



The clinico-epidemiological, diagnostic, and therapeutic aspects of methadone poisoning: a registry-based clinical study

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Objectives: Methadone is a long-acting synthetic agonist of opioid receptors, which is used as an analgesic and as an alternative treatment in opioid-dependent patients. Clinical manifestations of methadone poisoning include miosis, low levels of consciousness (LOC), respiratory depression or apnea, and coma and death. Considering the high consumption of methadone in society and the prevalent instances of overdose and poisoning, whether accidental or intentional, the authors decided to investigate the clinico-epidemiological, diagnostic, and therapeutic characteristics of methadone poisoning in the Mazandaran province, northern Iran, from 2020 to 2022.

Methods: This study was a retrospective and descriptive cross-sectional registry-based study, wherein data was collected from the Mazandaran Registry Center of Opioids Poisoning (MRCOP), on patients with methadone poisoning. Data based on various parameters such as individual characteristics, ingestion motivation, and clinical outcomes were collected in a checklist.

Results: Of the 385 patients, who entered the study, 264 were men and 121 were women. The mean age of the patients was 29.02 years. Two hundred forty-four patients had intentionally consumed methadone. The most common symptoms observed among individuals with methadone poisoning were decreased arterial blood oxygen (225 patients) and decreased LOC (173 patients). The length of hospitalization for most patients was less than 1 week. Except for seven of them who died, most of them were discharged in good general condition.

Conclusion: The study identified sex, age, marital and employment status, and suicidal intent as the most significant factors influencing methadone poisoning, which should be considered in the design and implementation of public education and prevention programs.

Keywords: apnea, intentional, methadone, poisoning, registry

Introduction

Opioids play a crucial role in forensic toxicology as they are widely used in both medical and illicit contexts. Despite their natural, semi-synthetic, or synthetic origins, these compounds are classified as opioids due to their ability to interact with opioid receptors in the central nervous system, despite varying chemical

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HIGHLIGHTS

- Methadone is a long-acting synthetic agonist of opioid receptors.
- Methadone is usually safe in therapeutic doses, overdose, especially in maintenance therapy, can lead to respiratory depression.
- Cardiac manifestations are indeed serious and potentially fatal complications of methadone poisoning.

structures^[1]. Methadone maintenance treatment (MMT) centers administer drugs like opium tincture, methadone, and buprenorphine for addiction treatment, but these substances are prone to abuse and overdose due to their potential to induce euphoria for nonmedical purposes among addicts^[2].

In Iran, opioid poisoning has become a prevalent and hazardous public health issue in recent years. Despite the successful implementation of methadone maintenance treatment (MMT) programs, the increasing trend in methadone-related poisoning and fatalities is cause for grave concern. To address this public health crisis, it is imperative to study and understand the factors contributing to these nonfatal and fatal poisonings, and to develop effective strategies to mitigate the harmful consequences of methadone use^[3]. Accidental poisoning, often resulting from improper storage and packaging of methadone formulations such as methadone syrup, has been well-documented. A significant contributor to these incidents is the practice of keeping

methadone in nonmedical containers, such as mineral water bottles, which increases the risk of accidental ingestion, especially by children who may mistake the contents for something else^[4]. The increasing use of methadone on the one hand and the lack of sufficient preventive measures have turned methadone poisoning into a serious threat to the entire society^[5].

Methadone, a synthetic opioid belonging to the diphenylheptane derivative class, functions as an agonist of μ -opioid receptors. Its analgesic effects are similar to morphine in both quality and quantity; however, methadone's longer duration of action and higher oral efficacy make it a preferred choice for certain applications^[6–8]. Following oral administration, methadone, a lipophilic compound, is rapidly absorbed with an oral bioavailability ranging from 60 to 80%. The plasma half-life of methadone is ~24 h, though it exhibits wide interindividual variability, ranging from 5 to 130 h^[9,10].

Clinical manifestations of methadone poisoning include miotic pupils, respiratory depression and apnea, low level of consciousness (LOC), coma, and death^[11]. Although methadone is usually safe in therapeutic doses, overdose, especially in maintenance therapy, can lead to respiratory depression. Cardiac manifestations are indeed serious and potentially fatal complications of methadone poisoning. Complications like prolonged QT interval, torsades de pointes, cardiomyopathy, and pseudo-Brugada syndrome have been reported in cases of methadone poisoning^[12–14]. Respiratory depression is a serious symptom of methadone poisoning, observed in 50% of affected individuals^[15]. Nearly 25% of fatalities due to methadone poisoning have been reported within the first 14 days of starting MMT^[16].

