Original article

Evaluation of QTc interval in Iranian causalities *(Janbazan)* of Iran-Iraq war receiving maintenance methadone treatment

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Background: Methadone is a synthetic opioid, used in treatment of chronic pains. The current study was carried out to evaluate the QTc interval in Iranian causalities (Janbazan) of Iran-Iraq war receiving maintenance methadone treatment. **Materials and Methods:** In 2010, one hundred war causalities in Isfahan who chronically take daily dose of 20 mg or more of methadone (more than 2 weeks), and did not have the history of cerebrovascular or coronary artery diseases, cardiac pacemaker, congenital prolonged QTC, or taking drugs affecting QTc, or having electrolyte abnormalities, were selected for the study. An electrocardiogram was taken from each patient using cardiofax instrument, and QTC was calculated manually. The data was analyzed using SPSS software with descriptive statistical methods and Pearson's correlation coefficient. **Findings:** All patients were male and had the mean age of 45.6 ± 6.1 years. The patients received 20-240 mg methadone daily for 1 to 108 months. The QTc was prolonged in 25% of the patients (QTc ≥ 450 ms), with the mean of 472.72 ± 18.5 ms (range 450-508 ms) and the mean daily dose of methadone 85.2 ± 59.0 mg. No significant relationship was observed between QTC interval on the one hand, and methadone dose ($R = 0.025$, $P = 0.8$), duration of treatment ($R = -0.048$, $P = 0.68$), age ($R = 0.037$, $P = 0.71$), and weight ($R = 0.1$, $P = 0.21$) of the patients, on the other hand. None of the patients had faint, syncope, arrhythmia, or sudden death. **Conclusion:** Oral methadone causes prolongation of QTC interval. However, the dosage of methadone and duration of treatment were not statistically related to QTC interval.

Key words: Methadone maintenance treatment, methadone, prolonged QTC interval, war

INTRODUCTION

Methadone is a synthetic opioid that is extensively used for maintenance treatment of addicts and also as a palliative analgesic. Many retrospective and prospective studies have shown that the drug may prolong the rate corrected QT interval (QTc) in electrocardiography (ECG) and also leads to *torsade de pointes* cardiac arrhythmia and consequently sudden death.[1-8] Although many drugs can prolong QTc interval, development of *torsade de pointes* arrhythmia is the result of several factors including hypokalemia, structural cardiac diseases, bradycardia, hepatic inhibitors of cytochrome P450 (CY P450), and the genetic susceptibility.[1]

Mechanism of QTc prolongation and development of *torsade de pointes* arrhythmia by methadone is inhibition of the human *Ether-à-go-go* Related Gene (hERG).[1] The gene encodes *IKr* mediator, and inhibition of the gene leads to blockage of transferable potassium flow through this potassium channel. Blockage of this cardiac ion channel in turn leads to prolongation of the end part of cardiac action potential and then delayed repolarization, which is represented in ECG as prolongation of QTc interval. Because of hERG polymorphism in some races, these channels may be more susceptible to blockage by methadone.[1,5,9,10] Furthermore, since methadone is metabolized in liver by CY P450, inhibition of CY P450 as a result of any liver abnormality or the drugs that interact with the enzyme system, will lead to an increased serum level of methadone.[1,5,11]

In addition to the effect of methadone on cardiac repolarization through blockage of hERG channels, methadone makes a person more susceptible to *torsade de pointes* arrhythmia with other mechanisms. The

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arrhythmia develops in patients with bradycardia more frequently, and with producing negative chronotropic effects via calcium channel antagonism and anti-cholinesterase effect, methadone leads to bradycardia.[1]

