

## QTc Prolongation in Acute Methadone Poisoning

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### ARTICLE INFO

*Article Type:*  
Case Report

*Article History:*  
Received: 9 Aug 2013  
Revised: 28 Aug 2013  
Accepted: 9 Sep 2013

*Keywords:*  
Methadone  
Arrhythmia  
ECG Changes

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### ABSTRACT

**Background:** Methadone is considered as a good choice for maintenance treatment program (MMTP) in opioid addicted individuals. QT interval prolongation was reported previously in methadone chronic users especially in high dose prescription. QT-interval prolongation predisposes patients to lethal dysrhythmia. This is a report of corrected QT (QTc) prolongation due to acute methadone poisoning. To the best of our knowledge, in review of literatures, there is no previous report of QTc prolongation in cases that are not on chronic methadone therapy.

**Case Report:** The patient was a 20 years old man who has occasionally used opium and ice since 8 month before admission. One night before admission he consumed ice and found psychotic state so he was referred to the addiction treatment center and they put him on methadone maintenance treatment with high dose of methadone. After 40 minutes the patient was drowsy and then hypopnea was started. The patient was referred to the hospital and resuscitation was done after naloxone prescription. After stabilizing general conditions the electrocardiograph shows QTc prolongation which was returned to normal status after 2 days. After 5 days the patient was transferred to psychiatric service with normal sinus rhythm and stable condition.

**Conclusion:** QT interval prolongation in chronic methadone maintenance therapy is defined previously especially in patients on other drugs that interact with the CYP3A4 isoenzyme system and who are on high dose methadone treatment, but it seems that acute methadone intoxication also may prolong the QT interval which should be investigated in future studies.

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► *Implication for health policy/practice/research/medical education:* QTc Prolongation in Acute Methadone Poisoning

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► *Please cite this paper as:* Salimi A, Okazi A. *QTc Prolongation in Acute Methadone Poisoning. International Journal of Medical Toxicology and Forensic Medicine.* 2013; 3(4): 135-139.

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### 1. Introduction:

Opioids are broad class of agents which are available in various formulations.

Natural, synthetic and semi-synthetic remedies are used for different therapeutic purposes for a long time. In addition to therapeutic effects, opioids are associated with various adverse and toxic effects that some of them can also occur even at therapeutic doses. Cardiovascular complications, convulsion, respiratory depression, dysphoria, hypoglycemia, miosis, gastrointestinal motility disorders, and hypothermia are some of these effects (1). Methadone is a synthetic opioid which is used for chronic pain control and treatment of opioid dependency. Analgesic properties of methadone are about 100 times greater than morphine. Because its features, methadone is considered as a good choice for methadone maintenance treatment program (MMTP) in addicted individuals. Although methadone therapy is the most successful method for opioid replacement, but still some patients continue to use opioids (2). Excessive consumption of methadone and the co-ingestion with other sedatives induce complications like decreasing level of consciousness, and symptoms will respond quickly to treatment with naloxone, but due to short term effects of naloxone and long half-life of methadone, antidote in methadone poisoning should continue longer than other short half-life opioids (3).

Therapeutic doses of methadone (100mg per day) interference with normal heart repolarization and increase the QTc interval. These factors predispose patients to lethal arrhythmia such as Torsades de pointes (4). Positive genetic factors and congenital long-QT syndrome before initiation of methadone play a role in creating this problem (5).

The basic ECG prior to treatment can predict the risk of arrhythmia. Due to the low cost of this non invasive method, ECG has been performed as a screening test in these patients. ECG test should be taken at the beginning and after 30days of treatment (5).

## 2. Case Report:

The patient was a 20 years old man who used ice and opium intermittently. One day before hospital admission, the patient smoked ice and became agitated and found psychotic states. The next day, the patient's family took patients to addiction treatment center at 11am. Methadone maintenance treatment was started for the patient and the doctor gave him 50mg of methadone syrup. After about 40minutes the patient was sleepy and after about 1.5 hours the level of consciousness and the respiratory rate were decreased. The patient referred to the hospital and dramatically responds to 0.8mg intravenous naloxone. Patient's family discharged patient with self-consent but after about 5 to 6 hours they brought him back with cardiopulmonary arrest. On arrival, the cardiopulmonary resuscitation was started and 2mg naloxone was prescribed after intubation. The patient had a good response to resuscitation except a wide complex arrhythmia in electrocardiogram; but after about an hour it changed to normal sinus rhythm (Figure 1). According to the recovery of consciousness and respiratory status, patient was extubated after 2-3 hours.

The first laboratory investigations revealed normal levels of electrolytes. Patient was admitted to IUC with naloxone drip infusion with no withdrawal symptoms.

Laboratory data was as below:

