

# Methadone Overdose and Its Complications in Patients Admitted to the Toxicology Emergency Ward of Baharloo Hospital of Tehran in 2011-2012

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## ABSTRACT

**Background:** To date, studies on methadone overdose in adults have not been reported in Iran. Hence, this study was performed to determine the frequency of methadone overdose and its associated complications in Baharloo Hospital of Tehran between August 2011 and August 2012.

**Methods:** This cross-sectional study was done on 390 cases. All patients with methadone overdoses and positive urine screen test for methadone were included in this case study through census method. Demographic data and overdose complications, such as loss of consciousness, respiratory complications, arrhythmia, hemodynamic disturbances, and QTC interval, were recorded in the questionnaire. Data were analyzed by SPSS software and Kolmogorov Smirnov, t-test, and Chi-square tests were used for data analysis.

**Results:** Overall, 84.1% of the samples were male and the mean age of the samples was 35.53±11.25 years (range: 15-84 years). Mean of the methadone dose used in current admissions was 96.13±52.34 mg. Concomitant drug abuse and concomitant uses of medications were seen in 25.9% and 36.9% of the patients, respectively. Respiratory depression, pulmonary edema, pneumonia, aspiration, and arrhythmia were seen in 87.9%, 26.2%, 3.3%, 7.4%, and 15.4% of the patients, respectively. There were significant differences between concomitant medications, duration of methadone use, and QTc interval prolongation and arrhythmia ( $P<0.05$ ).

**Conclusion:** Based on the findings of the present study, initial screening of ECG changes and QT interval prolongation as well as arrhythmias should be considered in patients on methadone therapy and concurrent drug abuse and co-administration of medications that lead to QT prolongation should be avoided in them.

**Keywords:** Arrhythmia, Complications, Methadone, Overdose, Qtc Interval.

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## INTRODUCTION

Due to the ease of access to heroin, the prevalence of injecting drug use has increased rapidly in the past decade [1-3]. Methadone is a synthetic long-acting analgesic agent with central function and high affinity to  $\mu$  receptors which are used for the treatment of opioid dependency (Methadone Maintenance Therapy). Although methadone has significantly reduced the risk of death due to accidental heroin overdose [4], very serious and often fatal complications due to accidental or suicidal use of Methadone in the addict population are observed [5].

Methadone poisoning is already an expanding phenomenon in different countries. This propagation is due to the increase in the availability and administration of this compound in recent years [5, 6].

Since 1987, a growing trend in the rate of deaths related to methadone has been observed which can be attributed to several factors, such as the type of drug administration and receiving methadone from two or more prescribed or illicit drugs [7]. There is little epidemiological data on mortality and morbidity associated with methadone overdose in comparison to the other opioids [8].

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In a study done in Scandinavian counties in 2007, a growing trend in deaths related to methadone overdose was seen in Denmark, Finland, Norway, Sweden, and Iceland in comparison with 1991, 1997, and 2002 years [6].

Reported complications for methadone overdose in previous studies included QT interval prolongation in ECG [9-12], respiratory depression and pulmonary edema [13, 14], aspiration pneumonia [15, 16], hemodynamic instability [5], impairment of consciousness, coma, and death [17, 18], respectively.

To date, results of studies on the prevalence and morbidity and mortality of methadone overdose in adults have not been reported in Iran and only one study has been reported on methadone overdose in children [19].

Considering the increasing use of methadone and the emergence of methadone therapy centers across Iran, the present study was performed to determine the frequency of methadone overdose and its complications in patients admitted to the Toxicology Emergency Ward of Baharloo Hospital of Tehran during 2011-2012.

## MATERIALS AND METHODS

In this descriptive cross-sectional study, the study population included all patients admitted to the Toxicology Emergency Ward of Baharloo Hospital between August 2011 and August 2012. The sample size included 384 cases that were admitted with methadone overdoses and had positive urine screen tests for methadone during the study period. The patients were enrolled in the study through census method.

The variables in this study included demographic data, consciousness impairments, respiratory complications, arrhythmia, hemodynamic disturbances, and QTc interval recorded in the questionnaire.

QT intervals more than 440 millisecond in men and 460 millisecond in women were considered as QT interval prolongation [20] and in patients with a faster than 100 beats per minute heart rate, corrected QT was calculated by  $QTc = QT / \sqrt{RR}$  formula. In

order to confirm suspected aspiration, a chest radiograph was taken.

Demographic data and drug complications in patients were obtained from hospital records. Confidentiality and protection of personal information obtained from the hospital records were observed throughout the study. The study was approved by the Ethical Committee of Research of Tehran University of Medical Sciences.