The International Regulatory Guidance for Drug Development suggests QTc interval of 450 ms as the threshold of QTc prolongation without considering sex differences.[1,2,4] Moreover, the QTc interval of more than 500 ms is considered as the consensus threshold for the significant risks of arrhythmia, including syncope and sudden death, probably as the result of *torsade de pointes*.[1,5,6] Some conditions which lead to acquired prolongation of QTc interval include structural diseases of heart including heart failure and left ventricular hypertrophy, and myocardial ischemia or infarction in an acute phase (up to 3 months), as well as stroke and HIV infection. Electrolyte abnormalities (hypomagnesemia, hypokalemia, and rarely hypocalcemia) and drugs (antiarrhythmic, antimicrobial, antihistamine, psychotropic and antidepressant, diuretic and other drugs) also cause prolongation of QTc interval.[12] In our country, two main groups of patients generally take long term high doses of methadone; addicts and those who take the drug for tolerating chronic intolerable pains. The latter group includes many of the casualties of Iran-Iraq war, who have to take the medicine to control their physical and psychological injuries (PTSD), resulted from the war. In the current national protocol, screening for *torsade de pointes* is not performed in these patients. Moreover, taking various drugs, such as benzodiazepines, antidepressants [tricyclic agents and selective serotonin release inhibitor (SSRIs)], non-steroidal anti-inflammatory drugs (NSAIDs), other opioid analgesics increases the risk of cardiac arrhythmia. Considering these points and also the genetic susceptibility for *torsade de pointes*, the current study was performed to determine the QTc interval in Iranian casualties (*Janbazan*) of Iran-Iraq war who take long term methadone. An aim of the study is to determine the relationship between the QTc interval on the one hand, and dosage and duration of taking the drug on the other hand.

MATERIALS AND METHODS

This cross-sectional study was performed on the Iranian casualties of Iran-Iraq war who take daily dose of 20 mg or more of methadone for more than 2 weeks, and in 2010, referred to health centers affiliated with Isfahan Province *Bonyad-e Shahid va Omur-e Isargaran*.

Inclusion criteria: The war casualties who received daily 20 mg or more of methadone for more than 2 weeks and took the drug daily. Moreover, in history and in physical examination, they should not belong to the following groups:

- Taking drugs that prolong QTc interval, including: Antiarrhythmic, antimicrobial, antihistamine, psychotropic and antidepressant, diuretic and other drugs, 2- An ischemia or infarction in the past 3 months, 3- Stroke, 4- HIV infection, 5- Structural heart disease including heart failure or left ventricular hypertrophy.

Exclusion criteria

1- Having pacemaker, 2- Existence of cardiac arrhythmia or block, 3- Hypokalemia (K < 3.5 mmol/lit), 4- Hypomagnesemia (Mg < 1.2 mg/dl), 5- Hypocalcemia (Ca < 8.5 mg/dl), 6- Signs of left ventricular hypertrophy in ECG, and 7- Suspicious of congenital long QT syndrome according to history and physical examination, and biphasic or notched T wave in ECG (at least in 3 leads).

By attending the war casualties care center (with gaining the satisfaction), the files of casualties were evaluated by the researcher. Then, a check list was devised to collect the data. Then, 100 patients who met the inclusion criteria were consecutively selected for the study. In the following, they were visited by a general practitioner and then were referred to an assistant physician for further evaluations. The assistant visited the patients and took a complete drug history. If a patient used one of the drugs that may cause QTc prolongation or had one of the exclusion criteria, the patient was excluded. After taking a complete history, a physical examination was performed, and the patients were evaluated for the signs of heart failure including S3 gallop, elevated jugular venous distention, and crackles upon auscultation or the signs of left ventricular hypertrophy in ECG or cardiomegaly in CXR. In case of having any of the signs indicating heart failure, the patient was excluded from the study. The patients were then asked to lay down on the bed for 5 minutes and a 12-lead ECG was taken using cardiofax instrument, and QTc interval was manually calculated according to the Bazett's formula ($\frac{QTc}{\sqrt{R}}$). After that, a blood sample was taken and sent to the laboratory for determination of albumin, calcium, and magnesium levels using calorimetric method with the autoanalyzer instrument and the level of potassium using the Flame method.

The researcher-devised check list included items such as age, weight (using Jupiter digital instrument), daily dosage of methadone (mg), duration of drug taking; history of cardiac arrhythmia, faint, syncope, or any decreased consciousness level, history of hospital admission for any cause, and drug history other than the agents mentioned above and other opioids. The data was collected by the researcher and recorded in the check list. The data was analyzed using SPSS statistical package for the social sciences, IBM Company, version 15, United States software with descriptive statistical methods and Pearson's correlation coefficient.

