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Original Article

A clinical survey on methadone poisoning: Predisposing factors and clinical expression

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Abstract

Background and aims: Ongoing methadone intoxication parallels the generalization of the implemented addiction cession programs, as well as the necessity to sustain an effectively durable addiction treatment course. This study aimed to investigate the predisposing factors and clinical features of methadone intoxication.

Methods: During a one-year period (March 2018 to March 2019), patients admitted for methadone intoxication were investigated retrospectively. Demographic data, the consumed methadone dose, electrocardiogram findings, and the level of creatinine phosphokinase (CPK) at admission were collected and entered into a statistical analyzing platform (SPSS version 22) for further statistical testing.

Results: Seventy-five eligible patients were investigated. The mean age was 23.63±16.66, 66.7% were male, and 15 patients were children. The unemployment status led to an increased methadone poisoning (MP) incidence ($P<0.05$). The incidences of an increased CPK or QT segment prolongation were 17% and 7%, respectively. There was not any statistical correlation between the incidence of MP, the demographic and clinical data, as well as the used methadone dose. Moreover, the duration of the QT segment was not statistically influenced by the CPK.

Conclusion: MP incidence seems to be influenced by social status. The increase in CPK and QT prolongation was not influenced by the methadone dose. It seems that more studies are required to further investigate the risk and prognostic factors of MP.

Keywords: Methadone, Poisoning, Clinical findings

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Introduction

Poisoning by substance abuse represents the prevalent poisoning cause worldwide, which is potentiated by the increasing number of drug abusers in an ever-expanding population (1). The mortality rate among drug abusers is estimated to exceed 13 times compared to the general population (2). Resorting the long-acting synthetic opioid, regarded as methadone and in the frame of cession addiction programs, has inexorably increased. The latter reduces withdrawal symptoms as in the setting of opium or heroin addiction (3). Methadone treatment may lead to dependence in such a way that higher doses of the drug will be needed, and subsequently, the risk of methadone poisoning (MP) may be intensified.

The inherent and potentially irreversible side effects of methadone presage the deleterious and lethal ensuing poisoning. Rhabdomyolysis, respiratory depression, cardiac arrhythmias (e.g., the prolongation of the QT interval), and orthostatic hypotension are listed among the serious methadone side effects (4). Nevertheless, the suppression of the immune system and the occurrence of ventricular arrhythmias represent the two major causes of death at the time of MP (5, 6). Compounding the latter and given the widespreading and increasing methadone appeal, caution should be exercised to prevent iatrogenic and accidental MP (3). The present retrospective clinical study was thus conducted to determine the risk factors and the clinical and para-clinical expression of methadone intoxication among patients referred to an Iranian state tertiary health care facility.

Materials and Methods

A retrospective observational study was conducted at Amir-Al-Momenin University Hospital (Zabol in Sistan and Baloochestan province) on MP from March 2018 to March 2019. The patients to be enrolled were selected based on the following inclusion and exclusion criteria:

Inclusion criteria

- Being admitted for MP and aged over 1-year-old,
- Having at least one of the life-threatening symptoms (MP symptomatic Triade), including the loss of

consciousness (e.g., seizures), respiratory depression, and miotic pupil,
- A documented urinary-positive qualitative reaction to methadone provided by the screening rapid test kit based on the immune-chromatographic assay (Hannan Teb Pars, Tehran, Iran).

Exclusion criteria

- Having any documented previous iatrogenic electrocardiogram disorder (e.g., anti-depressant psychotropic drugs, anti-psychotic drugs, lithium, benzodiazepines, anticonvulsants, lidocaine, amiodarone, verapamil, digoxin, beta-blockers, and adenosine),
- Taking an undocumented used methadone dose,
- Being a non-cooperative patient,
- Dying before admission.

The chart of each enrolled patient was investigated. The demographic data (e.g., age, occupational status, and educational status), the medical history (the amount of used methadone, underlying diseases, and emergency admission), the presenting symptoms, the disorders on serial electrocardiograms, and the plasmatic level of creatinine phosphokinase (CPK) assessed by immune-inhibition technique were extracted and recorded. Moreover, a child was defined as a patient aged between 1 to 18 years old.

Statistical analysis

The descriptive data for categorial and non-categorial variables were expressed by percentages and means ± standard deviation. The statistical comparison of the categorial and non-categorial data was performed by chi-square test and student *t* tests, respectively. The correlation between categorical data was estimated using the Spearman correlation coefficient, while the relationship between non-categorical data in the case of normal distribution was investigated by the Pearson method and, otherwise, affected by Spearman testing. The level of significance was set at $P<0.05$ with a confidence interval of 95%. Then, the statistical tests were conducted by SPSS statistical software version 22 (IBM, Chicago-IL, USA).