Due to the high prevalence of addiction in society and the risks associated with overdose and impurities in opium, as well as the necessity of treating these patients with maintenance drugs, especially methadone, and the occurrence of intentional and unintentional poisonings in the community, it is important to investigate the various individual characteristics of methadone poisoning referred to teaching hospitals registered in the Mazandaran Registry Center of Opioids Poisoning (MRCOP) during the 2020–2022 years.

Patients and methods

This registry-based study was conducted in compliance with ethical guidelines, as it was approved by the Mazandaran University of Medical Science Ethics Committee (No. IR.MAZUMS.REC.1401.022) and followed the principles of the Helsinki Declaration. Furthermore, written informed consent was obtained from all of the participants involved in the study.

This study was conducted to determine the different demographic characteristics of patients with methadone poisoning referred to teaching centers registered in the MRCOP from 2020 to 2022. After obtaining informed consent and providing a comprehensive explanation to both the patients and their families about the significance of confidentiality, the checklist was completed. The data was analyzed based on various parameters, including individual characteristics, ingestion motivation, diagnostic and treatment routes, as well as clinical outcomes (recovery or death). The data was presented in terms of means, SDs, medians, and interquartile ranges for categorization. The inclusion criteria include patients with a history of methadone ingestion

(intentional and unintentional) who have symptoms of intoxication, as well as a positive urine screening test for methadone, specifically in those with reduced LOC or who have responded to naloxone therapy. Patients with poisoning from other opioids were excluded from the study.

The management of methadone poisoning primarily involves early airway support and ventilation, as well as the administration of naloxone. Naloxone, a competitive opioid receptor antagonist, effectively blocks the binding of methadone to opioid receptors, permitting the resumption of spontaneous respiration in most patients. A typical intravenous dose of 0.04 mg of naloxone is usually sufficient, although if there is no response, the dose may be repeated at 3 min intervals, up to a maximum of 10 mg.

The normal distribution assumption was evaluated using the Shapiro–Wilk test. To compare the frequency of findings and other variables between the two groups, either the *t*-test or the Mann–Whitney test was utilized. Furthermore, a multivariate regression test was carried out to account for potential confounding variables. Data analysis for this study was conducted using SPSS V.24 software and a *P*-value level less than 0.05 was considered statistically significant. The work has been reported in line with the strengthening the reporting of cohort, cross-sectional and case–control studies in surgery (STROCSS) criteria^[17].

Results

Out of 385 patients, 68.57% were male and 31.43% were female. The mean age of the participants was 29.14 ± 2.29 years. The results showed that 64.93% were single, 35.07% were married, 38.18% of the patients were unemployed, and 7.52% were university students. The main cause of poisoning was intentional (Table 1). The most common symptoms in hospitalized patients included drowsiness (74.02%), decreased arterial blood oxygen (58.44%), miotic pupils (46.49%), and reduced LOC (44.93%) (Table 2). Fifteen patients (9.9%) had ECG changes, and 35 patients (9.09%) had changes in chest radiography as aspiration pneumonia. In addition, 17.92% of patients experienced respiratory complications.

The study revealed that the average amount of methadone ingested by the participants was 178.01 mg, and the mean dosage of naloxone administered to patients was 0.64 mg. The majority of hospitalized patients who had attempted suicide with methadone had consumed the drug in tablet form (88.05%). The most common drug used simultaneously with methadone was benzodiazepines (21.55%). Laboratory test results for patients are also listed in Table 3. The duration of hospitalization for most of the patients was less than 1 week (95.06%). Furthermore, the majority of patients (99.22%) were successfully treated and discharged with good general health. However, tragically, seven patients did not respond to the treatment and died.

Discussion

Methadone poisoning is prevalent among individuals seeking to overcome drug addiction, as well as among those who intentionally and unintentionally consume this medication. Since 2003, methadone has served as an alternative therapy for addiction, leading to the establishment of 1500 treatment facilities in Iran. Unfortunately, these centers not only deliver

Table 1
Individual characteristics, ingestion motivation, and clinical outcomes.

