

## ORIGINAL ARTICLE

# Dose-Dependent Effects of Methadone on QT interval in Patients under Methadone Maintenance Treatment

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## Abstract

**Background:** The role of methadone in QTc prolongation, Torsades de Pointes (TdP) arrhythmia and sudden cardiac death has been debated. Because of widespread use of methadone in methadone maintenance treatment (MMT) centers, we aimed to study dose-related effects of methadone on QTc prolongation.

**Methods:** In a comparative observational study, 90 patients who were under MMT were evaluated. Patients were divided into three groups according to methadone daily dose (G1: 0-59 mg, G2: 60-109 mg, G3: 110-150 mg). Twelve-lead electrocardiograms (ECG) were performed at baseline and two months later, after reaching the maximum daily dose of methadone. The QTc were calculated for each patient. Comparison of mean QTc and mean QTc prolongation between baseline and follow up ECGs were analyzed.

**Results:** In total, mean (SD) age was 32.4 (8.5). TdP was not detected in any patients. Mean QTc was 405.2 (17.0) and 418.5 (23.1) msec before and two months after MMT respectively. There was a significant difference between mean QTc in each group before and after treatment ( $P < 0.001$ ). In total, mean QTc prolongation was 13.5 (8.1). Univariate analysis showed that there was a significant difference in means of QTc prolongation between G1 and the other two groups ( $P = 0.001$ ), but not between G2 and G3. This indicates that patients receiving methadone over 60 mg/day are at a risk of greater QTc prolongation.

**Conclusion:** Methadone can cause QTc prolongation in different doses. However, the extent of this effect is dose dependent. Daily dose of less than 60 mg methadone is a safer cardiac dose. Nevertheless, it is not possible to administer this low dose for all opioid addict patients. Therefore, it is necessary to closely monitor patients under MMT, especially those receiving higher methadone doses, with constant scheduled ECGs before and during treatment.

**Keywords:** Methadone; QT Interval; Methadone Maintenance Treatment; Torsades de pointes; QTc prolongation

## INTRODUCTION

Methadone is a synthetic opioid which has been used medically as an analgesic in severe and chronic pains and also as a maintenance treatment for opioid addiction (1,2). Methadone is known to cause adverse effects on various organs especially gastrointestinal, respiratory, cardiovascular and central nervous system (3). One of methadone side effects on cardiac system is rate-corrected QT (QTc) interval prolongation which may predispose patients to torsades de pointes (TdP) arrhythmia and sudden death (4). It has been ascertained that about 30% of patients treated with methadone are susceptible to experience QTc prolongation (5). Based on previous reports and studies, it can be said that higher doses of methadone (100-400 mg/day) are a strong risk factor of inducing QTc prolongation (5-9). However, in these studies, the exact dosage of methadone which can induce QTc prolongation has not been established.

Currently in Iran, use of methadone as a maintenance treatment in opioid addiction is becoming increasingly widespread. However, in methadone maintenance therapy (MMT) clinics, performing an electrocardiogram (ECG) on each patient before and during receiving methadone is not a standard routine. Therefore, QTc prolongation might become unnoticed. Moreover, because of prescription of other medications with cardiac effects during MMT, prolongation of QTc is a constant threat (10).

The lowest dose of methadone at which QTc prolongation occurs, has not been clearly established. This study is designed to investigate possible cardiac complications following methadone administration in different doses and to determine a safer methadone dosage without affecting QTc.

## METHODS

In this prospective comparative observational study, 90 opioid addict patients who were receiving methadone as

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Received 1 January 2013; Accepted 28 February 2013

maintenance treatment in Drug Dependence Treatment Clinic of Isfahan University of Medical Sciences were evaluated.

Patients were selected with simple random sampling method. Inclusion criteria were male patients who received methadone for at least 2 months, QTc (QT/ $\sqrt{RR}$ ) was normal in their baseline electrocardiogram, did not take daily medications which can potentially prolong QT interval including amitriptylin, nortriptyline, maprotiline, flouxetine, pimozone, risperidone, chlorpromazine, and did not have any predisposing factors of TdP arrhythmia. Patients who had to take medications with potential cardiac effects before and during MMT were excluded.

