Electrocardiographic Findings in Patients with Acute Methadone Poisoning

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A R T I C L E I N F O

Article Type:
Original Article

Article History:
Received: 12 Dec 2013
Revised: 26 Dec 2013
Accepted: 3 Jan 2014

Keywords:
Methadone
Electrocardiogram
Acute poisoning

A B S T R A C T

Background: Methadone as a synthetic opioid is widely used for treatment of opioid dependency. One of the causes of methadone related sudden death is cardiac toxicity. This study was aimed to determine the electrocardiographic changes in acute methadone poisoning.

Methods: This is a cross sectional study on patients older than 12 years old with acute methadone poisoning who were admitted in Loghman poisoning center at 2010-2011. Data analysis was done by means of SPSS version 16 and appropriate statistical tests at the significant level of $P<0.05$.

Results: In one year period, 51 patients with mean age of 40.59±18.27 (31-51) years, including 39 males, with acute methadone poisoning were included in to the study. Seven patients (13.7%) were acutely poisoned, 29 patients (56.8%) had acute on chronic methadone poisoning and others had not reliable history. The mean time of PR, QRS and QTc were 150.2±34.22, 77.06±13.89 and 421.76±43.04ms, respectively. The prolongation of PR, QRS and QTc were observed in 9.8%, 1.96% and 17.6% of patients, respectively. A significant statistical association was observed between PR prolongation and type of poisoning and QRS prolongation and outcome ($P=0.035$ and 0.009).

Conclusion: The findings of this study indicate the occurrence of cardiac toxicity in patients with acute methadone poisoning. Further studies are required on acute methadone poisoning in patients with known previous cardiac status.

►*Implication for health policy/practice/research/medical education:* Electrocardiographic Findings in Patients with Acute Methadone Poisoning

► *Please cite this paper as:* Salimi A, Okazi A, Sangsefidi J. *Electrocardiographic Findings in Patients with Acute Methadone Poisoning. International Journal of Medical Toxicology and Forensic Medicine*. 2014; 4(1): 11-16.

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1. Introduction:

Methadone is a synthetic opioid which has agonist effects on opioid receptors (1). Because of its long half-life, affordability and its efficacy -in case that other opioids

are not efficient as an analgesic- using this drug has been increased (2, 3). The most use of it is for opioid dependency. Inattentive use an overuse of methadone could cause death (4). There was a 39% increased overdose death rate for methadone from 1999 to 2004 (5). Methadone is associated with cardiovascular complications, even in therapeutic doses. One of these effects is low blood pressure, which seems to be caused by the release of histamine, but not by opioid receptors. Rapid intravenous administration of this drug can cause bradycardia and respiratory failure. Methadone, especially in therapeutic dose has interference with heart repolarization and caused increased QT interval. This factor predisposes patients to arrhythmias such as Torsades de point (6).

Status of the patient's ECG before starting treatment could reasonably predict the possibility of arrhythmia. Due to low prices and invisibility of this test, ECG has been accepted as a screening test and patients may undergo it at the beginning and also after 30 days of treatment (7).

To the best of our knowledge, most of the previous studies were conducted on patients who had suffered cardiac complications of chronic long-term methadone therapy and no one had evaluated cardiac complications in patients who were acutely poisoned with methadone (8, 9).

Knowing the ECG changes, especially in patients with unknown poisoning and loss of consciousness, can lead us to better management and early diagnosis. Furthermore, these changes may have a role in increasing the patient's morbidity and mortality. So the aim of this study is the evaluation of ECG changes in acutely poisoned patients with methadone.

2. Materials and Methods:

This cross sectional study was conducted upon the over 12 years old patients which had referred to the poisoning center of Loghman Hospital with clinical manifestation of the methadone poisoning during 2010-2011. Patients with acute methadone intoxication who have consumed other drugs or substances or have underlying diseases were excluded from the study.

The main variable consisted of age, sex, case number, initial symptoms, the patient's clinical manifestations, vital signs, therapeutic and protective actions including intubation, mechanical ventilation, received naloxone and its duration, history of previous use of methadone, medical history, diagnostic procedures including arterial blood gas, ECG, electrolytes, and blood biochemistry, side effects of poisoning, and the prognosis were inserted in to the check list and analyzed by a statistical software, SPSS v. 16, through t–test for quantitative variables and chi^2 for qualitative variables and regression.