Variable	No (%)
Cause of poisoning	
Intentional	244 (63.37)
Unintentional	141 (36.62)
Familial disputes	
Yes	90 (23.37)
No	295 (76.62)
Familial addiction	
Yes	117 (30.38)
No	268 (69.61)
History of addiction	
Yes	122 (31.69)
No	263 (68.31)
History of suicide	
Yes	140 (36.36)
No	245 (63.63)
History of underlying disease	
Yes	111 (28.83)
No	274 (71.16)
Place of hospitalization	
ICU	44 (11.42)
ER	17 (4.41)
Poisoning ward	324 (84.15)
Place of poisoning	
Home	282 (73.24)
Outdoors	103 (26.75)
Refer to the ER (h)	
Unknown	216 (56.10)
6–12	125 (32.46)
1–6	44 (11.42)

ER, emergency room.

methadone syrup in inadequate and insecure packaging but also provide it to patients without proper storage training or sufficient information on the potential risks of drug toxicity. Frequently, patients resort to using mineral water bottles, soda bottles, or other drug containers to store methadone syrup obtained from

Table 2
The frequency of clinical manifestations methadone poisoning.

Variables	No (Frequency %)
Drowsiness	285 (74.02)
Reduced LOC (GCS: 8-13)	173 (44.93)
Decreased SpO ₂ (< 90%)	225 (58.44)
Miosis	179 (46.49)
Apnea	90 (23.37)
Coma	76 (19.74)
Seizure	4 (1.03)
Nausea and vomiting	35 (9.09)
Dizziness	38 (9.87)
Agitation and restlessness	9 (2.33)
Respiratory depression (RR < 12)	12 (3.11)
Itching	12 (3.11)
Abdominal pain	7 (1.81)
Fever	5 (1.29)
Hypotension (SBP < 90 mmHg)	6 (1.55)
Mydriasis	5 (1.29)
Arrhythmia	3 (0.77)

GCS, Glasgow coma scale; LOC, level of consciousness; RR, respiratory rate; SBP, systolic blood pressure; SpO₂, arterial oxygen saturation.

Table 3
The results of laboratory findings.

Variables	Mean	SD	Max	Min	Reference value
Na	139.82	3.68	164	120	136–145 mEq/l
K	4.02	0.54	6.5	2.1	3.5–5.1 mEq/l
Cr	0.97	0.35	3.1	0.4	0.6–1.2 mg/dl
BUN	17.38	9.23	74	9	9–26 mg/dl
BS	133.88	77.20	546	67	< 200 mg/dl
pH	7.28	0.24	7.67	6.65	7.35–7.45
PaCO ₂	55.92	13.30	99	34	35–45 mmHg
HCO ₃	26.68	4.55	57	15.6	22–28 mEq/l

BS, blood sugar; BUN, blood urea nitrogen; Cr, creatinine; Max, maximum; Min, minimum.

these centers, storing it in refrigerators. This action contributes to the rising unintentional incidence of methadone poisoning in society, as observed in our study^[18].

In a study conducted in Norway, 7000 patients participated in opioid maintenance treatment (OMT) programs. The research noted a correlation between the rise in methadone-related deaths and the increasing sales of methadone from 2000 to 2006. However, the specific factors leading to these fatalities remained unclear. The study analyzed individual characteristics, methadone concentration, and other toxicological findings. The study on methadone intoxication deaths revealed important findings. Methadone blood concentrations were higher in decedents enrolled in OMT compared to those not in treatment. Fatal multidrug intoxications in OMT patients often had methadone blood concentrations around 1 mg/l. It was noted that combining therapeutic levels of methadone with other psychoactive substances could increase the risk of death for some patients. Methadone concentrations below 0.1 mg/l were also linked to intoxication, whether used alone or in combination with other drugs. Additionally, younger male users, with a mean age of 34 years, appeared to be more susceptible to methadone intoxication^[19].