Results

Seventy-five patients out of 100 admitted due to MP during the study period were considered eligible to be enrolled. The mean age of patients was 23.63 ± 16.66 (ranging from 1 to 75) years with 66.7% of patients being male, 60 patients (80%) were adults, and 15 patients were considered children who were poisoned accidentally. All of the 75 patients were presented with classical MP symptomatic triad at admission. Of the 60 adult patients, 29 patients (48 vs 23%) were unemployed (Table 1). Moreover, there was a significant difference in the incidence of MP between the unemployed and employed adult patients ($P<0.05$); nevertheless, the educational status did not reach any statistical significance ($P>0.05$).

By the time of admission, 8 patients (11%) were affected by concomitant diseases (Table 2). Moreover, 14 (18.7%) patients concomitantly used additional stimulant drugs listed in Table 2, the most common of which were opium, tramadol, morphine, methamphetamine, heroin, and amphetamine. In addition, the mean dose of used methadone was 3 ± 5.11 mg (ranging from 1 to 30 mg).

Seizures occurred in 7 patients (9%), with 3 patients (4%) presenting more than 2 episodes of seizures during the hospitalization. By analyzing serial electrocardiograms, 84% of patients had a normal electrocardiogram during hospitalization. The frequent electrocardiographic disorders were found to be bradycardia (12%), QT prolongation (7%), and tachycardia (4%), and the average time of hospitalization was 4.3 days (ranging from 1 to 30). One patient (1%) was complicated by a neurologic comatose state, 70 patients (93%) recovered from MP and were uneventfully discharged, and 4 patients (5%) died during the hospitalization (Table 3).

The mean value of measured CPK plasmatic levels was 142.59 ± 55.93 mg/dL (ranging from 35 to 458). The laboratory findings are reported in Table 4. The mean doses of used methadone in patients with normal and high CPK were 27.68 mg and 21.77 mg, respectively, as depicted in Table 5. Therefore, 17% of patients displayed increased CPK plasmatic levels more than normal, and 82.7% of patients presented normal CPK plasmatic levels (Figure 1). Additionally, there was no statistical difference between the means of methadone used doses and the increased level of plasmatic CPK ($P=0.373$).

As observed in Figure 2, the mean QT interval in patients was 0.42 ± 0.014 seconds (ranging from 0.41 to 0.47). Furthermore, the means of used methadone doses in patients with normal versus prolonged QT were 26.84 ± 49.72 and 24 ± 15.57 mg, respectively (Table 5), which is not statistically significant ($P=0.413$). Having adjusted for the raw and odds ratio (age, underlying disease, and other used drugs), no statistical correlation was displayed between the methadone dose, CPK

Table 1. Demographic information of the patients

Demographic variables		N	%
Gender	Male	50	66.7
	Female	25	33.3
Age groups	Adult	60	80
	Child	15	20
Occupational status (Adults)	Employed	14	23
	Unemployed	29	48
	Retired	1	2
	Student or housewife	16	27
Educational status (Adults)	Illiterate	16	21
	Under bachelor's degree	23	31
	Bachelor's degree	29	39
	Graduated or higher	N	9

plasmatic levels, and QT segment duration (Table 5).

Discussion

Methadone maintenance therapy is necessary for the therapeutic cessation programs facing morphine-based addiction. Due to its long-duration analgesia feature, methadone is also regarded as an advantage for chronic pain control (7). Consequently, an increasing appeal to methadone is witnessed, mainly for outpatient methadone prescriptions. The latter does raise the hazard of MP. Given MP's lethal potential, investigating and reporting MP clinical data are crucial to regularly upgrade health professional awareness, as well as to take further health and social steps to remind MP occurrence likelihood. Consequently, it can be stressed that evoking health-givers and patients' awareness should be demised through the promoting programs intended to train methadone misuse prevention, to timely recognize MP symptoms, and to timely refer the patient to an appropriate medical center in view of boosting MP prevention strategies (8-11).

Many factors leading to MP occurrence were previously reported, out of which age, gender, economic status, the residential category, and maternal literacy level were the main recognized demographic factors influencing the MP hazard and its severity, which are yet to remain controversial (9,10). The current findings revealed that MP can affect anyone with any social or educational category; however, a significant difference was found in favor of the unemployment status.

