Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Original article | Published 6 September 2013, doi:10.4414/smw.2013.13852
Cite this as: Swiss Med Wkly. 2013;143:w13852

QTc prolongation in methadone maintenance – the role of HCV infection

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Summary

OBJECTIVES: Several studies have reported prolonged QTc intervals in patients under methadone maintenance treatment, including development of torsade-de-pointes arrhythmia and death. It is still not clear why some patients develop critical QTc extensions while others do not.
METHODS: ECG findings in a convenience sample of 210 methadone-maintained heroin-dependent patients, taking HCV-infection status and methadone dosage into account simultaneously by means of a multiple linear regression model with QTc-interval as the dependent variable.
RESULTS: Prolonged QTc-time is associated with hepatitis C infections ($p = 0.005$) and higher doses of racemic methadone ($p = 0.012$).
CONCLUSION: Infection with hepatitis C increases the likelihood of critical QTc prolongation in patients in methadone maintenance treatment.

Key words: *QT-prolongation; methadone; hepatitis C*

Introduction

Methadone maintenance treatment is the best-evaluated therapy for heroin dependence, and its effectiveness in retaining patients in treatment and in reducing consumption of street-heroin has been demonstrated by a great number of studies [1]. Methadone is also prescribed for the management of pain to many patients in the Americas, Australia and Europe [2].
Methadone – as with many other drugs – blocks the human Ether-à-go-go Related Gene (hERG) voltage gated potassium channel in the heart [3]. This blockade results in delayed re-polarisation [4] that can be seen as QT interval prolongation in the ECG. A prolonged QT interval is associated with an elevated risk of life-threatening cardiac tachyarrhythmias called torsades-de-pointes.
QT prolongations and torsades-de-pointes in patients on methadone have been increasingly reported since its first description by Krantz and colleagues [5]. There is no clear evidence of whether methadone doses (or its blood-levels) and QT times are inter-related [6–12].
Chronic hepatitis C virus (HCV) infection is common in patients under methadone substitution treatment [13, 14]. Extra-hepatic manifestations of hepatitis C may also include the myocardium. Hepatitis C related cardiomyopathies – dilated and hypertrophic cardiomyopathy due to chronic myocarditis – have been described in several studies [15–18]. The hepatitis C core protein inhibits several signal proteins in myocytes of mice. HCV is presumed to replicate within myocardial tissue. Successful anti-viral therapy of HCV is supposed to improve HCV related cardiomyopathy. The frequency of HCV related cardiomyopathy seems to vary between different regions and populations [18].
To our knowledge, only one study has so far reported a correlation between HCV infection and prolonged QT interval in HIV-infected patients [19]. The presence of liver-cirrhosis or markers of impaired liver function like lower prothrombin activity or lower serum concentrations of albumin, elevated bilirubin or plasma bile salt levels has also predicted prolonged QTc-time independent of aetiology [20]. Furthermore, a study on QTc-length among methadone-maintained former injection drug users found impaired liver-function – as measured by prothrombin-levels – to negatively influence QT-time, synergistically together with hypokalaemia and co-medication that inhibit CYP3A4 function [21].
Thus, since there is some evidence that HCV-infection might contribute to prolonged QTc-times in methadone-maintained patients, we assessed cardiac activity in a large sample of methadone-maintained patients, taking account of their HCV-status.

Methods

ECG-registration was performed in a supine position with a Cardiette ar1200 view instrument (12-lead ECG). QT-intervals were measured manually all by the same physician using a lead II as long as T-wave morphologic characteristics were distinct. Otherwise a lead V5 was used [22]. The T-wave endpoint was defined by the tangent method (intersection of a line extrapolated from the iso-electric baseline and the tangent line, which touches the terminal part of the T wave at the point of maximum down-slope). To account for potential arrhythmias, RR-intervals were measured at three different time points of the ECG and the mean value

was then used for the calculation of QTc-time. QTc-values were calculated according to Bazett's formula [23].

The following variables with a potential influence on QTc-time at the time of ECG-recording were entered as covariates into the analysis: Continuous covariates were age (years) and daily methadone dosage (mg). In accordance with the study by Kornick et al. [24], the log of daily methadone dosage was entered into the analysis, to account for skewed distribution of untransformed data. Categorical covariates were sex (male/female), and the presence or absence of alcohol-dependence (ICD-10; F10.2x), cocaine dependence (ICD-10; F14.2x), and infections with HBV, HCV, and HIV. Furthermore, a binary variable indicating whether a patient was receiving any additional medications with a potential for QT-prolongation (according to the list on http://www.qtdrugs.org; accessed on the 15/09/2011) was entered into the calculations.