Patients were equally categorized into 3 aged-matched groups according to methadone daily dosage: 0-59 mg/day (G1), 60-109 mg/day (G2) and 110-150 mg/day (G3).

For each patient, two 12-lead ECGs were performed, baseline and 2 months after initiating the MMT, 4 hours after taking the maximum daily dose of methadone. The QT interval of baseline and follow-up ECGs was measured in lead II and QTc was calculated.

Confidence interval was considered as %95 and power coefficient as 80%. The difference between these intervals was evaluated with analysis of variance (ANOVA) test. Data were analyzed using Statistical Package of Social Sciences (SPSS) for Windows version 11.5 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Demographic

In total, 90 male patients were included with a mean (SD) age of 32.4 (8.5) ranging from 19 to 56 years. One-way ANOVA test did not show any significant difference among

mean age of three groups (Table 1). Mean (SD) duration of opioid addiction in our patients was 5 (2) years.

### Hemodynamic Findings

Mean systolic and diastolic blood pressures on admission were 123 (18) and 78 (5) mmHg and after two months of MMT were 117 (16) and 85 (5) mmHg respectively. There was no significant difference in systolic and diastolic blood pressure of patients before and after treatment. Mean heart rate during treatment in these three groups were 84 (9), 89 (11), 91(8) beats per minute which also did not show any significant difference among them.

### Electrocardiographic Findings

TdP arrhythmia was not seen in any patient. In total, mean QTc of patients before MMT was 405.2 (17.0) ranging from 360 to 440.3 msec and 2 month after initiating MMT was 418.5 (23.1) ranging from 362.3 to 466.2 msec.

Mean QTc in three groups before and after MMT are illustrated in table 2. As it is shown, there was a significant difference between mean values in each group before and after treatment ( $P<0.001$ ).

In total, mean QTc prolongation was 13.5 (8.1). Mean of QTc changes in each group are shown in table 3. Univariate analysis showed that there was a significant difference in means of QTc prolongation between G1 and the other two groups ( $P=0.001$ ), but not between G2 and G3.

## DISCUSSION

Methadone induces QTc prolongation by blocking rapid component of a cardiac potassium channel (IKr) which is active in cardiac action potential (11,12). Hence, terminal portion of the cardiac action potential (delayed repolarization) elongates which shows itself in the form of QTc prolongation on ECG (4,12).

**Table 1.** Comparison of age and heart rate among 3 dose-groups

Treatment Groups (daily dosage)	Age (year), mean (SD)	Heart Rate (beat/min), mean (SD)
G1 (0-59 mg/day)	32.6 (9.5)	84.3 (9.1)
G2 (60-109 mg/day)	31.2 (7.4)	88.9 (11.0)
G3 (110-150 mg/day)	32.6 (8.5)	90.2 (8.2)
P value	0.8	0.7

**Table 2.** Comparison of mean QTc before and after MMT

Treatment Groups (daily dosage)	Pre MMT QTc (msec), mean (SD)	Post MMT QTc (msec), mean (SD)	P Value
G1 (0-59 mg/day)	403.8 (20.8)	411.5 (23.8)	<0.001
G2 (60-109 mg/day)	405.8 (19.8)	421.4 (23.3)	<0.001
G3 (110-150 mg/day)	405.9 (16.1)	422.7 (22.3)	<0.001

**Table 3.** Mean QTc prolongation before and after MMT

Treatment Groups (daily dosage)	QTc prolongation (msec), mean (SD)
G1 (0-59 mg/day)	7.7 (6.3)
G2 (60-109 mg/day)	15.6 (9.5)
G3 (110-150 mg/day)	17.4 (8.6)

Mean QTc prolongation of G2 and G3 were significantly higher in comparison to G1 ( $P=0.001$ )

Normal QTc is defined as  $QTc \leq 430$  msec for males and  $\leq 450$  msec for females. Borderline QTc prolongation is considered as  $QTc = 431-450$  msec for males and  $451-470$  msec for females, while QTc prolongation is considered as  $QTc > 450$  msec for males and  $> 470$  msec for females (4). As QTc prolongs, the risk for life-threatening arrhythmias such as polymorphic ventricular tachycardia or TdP increases (4,5). Although TdP is mostly self-terminating, it may degenerate into ventricular fibrillation and subsequently sudden cardiac death. The risk of sudden cardiac death increases 4-fold when QTc is  $\geq 500$  msec (13).