It should be noted that all the provisions of the Helsinki Declaration on research projects has been respect in this study. Name and personal information of all patients were maintained.

3. Results:

In this one-year period study, 51 patients were enrolled. The mean of patient's age was 40.59±18.27 years (range: 13 to 51 years). There were 39 (76.5%) men and 12 (23.5%) female. The average period of time between methadone consumption and hospital admission was 10.36±7.97 hours (1 to 72 h).

Seven patients (13.7%) had no history of methadone use, and they were acutely poisoned. Twenty nine patients (56.8%) were chronic methadone users and were being referred to our center as an acute on chronic poisoning. The histories of methadone usage in 15 (29.5%) other patients were not available.

Vital signs and examinations on admission

Twenty patients (39.2%) were conscious on arrival. Table 1 shows the state of consciousness at the time of admission.

The average of pulse rate was 87±14 and respiration rate was 15±6 per minute,

Table 1: Frequency and percentage of consciousness at arrival to the emergency.

Level of consciousness	Frequency	Percentage
Alert	20	39.2
Lethargic	19	37.3
Response to painful stimuli	7	13.7
Coma	4	7.8
Coma + Abnormal vital signs	1	2.0
Total	51	100.0

Table 2: lab data of patients.

variables	number	min	max	mean	S.D.
Blood sugar	48	67	336	123.6	53.5
Na(meq/L)	50	118	154	141.9	6.2
K(meq/L)	50	3.1	6.2	4.38	0.69
Ca(meq/L)	14	7.2	9.8	8.40	0.7
P(meq//L)	9	2.2	7.0	3.41	1.6
SGOT	23	16	3450	375.5	911.5
SGPT	23	10	3950	442.3	989.4

systolic blood pressure was 112.6±13 and diastolic blood pressure was 71.8±10 mm Hg.

One patient (2%) experienced hallucination, 4 (7.8%) experienced agitation and 29 patients (56.9%) were lethargic. Also, 4 patients (7.8%) had convulsive attacks, 3 (5.9%) had ataxia, 9 (17.6%) had apnea, 7 (13.7%) developed gasping respiration, 13 (25.5%) had dyspnea, 14 (27.5%) had bradypnea and 16 (31.4%) had cyanosis. None of the patients had diarrhea or itching. Vomiting was observed in 3 patients (5.9%). Miotic pupils were seen in 26 patients (76.6%). Fourteen (27.5%) patients had mid-size pupil and only one patient had mydriasis. All patients responded to light.

Seventeen patients (33.3%) due to respiratory depression underwent intubation. Twenty three patients (45%) were treated with naloxone.

Lab data

The acid base titer was evaluated on arrival and the result is: the mean of bicarbonate was 25.3±5.6, arterial CO_2 pressure was 49.9±14.3 and PH was 7.3±0.11, respectively.

Other laboratory data are shown in Table 2.

ECG findings

The first ECG of patients were studied in point of arrhythmia and some important indicators. Mean of QRS intervals was 77.06±13.89ms, and mean of PR intervals was 150.2±34.42ms, respectively. Mean of QTC interval was 421.76±43.04.

In view of the considering PR> 200 as prolonged PR interval, only 5 patients (9/8%) had prolonged PR. Wide QRS (greater than or equal to 120 milliseconds) was observed in only one patient. Prolonged QTc interval (greater than or equal to 450ms) was observed in 9 patients (17.6%).

The most common arrhythmia which observed in ECG of patients, were sinus tachycardia, U wave, T inversion and RBBB. Table 3 shows the common arrhythmia in our cases. None of the patients had WPW, LBBB, PVC, PAC and Brugada syndrome.

Complications and outcome

During hospitalization which lasted for about 138.62±110.9 hours, 7 patients (13.7%) developed ARDS symptoms and 5 patients (9.8%) had found pneumonia.

Table 3: The most common arrhythmia which observed in ECG of patients.

	U wave	Sinus tachycardia	T inversion	RBBB	AF	Early repolarization	ST depression	Block grade 1
Frequency	8	8	8	5	2	4	2	1
percentage	15.7	15.7	15.7	9.8	3.9	7.8	3.9	2

Table 4: ECG changes and patient's prognosis.