BS: 93 mg/dl

Ca: 8.6mg/dl

Mg: 2.6mg/dl

Cl: 96mEq/l

PH: 7.2

PCO<sub>2</sub>:42.2mmHg

HCO<sub>3</sub>:16mmol/L

HB: 12.5

WBC: 9300

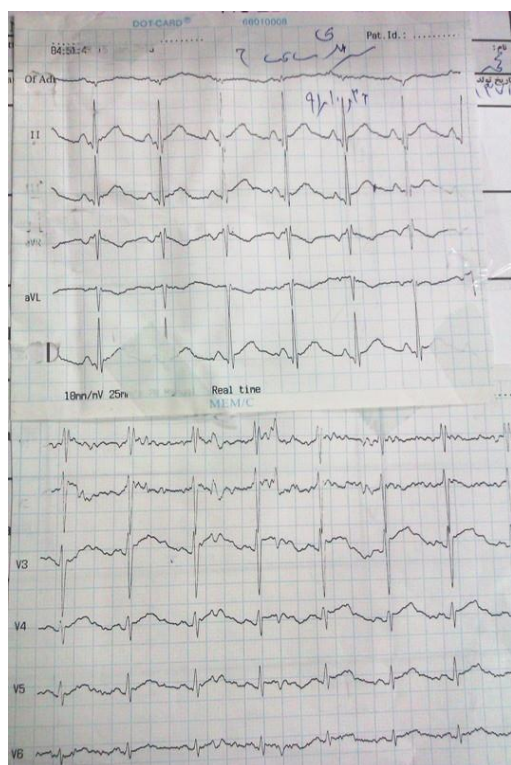
Plt: 204000/L

AST: 46 IU/L

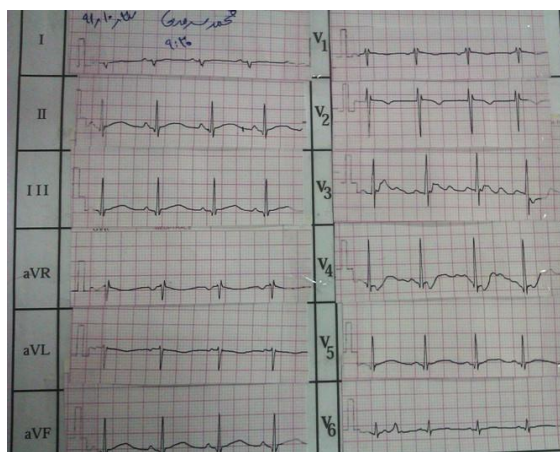
ALT: 29 IU/L

PT: 15.6 seconds

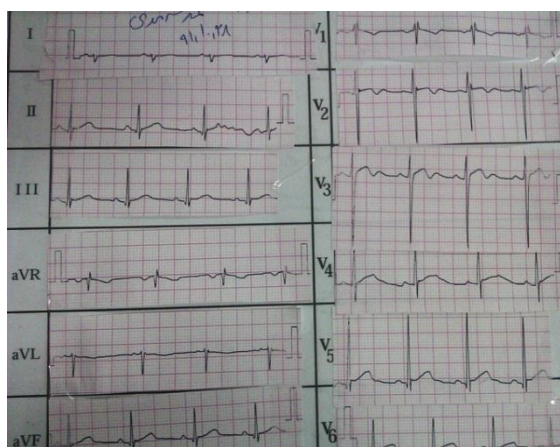
PTT: 37seconds



**Fig. 1.** ECG after 19 hours of ingestion.



**Fig. 2.** ECG after 46 hours of ingestion.



**Fig. 3.** ECG after 70 hours of ingestion.

After 33 hours, QTc interval in ECG became prolonged (523 ms) and remained prolog next day and became normal after 2 days (Figure 2). Urinary and serum screening for other drugs were negative, even in terms of opium. The patient had positive history of previous clonazepam, opium and ice consumption but he had not used methadone previously.

Laboratory data during prolongation of QT interval was as below:

Ca: 9mg/dL

K: 4.3mEq/L

Mg: 2mg/dL

After 70 hours, ECG changes resolved (Figure 3) and after 5days he was transferred to the psychiatric service with good general condition.

### 3. Discussion:

Addiction or drug dependency is one of the most important health problems in the world (6). Methadone is a synthetic long acting agonist of opium with half-life of about 24 to 36 hours, which is prescribed for controlling the withdrawal symptoms of opioid dependent patients and chronic pain (7, 8). Administration of 20 to 80mg of methadone per day can stabilize the patient's symptoms (9). Numerous studies have demonstrated the effectiveness of MMT for reducing illicit opioid use, morbidity and mortality, risk of human immunodeficiency virus (HIV) infection, illegal activities, and improving overall functioning (10). However methadone has some adverse effect especially in high dose administration, like: respiratory depression, respiratory arrest and even death (11). In addition to respiratory effects, it appears to be associated with prolongation of the QTc interval during methadone maintenance therapy. The mechanism of this phenomenon is an inhibition of delayed rectifier potassium ion current which facilitates the bradycardia dependent TdP-VT (12, 13). Methadone like many other drugs which reported to cause torsade de pointes, is metabolized by the CYP3A4 isoenzyme. These include some psychiatric drugs,

antibiotics, antihistamines, which have proarrhythmic action due to blocking affects on the potassium currents (14) Drugs that interact with CYP3A4 may increase serum methadone level and cause toxicity (15). There are some other predisposing factors for QT prolongation and TdP in methadone users like, congenital long QT syndrome, hypokalemia, bradycardia and cocaine abuse (16). Experimental studies have shown that cocaine and methadone prolong the QT interval through the same mechanism (17). In recent years the role of Torsade de pointes (TdP) and severe ventricular arrhythmias, has been determined in the deaths of patients who are on chronic methadone treatment (18). It is important to take a 12 lead ECG and determine the QT interval before methadone maintenance therapy and it must be repeated during treatment. This is more important in patients who receive high dose methadone in long period of time. However it seems that the evaluation of electrocardiogram and QT interval in patients with loss of consciousness due to acute methadone poisoning especially in simultaneous consumption of methamphetamine could help the physicians to determine the ECG changes in early stages of poisoning so the excess diagnostic and therapeutic measures could be under taken in proper time. Furthermore, these changes may lead to morbidity and mortality in these patients and with identifying of them, treatment plans can be designed in better way.

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