This study was conducted to evaluate the effects of different doses of methadone on QT segment in patients under MMT. Our findings showed that methadone can prolong QTc in patients under MMT after reaching its maximum dosage in all 3 dose-groups. However, extent of this prolongation was significantly higher in patients who received over 60 mg daily methadone (G2 and G3). This indicates that patients receiving methadone over 60 mg/day are at a greater risk of QTc prolongation. Moreover, in all 3 groups, mean QTc was lower than 450 msec during MMT which shows that methadone below 150 mg/day is unlikely to induce QTc prolongation.

Methadone-induced QTc Prolongation has been reported in many studies (4-6,14,15). It has been revealed that methadone can cause a 12 to 42 msec increase in QTc (5). Similarly, in this study we found an average QTc increase of 13.5 msec in our patients.

TdP arrhythmia was not seen in any patient in our study, probably because mean QTc in all three groups before and after MMT were lower than 500 msec which has been accepted to be the threshold of inducing TdP (4,10,15). Correspondingly, it was demonstrated that in methadone treated patients who experienced TdP, the QTc ranged between 517 and 626 msec (5,14,17). Furthermore, in our clinic, maximum dosage of methadone administered to opioid addict patients (150 mg/day) is lower than what have been administered in previous studies (5-9,18). In this respect, in one study on 17 patients by Krantz et al., it was found that during daily administration of high-dose methadone (~400 mg/day), QTc increased to 616 msec which caused TdP (18). Similarly, Gil et al. reported 4 HIV positive cases receiving 200 mg/day methadone with these cardiac complications (6).

Besides, there are other predisposing factors of generating TdP arrhythmia including female gender (19), hypokalemia and sinus bradycardia (20-23), congenital heart failure (22), digoxin therapy (23), congenital long QT syndrome (24) and severe hypomagnesaemia (10) which were not present in our patients.

Recently, an independent panel of experts developed cardiac safety recommendations for physicians prescribing methadone (13). They recommended to physicians to: 1) inform their patients with history of arrhythmia about risks of methadone, 2) take a complete history of any previous structural heart disease, arrhythmia, and syncope from each patient, 3) obtain scheduled ECGs for all patients (before MMT, during the first month after initiating MMT and

annually) to measure the QTc, 4) monitor patients with QTc over 450 msec less than 500 msec frequently and discontinue or eliminate the dose of methadone in case of over 500 msec QTc, 5) update their knowledge about possible drugs with QTc prolonging properties or those which reduce the elimination of methadone (13). They also recommended obtaining additional ECGs and more vigilantly monitoring of patients who receive over 100 mg/day methadone as they are in more threat of QTc prolongation (13). This was very close and similar to over 60 mg/day methadone dosage which we found to be with lower cardiac safety.

## LIMITATIONS

In our clinic, patients under MMT do not receive methadone over 150 mg/day which is according to most recommendations. Since, this was an observational study; we could not evaluate the impact of daily methadone over 150 mg/day on QT segment. Moreover, in this study, subjects were categorized to 3 groups according to methadone daily dosage. These dose ranges were defined arbitrarily.

## CONCLUSION

Methadone can cause QTc prolongation in different doses. However, the extent of this effect is dose dependent. Methadone below 150 mg/day is unlikely to induce QTc prolongation and TdP. However, daily dose of less than 60 mg methadone seems to be a safer cardiac dose. Nevertheless, it is not possible to administer this low dose for all opioid addict patients. Therefore, it is necessary to closely monitor each patient under MMT, especially those receiving higher methadone doses, with constant scheduled ECGs before and during treatment.

## ACKNOWLEDGMENT

**Conflict of interest:** None to be declared

**Funding and support:** None

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