ECG	ECG change	Discharged	Died	Refer to other wards	total	P Value
PR interval	Normal	36(81.8%)	3(6.8%)	5(11.4%)	44(100%)	0.5
	Prolong	5(100%)	0	0	5(100%)	
QRS interval	Normal	41(82%)	4(8%)	5(10%)	50(100%)	0.009
	Prolong	0	1(100%)	0	1(100%)	
QTc interval	Normal	34(81%)	4(9.5%)	4(9.5%)	42(100%)	0.9
	Prolong	7(77.8%)	1(11.1%)	1(11.1%)	9(100%)	

Renal failure, DIC and liver failure was observed in 3 patients (5.9%). One person found sepsis.

41 (80.4%) patients were discharged in good condition. 5 cases (9.8%) died and others were taken to hospitals in other sectors.

Analytic study

No significant correlation was found between the mean of PR, QRS and QTc intervals based on acute or acute on chronic toxicity (Independent Samples T test).

Prolonged PR interval was seen in 2 patients with acute poisoning. None of acute on chronic patients had prolonged PR. This finding was statistically significant (Fisher's Exact Test, P Value=0.035).

Prolonged QTc was observed in 2 patients with acute toxicity and 2 patients with acute on chronic intoxication. No significant relationship was observed between QTc prolongation and toxicity (Fisher's Exact Test, P Value= 0.1).

Prolonged QRS was observed in one patient. Previous history of methadone consumption in this patient was unknown.

The relationship between PR, QRS and QTc intervals with patient's prognosis was shown in table 4. Based on available data, significant correlation was found between increased QRS and outcome of poisoning (P Value= 0.009).

4. Discussion:

Methadone as a synthetic opioid analgesic which has a prolong elimination half-life is an appropriate treatment for opium addiction.

Many studies have been reported the role of methadone as an induced factor in cardiac arrhythmias, prolonged QTc and torsade de pointes (10- 12), although some of these findings could be due to other causes of arrhythmias, such as hypokalemia, heart failure and other variables (13).

The mean PR, QRS and QTc interval was 150.2±34.42, 77.06±13.89 and 421.76±43.04ms, respectively. Increased QRS time was observed in only one patient. QTc prolongation was observed in 9 patients (17.6%). In a previous study in Iran, prolonged QTc was seen in 25% of chronic methadone abusers. Mean of QTc interval was reported 472.72±18.5ms in this study (13).

Fareed *et al* have reported the prolongation of QTc interval in 33% of patients who were on methadone maintenance therapy (MMT) (11). Results of a study on 180 patients who were on MMT showed that 11.1% of them had a prolongation in QTc

interval (14). The differences observed in our study and other reports related to many factors including dose of methadone that unfortunately, this study had a limited access to this variable. The results of a controlled study on patients who were receiving low-dose methadone showed that low doses of methadone has not been associated with an increase in QTc (15).

In our study, the most common arrhythmia which were seen in patients on admission include sinus tachycardia, U waves, and reverse T respectively (each of them 15.7%).

In this study, despite appropriate supportive treatment, 5 patients died. In a previous study that had been conducted in Western Australia, 18 cases of methadone poisoning deaths were reported from 1975 to 1980 (16). In South Australia during 1984 to 1994, 9 patients died due to drug toxicity and 12 patients was lost because of toxic effects of overdose of methadone syrup (17).

The result of a study carried out in 2005 in America, showed that deaths from methadone than other drugs declined between 1998 and 2002 (18). Although the widespread use of methadone results in reducing deaths from heroin, but unfortunately methadone is a toxic agent. Based on reported deaths due to methadone in 1996, methadone is known as seventh cause of deaths from drug abuse (19). In a 16-year period (1993 to 2008), 1307 deaths in Scotland and 4317 deaths in England had been reported from methadone overdose (20).

One of the limitations of this study is the lack of information about the administration dose of methadone among our patients. More attention on ECG is required in further studies on patients who have a history of methadone consumption or patients with symptoms of poisoning that use methadone for the first time.

The methadone is an acceptable drug for MMT; however cardiac evaluation must be done regularly at the beginning of the therapy and within the MMT process.

The results of this study, due to some agreement with previous studies, can be helpful for the design and definition of future research goals.

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