Data were analyzed by SPSS software version 16. In data analysis, the frequency and standard deviation were calculated. The Kolmogorov Smirnov test was run to determine the normal distribution of the quantitative variables and data were compared by means of Chi-square and t-test.

## RESULTS

Of the 390 cases with methadone overdose admitted to the Toxicology Emergency Ward, 328 patients (84.1%) were men (male to female ratio: 5.3 to 1), 235 cases (60.1%) were married, and 183 cases (46.9%) had an educational qualification below a high school diploma.

The mean age of the samples was  $35.53 \pm 11.25$  years (range: 15-84 years). The mean duration of history of addiction was  $8.64 \pm 6.63$  years (range: 0.3-40 years).

Overall, 81 cases (25.9%) had concomitant drug abuse and the most abused substances were opium, crack, and crystal in 33 (40.7%), 16 (19.75%), and 16 cases (19.75%), respectively. The current drug abuse status was unknown in 77 cases.

The mean duration of methadone use was  $13.56 \pm 17.19$  months (range: 0-96 months) and the mean dose of ingested methadone in current admission was  $96.13 \pm 52.34$  mg (range: 15-800 mg).

A total of 166 cases (42.6%) had underlying diseases. The most common underlying diseases were psychological and cardiac diseases in 105 (63.3%) and 23 cases (13.9%), respectively.

Moreover, 144 cases (36.9%) had concurrent drug use and the most common drugs used along with methadone were benzodiazepines, and concomitant benzodiazepines and TCA use in 84 (61.8%) and 19 cases (14.0%), respectively. The

current drug use status was unknown in 8 cases.

In the first physical examination, 146 cases (37.4%) had pin point pupils and 205 cases (52.6%) had miotic pupils.

Respiratory depression, pulmonary edema, pneumonia, aspiration signs, and ECG changes were seen in 343 (87.9%), 102 (26.2%), 13 (3.3%), 29 (7.4%), and 60 (15.4%) cases, respectively. The most common ECG changes in samples were sinus tachycardia, widening of QRS, PVC, and precordial ST elevation in 12 (20.0%), 8 (13.3%), 8 (13.3%), and 7 (11.7%) cases, respectively.

Arrhythmia was seen in 38 cases (9.7%) and the most common arrhythmias were sinus tachycardia and PVC in 12 (31.6%) and 8 (21.1%) cases, respectively. In addition, 5 cases (1.3%) died. Vital signs and ABG data are presented in Table 1.

QTc prolongation (over 440 millisecond in men and 460 in women) were seen in 15 cases (3.8%) and in 2 cases (0.5%), QTc intervals were >500 millisecond.

There was a significant relationship between QTc prolongation and presence of arrhythmia ( $P<0.05$ ), so that arrhythmia was seen in 33.3% (5 cases) of patients with QTc prolongation compared with 5.9% (22 cases) in patients without QTc prolongation (Table 2).

There was not any significant relationship between methadone overdose

complications (respiratory depression, pulmonary edema, pneumonia, aspiration, and arrhythmia) and the gender of the patients ( $P>0.05$ ).

There was a significant relationship between methadone overdose complications, including pulmonary edema, respiratory depression, and arrhythmia, and the presence of underlying diseases in patients ( $P<0.05$ ).

There was not any significant differences between concurrent drug abuse and methadone overdose complications ( $P<0.05$ ).

There was a significant relationship between age, duration of addiction, duration of use of methadone, and the dose of methadone and pulmonary edema in current admission ( $P<0.05$ ), so that patients and pulmonary edema were older, with longer addiction histories, longer duration of methadone use, and higher ingested dose of methadone in current admission.

There was a significant relationship between age and dose of methadone in current admission and aspiration ( $P<0.05$ ), so that patient with pulmonary aspiration were older and ingested higher dose of methadone in current admission.

There was a significant relationship between duration of methadone use and the presence of arrhythmia ( $P<0.05$ ), so that patients with arrhythmia had received methadone for longer duration (Table 3).

**Table 1.** Vital sign characteristics, ABG indices, GCS, and QTc interval of patients admitted with methadone overdose enrolled in the study.