A case-control study conducted by Pamela *et al.* found that the use of psychotropic drugs was associated with an increased risk of opioid-related deaths among individuals receiving methadone treatment. This finding highlights the importance of considering potential drug interactions and the use of psychotropic medications when treating individuals with methadone, as awareness of these factors could potentially help mitigate the risk of fatal outcomes in this population^[20]. According to the results of our study in northern Iran, the mean age of patients with methadone poisoning was 29.14 ± 2.29 years, and in men (68.57%), it was higher than in women (31.43%).

In the study conducted in US hospitals, the mean age of people poisoned with methadone was 41.9 ± 16.6 years, in another study in Tehran hospital, the mean age of poisoned people with methadone was determined to be 33 years. Like in our study, methadone poisoning in men was more common than in women. Also in this research, the average dose of methadone used was calculated to be 178.01 mg, while compared to other studies, the mean amount of methadone consumed in their patients was reported to be 111 ± 122 mg and 331.09 mg^[21–23].

In a study conducted by Izadi *et al.*^[24] in 2016, 80.19% of individuals used methadone alone, while 19.81% used methadone in combination with other substances. Aghabiklooei *et al.*'s study found that 83.2% of the cases were intentional methadone ingestions, which is in agreement with our findings. Furthermore,

in their study, methadone tablets were the source of poisoning in 66.25% of cases, while methadone syrup was responsible for 33.75% of the poisonings, a pattern that mirrors our study's results^[25]. Taheri *et al.*'s study, which is similar to our research, found that 85.7% of the patients had ingested only methadone, while 14.3% had ingested methadone with other drugs. The mean age of the patients was (range 1–90), with the majority being male (76.4%) and with intentional poisoning (57.7%). Common symptoms among patients in that study were similar to our study's findings, including reduced LOC, respiratory depression, and hypotension^[26]. In this study, the primary objective was to examine the clinico-epidemiological characteristics, as well as appropriate diagnostic and treatment methods in methadone poisoning patients in northern Iran. Our findings revealed that 73.24% of the individuals used methadone alone, whereas 26.76% used methadone in combination with other drugs and opioids. The most frequently used substance alongside methadone was clonazepam (15.06%), followed by alprazolam (5.45%), and, in smaller amounts, alcohol, methamphetamine, buprenorphine tablets, and other drugs.

In a study by Ramezanzadeh *et al.*, 240 patients were examined, with the majority being male (70.9%) and a mean age of 34.4 ± 16.55 years. The primary cause of poisoning was intentional, with methadone being the most commonly consumed opioid. Clinical findings included drowsiness, decreased consciousness, and reduced arterial oxygen saturation levels^[27]. Abusalah *et al.* have documented that stem cell therapy presents a significant opportunity to revolutionize treatment options, particularly for conditions with a genetic basis. In addition to its potential for enhancing screening for therapeutic agents, assessing drug efficacy and toxicity, and understanding patient-specific responses to treatments or disease progression, stem cell therapy also holds the potential to dramatically advance the field of regenerative medicine in surgery and surgical care. The potential of stem cell therapy to transform the approach to disease and injury treatment not only represents a milestone in medical science, but also provides a beacon of hope for an innumerable number of patients worldwide^[28].

Conclusion

This study highlights the significance of sex, age, marital and employment status, and suicidal intent as factors influencing methadone poisoning, which demonstrates the increasing prevalence of intentional poisoning with opioid compounds due to their availability, particularly among men who are single and unemployed. Since the primary cause of death in these patients is a decreased level of consciousness, arterial blood oxygen, and respiratory complications, prompt diagnosis and treatment of poisoning, as well as the implementation of public education programs, thorough monitoring, and preventive measures, are essential to address this growing public health concern.

Ethical approval

This study was approved by the Mazandaran University of Medical Science Ethics Committee (No: IR.MAZUMS.REC.1401.022) and carried out in accordance with the ethical guidelines of the Helsinki Declaration Principles.

Consent

Written informed consent was obtained from the patients for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

Z.Z. and F.A.: were designed for the interpretation and collection of data and editing of the manuscript; A.S.h. and S.M.H.: were involved in writing, editing, and preparing the final version of the manuscript; H.V. and Z.Z.: are responsible for submitting the manuscript. All authors reviewed the paper and approved the final version of the manuscript.

Conflicts of interest disclosure

The authors no conflicts of interest.

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Data availability statement

The data is available to the correspondent author and can be obtained upon request.

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