

Analyses were made using SPSS (Chicago, Illinois, USA; release 17.0.0, August 2008). All data are expressed as mean +*SD*, while variables with non-parametric distribution are expressed as mean and range. In a bivariate analysis, non-parametric Mann-Whitney U tests were used to analyze the association between QTc intervals and categorical variables (sex, origin, hepatitis C infection, chronic hepatitis C-induced cirrhosis, the use of QT-prolonging medications drugs, HAART and HIV-RNA viral load) and Pearson's correlation test to determine whether an association existed between the QTc interval and quantitative variables (age, CD4 cell count and methadone doses). Variables showing a relationship with the QTc interval were included in the

multiple linear regression analysis to assess the effect of independent variables on the QTc interval. Variables included in the model were methadone doses (per 10 mg/day increment), type of HAART (naive, current use of PI and current use of NNRTI), chronic hepatitis C-induced cirrhosis and the use of QTc-prolonging medications drugs. The QTc interval was studied as a continuous variable in the analysis to increase power and avoid choosing cut-off points. A *P*-value <0.05 was considered significant.

RESULTS

Five hundred and thirty-six intravenous drug user patients were monitored between August 2012 and January 2013 at CAS Barceloneta, 139 of whom were HIV-infected. Of these HIV patients, 6 were not receiving methadone, 24 had a positive toxicologic urine test, 13 had data missing for inclusion in the analysis and 5 had heart disease. Finally, 91 patients were included in the study. The clinical characteristics of the HIV patients included in the study are shown in Table 1.

Sixty-eight of 91 (74.7%) HIV patients were on HAART, and viral load HIV-1-RNA <20 copies/mL was observed in 67 of the 68 (98.5%) patients.

Median methadone doses were 70 (15-250) mg/day, and 28/91(30.7%) patients were receiving methadone doses higher than100 mg/day.

Compensated hepatitis C-induced cirrhosis was present in 11/84 (13%) co-infected hepatitis C patients and all were taking boosted PI.

QTc-prolonging medications were used in 53/91 (58.2%) patients: antipsychotics in 34 patients, antidepressants in 26, antiepileptics in 12 and antibiotics in 5.

Prolonged QTc interval QTc (QTc>450 ms) was documented in 33/91(36.3%) patients with no sex-related differences (*P* 0.893) and 3/91 (3.2%) patients had QTc >500 ms.

Comparison of the QTc interval according to clinical variables is shown in Table 2.

Only the presence of chronic hepatitis C-induced cirrhosis, HIV-positive antiretroviral-

naive patients, higher methadone doses and, marginally, the use of QTc-prolonging medications were associated with the QTc interval in bivariate analysis. A significant positive correlation was observed between the QTc interval and methadone doses but not for age or current CD4 cell count in quantitative variable analysis.

Results of multiple linear regression analysis including as independent variables those identified through bivariate analysis and Pearson's correlation test, are shown in table 3. Doses of methadone (per ten milligrams of methadone dose escalation), antiretroviral-naive HIV-patients and the presence of liver cirrhosis were variables independently predictive of prolonged QTc; however results of the use of QTc-prolonging medications were not statistically significant.

DISCUSSION

In this study, a prolonged QTc interval was found in 36.3% of patients and a significant relationship between the QTc interval and antiretroviral-naive HIV-patients, methadone doses and chronic hepatitis C induced-cirrhosis in a cohort of opioid-dependent HIV-infected patients on methadone maintenance therapy.

The prevalence of prolonged QTc interval studied in other HIV cohorts ranged from 5.4% in clinical trials to 45% in cohorts with advanced HIV disease (2-4, 24-27). The higher prevalence observed in the present study can be explained by the type of patients included, who were mainly antiretroviral-naive HIV patients in advanced stages of the disease, and a nadir CD4 cell count. The association of the duration of HIV infection, low CD4 cell count, high HIV-RNA viral load and QT interval prolongation has been documented (24, 28). The reason for this association remains unclear but could be related to the influence of chronic HIV infection on the heart and autonomic nervous system. In this respect, Villa et al (8) reported a longer QTc interval duration in HIV-

infected patients with asymptomatic autonomic neuropathy. In our study, we failed to demonstrate a significant negative relationship between CD4 cell count and prolonged QTc interval; however, we did observe that antiretroviral-naive HIV patients constituted a predictive variable of QTc length. In fact, patients on antiretroviral therapy had a shorter QTc interval compared with antiretroviral-naive HIV patients, which may reflect an improvement in disturbance of the autonomic nervous system after antiretroviral therapy is initiated (29-30).