Characteristics	Mean	Minimum	Maximum
Systolic BP (mmHg)	114.14±15.81	60	170
Diastolic BP (mmHg)	70.04±10.14	40	110
Heart Rate (/min)	87.5±14.32	58	140
Respiratory Rate (/min)	12.79±4.90	0	80
Temperature (°C)	37.06±0.25	36.0	39.0
GCS	12.71±2.16	3	15
pH	7.29±0.07	6.90	7.47
HCO <sub>3</sub> (mEq/L)	23.36±3.32	13.0	43.0
QTc interval (millisecond)	382±39	280	630

**Table 2.** Comparison between gender, Current drug abuse, Current medication use and presence of Arrhythmia with QTc prolongation in patients admitted with methadone overdose.

Characteristics	QTc		P value
	>440 ms	≤440 ms	
<b>Gender (%)</b>			
Male	11 (3.4%)	317 (96.6%)	0.245
Female	4 (6.5%)	58 (93.5%)	
<b>Current drug abuse*</b>			
Yes	5 (6.2%)	76 (93.8%)	0.290
No	8 (3.4%)	224 (96.6%)	
<b>Current medication use</b>			
Yes	7 (4.9)	137 (95.1)	0.430
No	8 (3.3)	237 (96.7)	
<b>Arrhythmia</b>			
Yes	10 (26.3)	28 (73.7)	0.000
No	5 (1.4)	347 (98.6)	

\*Current drug abuse status undetermined in 77 cases.

**Table 3.** Comparison between gender, Current drug abuse, Current medication use and underlying diseases with presence of Arrhythmia in patients admitted with methadone overdose.

Characteristics	Arrhythmia		P value
	Yes	No	
<b>Gender (%)</b>			
Male	31 (9.5%)	297 (90.5%)	0.654
Female	7 (11.3%)	55 (88.7%)	
<b>Current drug abuse*</b>			
Yes	12 (14.8%)	69 (85.2%)	0.184
No	22 (9.5%)	210 (90.5%)	
<b>Current medication use</b>			
Yes	24 (16.7)	120 (83.3)	0.000
No	14 (5.7)	231 (94.3)	
<b>Underlying Diseases</b>			
Yes	11 (4.9)	213 (95.1)	0.000
No	27 (16.3)	139(83.7)	

\* Current drug abuse status undetermined in 77 cases.

## DISCUSSION

Based on the findings of the present study, the majority of cases enrolled in the study were male (84.1%). Also, 25.9% of samples had concurrent drug abuse and 36.9% had concurrent use of medications. The most common underlying diseases in the patients were psychological diseases (63.3%). The most common methadone overdose complications were respiratory depression, pulmonary edema, and ECG abnormalities in 87.9, 26.2, and 15.4%, respectively. QTc interval prolongation was seen in 3.8% of the cases while 1.3% of the patients died.

With the development of methadone replacement therapy program, the serious and

fatal complications of methadone therapy in the addict population were mainly seen to be due to accidental or intentional methadone use [5].

Methadone replacement therapy was initiated in Iran in 2003 and developed gradually. Currently, there are over 1500 active methadone therapy centers in Iran [5, 21].

The development of methadone therapy centers and increases in the availability of methadone have led to an increase in methadone overdoses, especially among drug users.

Several studies have reported the increase in the risk of methadone overdose,

especially during the first few days of treatment [15, 22-25].

Unfortunately, only one study has been published about methadone poisoning in Iran which was performed on children [19]. Therefore, there was not any data for making comparisons in this field in Iran.

The frequency of methadone-related deaths in England and Wales increased from 371 cases in 1993 to 674 cases in 1997 [26].

Methadone overdose deaths have shown a clear increase in all Scandinavian countries [6]. Methadone was the most common cause of poisoning in Denmark in 2007 and was the main cause of toxicity in 51% of overdoses [6].

The increase in deaths due to methadone is largely justified by expanding the methadone treatment programs, and broad population of patients.

Despite the increase in deaths due to methadone overdoses and considering the development of methadone therapy centers in Iran and the frequency of deaths due to methadone overdose in the present study (1.3%) which was inconsistent with the reported figure in Thailand (1.6%) [27], it seems that with proper management of methadone therapy in Iran, the benefits of this treatment outweighed its complications (especially in reducing overdose-related deaths due to other drugs [28]) which has been emphasized in previous studies in other countries [28, 29].

The mean methadone dose in the current admission was  $96.13 \pm 52.34$  mg in the present study, this figure is higher than the values reported in the study by Huang *et al.* in Thailand [27] and a previous study conducted on children [19] in Iran, but it is lower than the figures reported in previous studies in the United States [7, 30].