Findings

The 100 patients studied were all male, with an age range of 33 to 77 (mean ± SD 45.6 ± 6.1). The weight range of the patients was 51 to 110 kg (mean ± SD 74.3 ± 10.9). The daily methadone dosage of the patients was 20-240 mg (mean ± SD 85.4 ± 65.4 mg), and the duration of methadone taking was 1 to 108 months (mean ± SD 17.5 ± 18.1). The QTc interval calculated was in the range of 357-508 ms (mean ± SD 431 ± 31.53 ms).

The QTc interval of 25 patients (25%) was equal to or longer than 450 ms [The International Regulatory Guidance for Drug Development suggests QTc interval of 450 ms as the threshold of QTc prolongation without considering sex differences[1,2,4]]. 2 patients had QTc equal to or longer than 500 ms. No statistically significant relationship could be found between QTc interval on the one hand, and daily dosage of methadone ($R = 0.025$, $P = 0.8$) , duration of taking the drug ($R = -0.048$, $P = 0.68$), patients' age ($R = 0.037$, $P = 0.71$), and patients' weight ($R = 0.1$, $P = 0.21$), on the other hand. For the 25 patients with QTc interval equal to or longer than 450 ms, the mean (± SD) age, weight, daily dose of the drug, duration of taking the drug, and QTc interval were obtained to be 45.6 ±7.1 years, 75.4 ± 9.7 kg, 85.2 ± 59.0 mg, 16.04 ± 15.4 months, and 472.72 ± 18.5 ms, respectively. No statistically significant relationship could be found between two groups of patients (QTc≥ 450 and QTc < 450) according to dosage and duration of methadone, patients' age and weight Table 1. The 2 patients with QTc interval equal to or longer than 500 ms were 41 and 44 years old, had 68 and 75 kg weight, and used the daily dose of 40 and 60 mg for 30 and 36 months, respectively. None of the patients reported faint, syncope, palpitation attacks, or ataxia. Moreover, there was no report of sudden death, receiving cardioversion shock or hospital admission due to arrhythmia in these patients, and all the patients studied were asymptomatic.

DISCUSSION

According to the results, methadone led to QTc interval prolongation in 25% of the war casualties studied. However, no statistically significant relationship could be found between QTc prolongation on the one hand and methadone dosage, duration of treatment, and patients' age on the other hand. Several large studies have been carried out to evaluate the relationship between the methadone duration of treatment and dosage on the one hand and QTc interval prolongation on the other hand. Some have reported significant relationship while others could not find such relationship.[1,5] In the study carried out by Maremmoni *et al*. on 83 patients, who on average received daily 87 mg methadone (ranging from 10-600 mg/day), it was showed that 83% of the patients had QTc interval longer than the standard value for their age and sex. Nevertheless, the relationship between the QTc interval and methadone dosage was not statistically significant.[13] Peles *et al*. performed a study on 138 patients who on average received daily 170.9 mg methadone (40-290 mg/day). They found a weak relationship between the QTc interval and dosage of methadone. However, the relationship was not statistically significant ($P = 0.1$, $R = 0.13$).[6] In another study, Huh *et al*. evaluated 130 patients, out of whom 90 patients used on average 30 mg methadone daily (5-80 mg/day). They also could not find a statistically significant relationship between methadone dosage and QTc interval ($P = 0.9273$).[5] In contrast, in some other study, an obvious relationship was found between methadone dosage and QTc interval. For instance, Ehret *et al*. studied 247 hospitalized patients, among whom 167 patients received on average 100 mg methadone daily (4-600 mg/day), and reported a statistically significant relationship between methadone dosage and QTc interval ($P < 0.01$, $R = 0.2$).[14] In the study carried out by Cruciani *et al*. on 140 patients with the daily average receive of 110 mg methadone (20-1200 mg/day), it was observed that there was a statistically significant relationship between methadone dosage and QTc interval ($P = 0.0009$, $R = 0.86$).[15] Martell *et al*. carried out 2 studies; one on 132 patients with the daily dose of 30-150 mg/day of methadone and the other one on 160 patients with an average daily dose of 90 mg (20-200 mg/day), and reported a significant relationship between methadone dosage and QTc interval ($P = 0.03$, $R = 0.18$).[16,17] In several published cases and case reports, it has been reported that methadone with the daily doses of above 100 mg can cause *torsade de pointes* arrhythmia and by reducing the methadone dose, the QTc interval became normal.[18-20] Fanoe *et al*. reported that the QTc interval increased 10 ms by an increase of 50 mg in methadone dose (CI: 1.1-1.4, odds ratio: 1.2).[21]