Methadone maintenance treatment has been shown to be medically safe in many prospective studies in the management of opioid dependence, and clinical guidelines on QTc screening exist for patients on methadone maintenance therapy (21,22).

However, cases of prolongation of the QTc interval and Torsades de Pointes have been reported, particularly in patients receiving higher doses of methadone (13-15). As with the results observed in HIV-negative patients (20, 31-33), a dose-dependent relationship between methadone and QTc interval prolongation was observed in our patients. This finding has significant clinical implications, since higher methadone doses are more effective than lower doses in retaining patients and in reducing heroin and cocaine use during treatment (32); however the risk of prolonged QTc interval is increased.

A further interesting topic of concern is the contradictory effect of antiretroviral therapy on QTc interval duration. Although PIs inhibit hERG current *in vitro* (11) and therefore are expected to prolong the duration of ventricular repolarization, we found no relationship between PI or NNRTI intake and QTc prolongation, in agreement with recent HIV cohort studies (24-28). Theoretical models suggest that such a degree of hERG blockade is expected to produce a prolongation of the QTc interval of <5 ms (34). This could explain the lack of a significant influence of PI on QTc prolongation in

clinical studies, a result consistent with recent data showing absence of the effect of atazanavir on ventricular repolarization during repeated administration (35). Abnormalities in cardiac electrophysiology, including prolonged QTc interval which is the electrophysiologic hallmark of "cirrhotic cardiomyopathy" have been documented in patients with liver cirrhosis (36). In our study, a significant relationship was found between the presence of liver cirrhosis and prolonged QTc interval in HIV-HCV co-infected patients. Concurring with our results, Nordin et al stated that co-infection with hepatitis C results in twice the risk of significant QTc prolongation in HIV patients (7). This clinical finding is important since the prevalence of hepatitis C virus (HCV) among intravenous drug users with HIV infection is close to 90%, and hepatitis C liver disease is an increasingly recognized cause of morbidity and mortality in these individuals (37).

In addition to methadone, other drugs can prolong the QT interval by blocking *hERG*-encoded potassium channels, or some drugs can act by modifying sodium channels (4). Our study showed a non-significant trend towards the use of QT-prolonging medications, probably due to the fact that we classified all drugs with effects on the QTc interval in the same categorical group, including those with different risks of prolonging the QTc interval. Furthermore, the small sample size of the study may have produced underestimation of the results. Nevertheless, as our study shows, the wider use of other drugs with effects on the QTc interval in this HIV patient group is noteworthy and highlights the importance of reviewing the use of concomitant medication for the treatment of co-morbidities in opioid-dependent HIV patients (4,38) and, particularly potential interactions between antiretroviral drugs and drugs with known QTc interval-prolonging effects. This is interesting to note since several antiretroviral drugs exhibit inhibitory and/or inducing effects on cytochrome P450 isoenzymes which are

responsible for the metabolism of many medications and, consequently, could greatly increase the plasmatic concentration of QTc-prolonging medications and, secondarily the risk of prolonging QTc.

Together with the high prevalence of prolonged QTc interval in HIV patients on methadone maintenance therapy, the clinical implications of prolonged QTc include the increased risk of cardiovascular disease and mortality (39). As seen in HIV-seronegative patients, the results of the SMART trial proved the significance of ECG abnormalities in the development of cardiac events in a well-defined multi-racial population who were cardiovascular disease-free at study baseline. In the multi-adjusted model, HIV patients with prolonged QTc had a six-fold greater risk of a cardiovascular event than HIV patients with normal-interval QTc (25). Hypothetically, the cardiovascular risk associated with a prolonged QTc interval may be higher in HIV patients on methadone maintenance therapy since this HIV patient group have more prevalent risk factors associated with prolonged QTc interval (advanced HIV disease, liver cirrhosis, concomitant use of drugs that prolong the QTc interval) (40) than patients included in the SMART trial.

Buprenorphine and morphine are opiate derivates with comparable efficacy to methadone for opioid dependence. They block the *hERG* channel with notably less potency than methadone and may constitute a safe alternative in HIV patients on methadone maintenance therapy with an increased risk of a prolonged QTc interval (41).

Despite the statistical limitations due to the small sample size and the observational nature of the study, patients with different methadone doses and those on antiretroviral therapy were included in the analysis so that the sample would be representative of this

specific HIV patient group. Moreover, the results achieved concur with those published in the literature.