Prolonged QTc was observed in 3.8% of the samples in the present study while in Fonseca *et al.*'s study [31], QTc prolongation was seen in 9.2% of the samples. Moreover, the mean daily dose in Fonseca *et al.*'s study was 120 mg, while the mean dose in the samples of the present study was 96.13 mg. This can help explain the higher prevalence of prolonged QTc in Fonseca *et al.*'s study compared to the present study. Hanon *et al.*

[30] evaluated 6500 methadone users in the United States and reported only 12 cases of QTc prolongation which is considerably much lower than the figures in the present study and Fonseca *et al.*'s study [31] while the mean daily dose of methadone in their study was 135 mg.

The mean QTc interval in the present study was  $382 \pm 39$  while the mean QTc interval in the study done by Fareed *et al.* [10] was  $442 \pm 25$ . There was a significant relationship between QTc interval prolongation and the presence of arrhythmia in the present study ( $P < 0.05$ ). Heart rhythm disorders (QT interval prolongation) are directly related to the LAAM (Levo-alpha-acetyl-methadol) analog of methadone in susceptible individuals [32].

Stringer *et al.* [33] indicated that methadone could interfere with the voltage-gated potassium channels in the heart and lead to action potential prolongation and QT prolongation. Wu and Henry [34] and Hanon *et al.* [30] also observed that methadone could block the heart nerve transmission in a dose-dependent manner. Therefore, particularly high plasma concentrations of methadone, alone or in combination with other drugs, have a potential for inducing QT interval changes or life-threatening arrhythmias.

Considering the results of the present study and previous studies [10, 30, 33, 34], it seem that performing initial and during treatment electrocardiogram for screening patients who received methadone for ECG abnormalities as well as patient education and referring patients with QTc interval prolongation to sub-speciality centers are essential in managing patients who are on methadone treatment.

In the present study, 36.9% of the patients had concomitant use of drugs in the current admission and the most widely used drugs in combination with methadone were benzodiazepines in 61.8%. Likewise, in Ernst *et al.*'s study [29], concurrent use of benzodiazepines was reported in 74% of the cases. The use of multiple drugs, particularly benzodiazepines, in combination with methadone is listed as the greatest risk factor for early mortality in patients on methadone treatment. Brands *et al.* [35] also reported

concurrent use of benzodiazepines with methadone as a complex situation and a negative impact on outcomes. In the present study, there were also significant differences between concurrent drug use and presence of arrhythmia ( $P < 0.05$ ).

Based on the findings of the present study, nearly one third of the samples had concurrent drug abuse which can increase the risk of overdose and mortality in these patients.

It seems that more preventive and educational activities are essential in order to prevent the concurrent use of drugs and other narcotics in patients on methadone therapy. Also, conducted surveillance on the activities of methadone therapy centers and performing more accurate opium screening tests in these centers can be effective in the prevention of concurrent drug abuse in patients on methadone therapy.

Another interesting finding in the present study is that 13.9% of the samples had underlying cardiovascular disorders and there was a significant relationship between methadone overdose complications and underlying diseases ( $P < 0.05$ ). This indicates a lack of careful screening of patients prior to methadone therapy and ignoring the underlying cardiovascular diseases in them. This also indicates the need for more training activities in MMT centers to enhance the awareness of doctors and medical staff in these centers regarding methadone complications, particularly complications with arrhythmia, and the need for more attention to their underlying diseases before induction of methadone therapy.

Respiratory depression is the most common complication observed in the present study with the 87.9% that this finding is consistent with the findings of most of the previous studies [19, 29, 36].

The mean age of subjects in this study was 35.53 years that is consistent with the result of a study conducted in Thailand [27].

In this study, there was a significant relationship between the duration of methadone use and presence of arrhythmia ( $P < 0.05$ ), so that patients with arrhythmia had longer durations of methadone use. Therefore, taking initial and serial ECG during

methadone therapy for screening QTc interval prolongation in patients is essential.

Moreover, as mentioned in some previous studies [28, 37], it seems that in methadone therapy cases with QTc interval prolongation or in patients at risk of arrhythmia, use of drugs, such as buprenorphine, can be considered in opium replacement therapy.

## CONCLUSION

Based on the findings of the present study, the frequency of mortality and complications of methadone overdose in Iran is largely consistent with the findings of previous studies. Initial screening of ECG changes, QT interval prolongation, and arrhythmias should be considered in patients on methadone therapy. Also, concurrent drug abuse and co-administration of medications that lead to QT prolongation should be avoided in them. Additionally, relevant education about methadone overdoses should also be provided for patients.

Monitoring the activities of methadone therapy centers and holding more training courses on methadone overdose complications for the personnel of these centers and more accurate screening of ECG changes, especially QT interval prolongations, are recommended in this population.

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