Table 1: The relationship between two groups of patients (QTc ≥ 450 and QTc < 450) according to dosage and duration of methadone use, patients' age and weight

Patient	QTC<450	QTC≥ 450	*P* value*
Age (year)	45.5 ± 5.7	45.6 ± 7.1	$P > 0.05$
Weight (kg)	74.02 ± 11.31	75.4 ± 9.7	$P > 0.05$
Methadone dose (mg)	85.4 ± 67.7	85.2 ± 59	$P > 0.05$
Duration of taking Methadone (days)	17.9 ± 19.08	16.04 ± 15.4	$P > 0.05$
Interval QTC (ms)	417.42 ± 21.08	472.72 ± 18.5	$P > 0.05$
Range of QTC (ms)	357-449	450-508	$P > 0.05$

*independent *t*-test

The above-mentioned studies were performed in prospective and retrospective manner and under various conditions, and a general conclusion cannot be obtained from them. However, it is important for physician to know that sudden death have been reported with methadone even at the dose of 29 mg/day.[1] This suggests that arrhythmia may occur in a wide range of therapeutic doses, including the doses frequently used in treatment of chronic pains and addicts.[1,22,23] As it was mentioned, in the current study, a significant relationship could not be found between the prolongation of QTc interval on the one hand, and dosage of methadone, duration of taking the drug, and the patients' age on the other hand. It was demonstrated that QTc prolongation may occur at the mean daily methadone doses of 85.2 ± 59.0 mg; therefore, a safe dose cannot be suggested in this respect. The current study had some limitations in its methodology; for instance, lack of baseline ECG. But, as it was mentioned in the Methods section, we tried to reduce the confounding variables as much as possible by performing physical examination and history taking, evaluation of serum electrolyte levels, and exclusion of patients who received drugs that may prolong QTc interval.

As it was mentioned, electrolyte abnormalities like hypokalemia and also some drugs, such as tricyclic and tetracyclic antidepressants, SSRIs, antipsychotic agents, anti-arrhythmic drugs, antibiotics, and antihistamines may lead to QTc interval prolongation. These conditions and agents may interact with methadone in QTc prolongation,[1,5,12] .herefore, to prevent cardiac arrhythmia and sudden death in those taking methadone, suggestions are provided:

In a study, replacement of R-S-methadone with R-methadone was suggested[24,25] since it seems that R-methadone leads to hERG channel block less frequently.

The authors provide the following recommendations for prevention of cardiac arrhythmia and sudden death in war casualties and those who receive methadone for any cause. The suggestions can be employed as a screening protocol by physicians prescribing methadone: (1)

Suggestion 1

Physicians are better to take a complete history of the patients on the history of structural diseases of heart, arrhythmia, and syncope. Physicians are better to warn patients on the risk of cardiac arrhythmia occurrence. Physicians should be aware of drug interactions of methadone with the agents which may prolong QTc interval or decrease an excretion of methadone.

Suggestion 2

Before initiating methadone, take an ECG from the patient and calculate the QTc interval. Moreover, in the follow-ups, one month after initiating the drug and annually, take ECG. In case of taking methadone doses above 100 mg or an occurrence of unexplainable syncope or convulsion, taking ECG at shorter intervals is recommended. If the QTc interval was more than 450 ms and less than 500 ms, the risks and benefits of the drug should be explained to the patient and monitor him / her more closely. If the QTc interval became more than 500 ms, the drug should be discontinued or the dose be reduced. Furthermore, the predisposing factors of hypokalemia should be removed, and if drugs with the risk of QTc prolongation are used simultaneously with methadone, they or methadone should be discontinued and an alternative medicine be prescribed.

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