HCV-status was categorised as follows: HCV+/RNA+ (presence of HCV-antibodies/observed viral load), HCV+/navl (no viral load at the time of ECG registration, but viral load in former analyses), HCV+/AB (diagnosis only by observation of antibodies; HCV-RNA-determination not (yet) done), HCV- (HVC negative), and unknown HCV-status.

Sample, setting and data analysis

A total of 219 patients, willing to participate, were in methadone maintenance treatment (MMT), and 218 of them had had at least one ECG-screening between March 2007 and October 2008, thus meeting inclusion criteria. Exclusion criteria were any cardiac diseases according to the medical files (n = 8). The final sample consisted of 210 patients. Patients' characteristics are listed in table 1.

The study was cross-sectional and took place in an outpatient facility of the Psychiatric University Hospital in the centre of Zurich, Switzerland, specialised in the treatment of substance use disorders. All patients on opioid maintenance treatment (N = 301) were approached by the research team, and the aim of the study was carefully explained. A total of 260 patients consented to participate. The ethic's commission of the canton of Zurich agreed with the study procedures.

Zero-order associations between independent variables and QTc were analysed by t-test for categorical covariates and by Pearson correlations for continuous covariates. Associations with p <0.05 were considered significant and corresponding variables were entered as predictors into a multivariate linear regression model with QTc as the dependent variable.

The model was represented by the formula

$$y_i = c + b_1 x_{i1} + b_2 x_{i2} + \varepsilon_i$$ (i= 1 to 210), where:

y_i = observed QTc-value (msec) of i^{th} patient, c = constant (msec), x_{i1}= belonging of i^{th} patient to the group "HCV+/RNA+" (no = 0, yes = 1), x_{i2} = methadone dose (log(mg/d)) of i^{th} patient, b_1 = regression coefficient of x_1, b_2 = regression coefficient of x_2, ε_i = error of estimated QTc for i^{th} patient (difference between estimated and observed value). We used OLS method for parameter estimation.

Data-analysis was done with PASW Statistics (version 18.0; IBM Corp., Sumers, NY).

Results

Patients' characteristics

A total of 151 (71.6%) patients were male and the mean age was 37.06 years. In the sample, 127 (60.5%) suffered from an additional cocaine-dependence and 46 (21.9%) from alcohol-dependence. A total of 96 (45.7%) patients had one or several prescribed medications with a QT-prolonging potential. 58 (27.6%) were HBV-positive, and 83

Table 1: Number of patients, means and standard deviations of QTc-time, and corresponding *p*-values of zero-order associations.

	Categories:	**n**	**mean QTc (ms)**	**SD[g]**	***p*-value**
Sex:	male: female:	151 59	442.7 445.6	30.4 29.4	0.532[a]
Cocaine-dependence:	yes: no:	127 83	445.9 439.9	31.2 28.2	0.156[a]
Alcohol-dependence:	yes: no:	46 164	447.2 442.5	28.6 30.5	0.351[a]
Medication with QT-prolongation	yes: no:	96 114	445.8 441.7	33.4 27.0	0.334[b]
HBV:	positive: negative: unknown:	58 83 69	442.6 445.0 442.5	27.3 31.9 30.5	0.646[a] 0.849[d]
HIV:	positive: negative: unknown:	14 153 43	451.3 444.7 437.0	22.1 31.3 27.5	0.443[a] 0.206[d]
HCV:	HCV+/RNA+: HCV+/navl: HCV+/AB: HCV-: unknown:	53 17 30 101 9	453.5 453.6 443.2 437.6 433.8	25.7 25.3 32.9 31.1 25.7	0.009[d] 0.020[f]
		n	**mean**	**SD[g]**	**r[e]**
Age [y]:		210	37.0	8.0	0.13
Methadone dosage [mg]:		210	113.6	80.6[c]	0.188**
Methadone dosage [log]:		210	1.94	0.33	0.162*

[a] t-test with equal group variances; [b] t-test with unequal group variances; [c] significant deviation from normal distribution; [d] one-way ANOVA; [e] Pearson correlation coefficient; [f] *post-hoc* test (Scheffé); [g] standard deviation

* p <0.05; ** p <0.01

(39.5%) were HBV-negative, whereas 69 (32.9%) patients had an unknown HBV-status. 14 (6.7%) patients were HIV-positive and 153 (72.9%) were HIV-negative, whereas 43 (20.5%) had an unknown HIV-status.