The sudden death by the time of MP has been assigned to heart rhythm disorders (HRDs), mainly the prolongation of the QT segment (8,12,13). The HRD incidence attached to MP was variously reported (14,15). It was obvious that a daily methadone dose above

Table 2. Clinical information of the patients

Variables		N	%
Concomitant disease	Present	8	10.7
	Absent	67	89.3
Additional substance intake	Amphetamine	1	1.3
	Heroin	1	1.3
	Methamphetamine	3	4
	Morphine	1	1.3
	Opium	4	5.3
	Tramadol	4	5.3

Table 3. Complications of methadone poisoning in patients

Complications		N	%
Seizure	None	90.7	68
	Once	5.3	4
	≥2	4	3
ECG disorders	None	5.3	58
	Bradycardia	12	9
	Tachycardia	4	3
	QT interval prolongation	6.7	5
Coma		1	1.3
Death		4	5.3

Note. ECG: Electrocardiogram.

Table 4. Laboratory information of patients

Variables	Mean ± SD	Lower and upper measurements
CPK	142.58 ± 55.92	35-458
WBC	9966.67 ± 8639.05	5000–80000
Hb	11.13 ± .74	8–16
PLT	252866.67 ± 83497.74	70000–450000
BS	98.95 ± 98.95	72–227

Note. BS: Blood sugar; CPK: Creatinine phosphokinase; Hb: Hemoglobin level; PLT: Platelet count; WBC: White cells count. The lower and upper measurements are reported in parentheses.

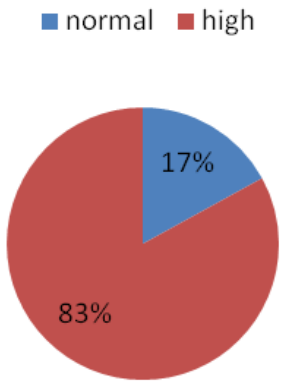

Figure 1. Distribution of CPK status in patients with methadone poisoning. *Note.* CPK: Creatinine phosphokinase

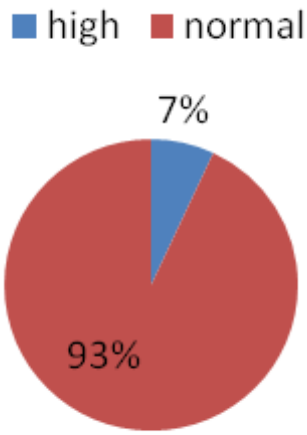

Figure 2. Distribution of QT interval status in patients with methadone poisoning

Table 5. Determining the relationship between methadone dose and QT interval and CPK levels in patients with methadone poisoning

	Variables	Methadone dose	*P* value	Adds Ratio	*P* value	Adjusted Ratio	*P* value
CPK	27.68 ± 51.90	21.77 + 23.93	0.373	0.99	0.7	0.99	0.8
QT	26.840 ± 49.728	24 + 150.572	0.413	0.99	0.9	0.99	0.8

Note. CPK: Creatinine phosphokinase. $P < 0.05$

100 mg can lead to HRD occurrence (12,15). In one of the previous reports, methadone therapy significantly increased the duration of the QT segment (63.2 ± 455.7 ms), while it statistically decreased the duration of the PR interval (36.2 ± 139 versus 24.4 ± 158.2 ms) compared to the general population (13). Considering the non-specific nature of encountered HRD, it is wise to perform an ECG before the initiation of methadone therapy or any further therapeutic changes (12,15). At present, HDR incidence was estimated to be 20%, while QT segment prolongation occurred in 7% of MP patients. Furthermore, not any statistical correlation was found between demographic or clinical factors to the QT segment prolongation incidence, and neither did the dose of methadone influence the latter. The impact of increasing the level of plasmatic CPK on the duration of the QT segment remains to be elicited (16). The current findings rejected any statistical relationship between an increase in plasmatic CPK level and the duration of the QT segment, which agrees with a previous study (16). Furthermore, the used dose of methadone did not display any relation paralleling the increase in the levels of plasmatic CPK.

The current study was intended to investigate demographic and clinical factors leading to MP occurrence. The retrospective nature and small size of the current investigation represent its obvious limitations. Therefore, further prospective and multi-centric investigations are needed not only to depict the MP predisposing factors but also to reveal the factors involved in MP prognosis.

Conclusion

Social status such as unemployment does lead to an increased incidence of MP. Furthermore, increasing CPK plasmatic levels and the prolongation of the QT segment were revealed to be the two predominant MP clinical expressions. However, the demographic, clinical, and laboratory findings failed to notice any statistical correlation regarding an increased plasmatic level of CPK or QT segment prolongation.

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Authors' Contribution

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Competing Interests

The authors declare that there is no conflict of interests.

Ethical Approval

This study was approved by the Ethics Committee of Zabol University of Medical Sciences (Approval code: IR.ZBMU.REC.1399.071).

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