In conclusion, the prevalence of prolonged QTc interval in opioid-dependent HIV-infected patients on methadone maintenance therapy is high; in fact, one in three patients may have a prolonged QTc interval. Risk factors for prolongation of the QTc interval are liver cirrhosis, higher methadone doses and antiretroviral-naive therapy. Clinicians should be aware of the risk of a prolonged QTc interval and the need for ECG monitoring in this specific HIV patient group so that cardiovascular morbidity and mortality can be minimized. Furthermore, physicians should take other secondary causes of prolonged QTc interval in methadone HIV patients into account , especially the use of drugs with known effects on the QTc interval and their potential interactions with antiretroviral therapy.

Future lines of research should, therefore, focus on the importance of pharmaco-dynamic gene-drug interactions in opioid-dependent patients.

Notes: The authors have no reported conflicts of interests.

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TABLES

Table 1. Baseline characteristics of opioid-dependent HIV-infected patients on methadone maintenance therapy.

	Subjects n 91
Age (mean±SD)	44.5±8
Male No.,(%)	58 (63.7%)
Origin No.,(%)	
Spanish	81(89.%)
Non-Spanish	10 (11.0%)
Race	
Caucasian	91(100%)
Hepatitis coinfection No.,(%)	
Hepatitis C virus	84 (92.3%)
CDC stage No.,(%)	
A	19(20.9%)
B	24(26.4%)
C	48(52.7%)
CD4 count nadir (cells/µL) (median,range)	232(7-665)
CD4 count nadir <350 cells/µL	61/77(79.2%)
CD4 count nadir <200 cells/µL	40/77(51.9%)
CD4 count (cells/µL) (median,range)	438(6-1536)
Viral load (median log_{10})	5.00+4.2
Baseline HAART regimen No.,(%)	
PI	56 (61.5%)
NNRTI	12 (13.2%)
Naïve	23 (25.3%)
Months on methadone (median,range)	31(9-92)
Methadone dose (mg/day) (median,range)	70(15-250)
Methadone dose>100 mg/day	28/91(30.7%)
Heart Rate (bpm)(mean±SD)	73.3±11
QTc (ms) (mean±SD)	438±34
Use of QTc-prolonging medications No.,(%)	44(57.1%)

HAART: Highly Active Antiretroviral Therapy; PI: boosted protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; ms- milliseconds; bpm- beats per minute

Table 2. QTc interval according to clinical characteristics

Table 2.1. Comparison of QTc interval according to clinical characteristics (qualitative variables)

Variable		QTc interval (mean±SD)(ms)	p-value
Sex	Male Female	437.8±39.1 438. ±28.32	0.968
Origin	Spanish Non- Spanish	435.9±34,4 451.8 ±34,7	0.180
Hepatitis C	Yes No	439.8 ±35,6 427.1± 27,4	0.266
Chronic hepatitis C-induced cirrhosis	Yes No	461.27± 29,1, 434.1± 34,2	0.015
Use of QTc-prolonging medications	Yes No	443.4 ±34,2 427.4 ±33,7	0.056
HAART exposure	Naive Current PI Current NNRTI	447±.82 9,4 435.3± 37,5 432.3± 28,2	0.04
HIV-RNA <20 copies/ml	Yes No	435.0±35,2 449.3 ±31.1	0.145

HAART: Highly Active Antiretroviral Therapy; PI: boosted protease inhibitor;

NNRTI: non-nucleoside reverse transcriptase inhibitor; ms- milliseconds

Table 2.2. Pearson correlation between QTc interval and clinical characteristics (quantitative variables).

Variable	r-value	p-value
age (years)	–0.94	0.414
methadone (mg/day)	0.371	0.001
CD4 cell count (cells/µL)	-0.146	0.205

r = Pearson's correlation coefficient

Table 3. Multivariate model of QTc interval (linear regression analysis)

Variable	β	(95%CI) Lower limit	Upper limit	P-value
Constant(ms)	405.02	387.6.	422.449	0.000
Doses of methadone	2.091	0.641	3.542	0.005
Chronic hepatitis C-induced cirrhosis	29.87	8.030	5.723	0.008
ARV-naive patients	18.27	1.215	35.336	0.036
Use of QTc-prolonging medications	14.53	-0.124	29.190	0.052

B: regression coefficient; ms: milliseconds; CI: confidence interval; ARV: antiretroviral therapy