A total of 53 (25.2%) patients were diagnosed with HCV+/RNA+; 17 (8.1%) were HCV+/navl, 30 (14.3%) were HCV+/AB, 101 (48.1%) were HCV- (HVC negative), and 9 patients (4.3%) had an unknown HCV-status. One-way ANOVA showed significant differences of mean QTc-values between these groups ($F = 3.99$; $df = 3$; $p = 0.009$). *Post-hoc* procedure according to Scheffé (assumed homogeneity of between-group variances; Levene-Statistics: 1.41; df1 = 3; df2 = 197; $p = 0.23$) revealed a significant difference between the HCV+/RNA+ and HCV-groups ($p = 0.02$).

Mean daily methadone dosage was 113.6 mg and distribution differed significantly from normal distribution (Kolmogorov-Smirnnov: $Z = 2.63$; $p < 0.001$) whereas the distribution of the log of daily methadone dosage did not (Kolmogorov-Smirnnov: $Z = 1.02$; $p = 0.25$). QTc-values were normally distributed (Kolmogorov-Smirnnov: $Z = 0.49$; $p = 0.96$) and mean QTc-time was 443.5 ms (SD = 30.1). No relevant arrhythmic events were detected in the ECGs done for this study.

Covariates of QTc-values

As shown in table 1, among all considered variables only the daily methadone dosage and HCV+/RNA+ status were correlated significantly with QTc-time. The log of daily methadone dosage and HCV+/RNA+ were not significantly associated with each other (Spearman's Rho = –0.021; $p = 0.76$) and were therefore entered into a multiple linear regression model with QTc as the dependent variable. A total of nine patients with unknown HCV-status were omitted from this analysis. The result (table 2) was an overall significant model ($n = 201$; $F = 6.979$; $df = 2$; $p = 0.001$), predicting QTc-values with an adjusted R-Square of 0.06. Both regressors showed similar standardised effects prolonging QTc (HCV+/RNA+ (yes/no): $\beta = 0.195$; $p = 0.005$; methadone dosage (log mg/d): $\beta = 0.174$; $p = 0.012$). The regression line intercept (constant) was 409.7 msec.

Discussion

An infection with hepatitis C-virus is correlated with a longer QTc-interval in heroin dependent patients who are maintained on methadone. To our knowledge, our study is the first to report this association. We also found the dosage of methadone to be a predictor of QTc-times, but to a slightly lesser degree. This might partially explain the discrepancy of results from studies on the link between methadone dose and QTc-times [12, 25–28]. The presence of an HCV-infection in a patient might point to a more severe course of the disorder of compulsive heroin use. Thus, HCV-carriers might need higher-dosages of methadone, confounding the influence of HCV-status and dosage-level on cardiac action, even though that was not the case in our study.

Furthermore, the current study showed that the presence of viruses is needed for HCV infection to prolong cardiac re-polarisation and that antibodies alone do not seem to have this effect. There seems to be little knowledge about the cardiac consequences of an HCV-infection. The potential patho-mechanisms for our findings need further elucidation. Both, hepatitis C induced myocarditis causing QT prolongation or indirect effects, involving impaired liver function, have to be considered.

The current study has several shortcomings that deserve mentioning. Due to the cross-sectional design of our study, nothing can be said about the stability of the QTc-time assessed at one time point.

Furthermore, we were unable to determine the specific type of hepatitis C virus or the genes of the major histo-compatibility complex class II. These genes may influence the development of different phenotypes of HCV cardiomyopathies [18].

Measures of liver-function like prothrombin or other liver enzymes would have been helpful for elucidating the pathway by which HC-viruses influence cardiac action. However, since our result of HCV contribution to prolonged QT-time was unexpected, we did not systematically determine these values. Furthermore electrolyte measures as additional factors influencing QT time were not routinely assessed and the ECG interpreter was not blinded. It would have been interesting to compare QTc-times in HCV-infected patients before and after successful treatment. However, we only had this data in a small sample of patients not allowing statistical evaluation. Therefore, further studies are needed to replicate our findings in other samples and to evaluate the influence of different HC-virus strains and of successful treatment of HCV-infections.

Funding / potential competing interests: No financial support and no other potential conflict of interest relevant to this article was reported.

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Table 2: Coefficients of the multivariate linear regression model with QTc time as dependent variable.

	B	SE	β	T	*p*-value
Constant	409.78	12.4	–	32.9	0.000
Methadone dosage [log]	15.7	6.2	0.174	2.5	0.012
HCV+/RNA+ [y/n]	13.3	4.7	0.195	2.8	0.005

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