

Brief Communication

Prevalence of pulmonary edema among the deceased cases with acute Methadone poisoning: A report from Iran

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ABSTRACT

Objective: Methadone poisoning is common in our society, mainly in drug addicts. One of its lethal complications is pulmonary edema. Therefore, we evaluated the prevalence of pulmonary edema in the deceased cases with methadone poisoning and its possible relationship with some medical variables.

Methods: In this cross-sectional study which was done in 2014, we have investigated the deceased patients with methadone toxicity who underwent autopsy at Isfahan Forensic Medicine Department (Iran). All variables including age, gender, and autopsy findings were recorded and analyzed. Demographic characteristics and medical complications of the patients were compared between the patients with or without pulmonary edema in the autopsy findings.

Findings: There were 64 cases who died with methadone poisoning during the 1-year study period. The average age of cases (\pm standard deviation) was 32.1 ± 10.29 years, among which 92.2% were male. Based on the autopsy findings, 64.1% were diagnosed with pulmonary edema. There was no statistically significant relationship between pulmonary edema and age, gender, history of addiction, and hepatic or cardiovascular complications.

Conclusion: Pulmonary edema is a common finding in deceased methadone poisoning cases and must be considered and ruled out in patients with acute methadone toxicity.

Keywords: Methadone poisoning; mortality; pulmonary edema

INTRODUCTION

Based on medical experiences, the dependency to opium is a chronic problem in human societies. Agonists' maintenance therapy is one of the current treatments for addiction to opioids, and it is considered the first-line treatment of chronic opiate dependency. One of these opiate agonists for addiction treatment is methadone. Despite its efficacy, there are no comprehensive care facilities for the people who are still under treatment.^[1-6]

Methadone's metabolism in human has been previously indicated for its lethal poisoning. In recent years, due to the use of methadone in the methadone maintenance treatment (MMT) programs for addiction treatment, many cases with methadone poisoning are reported in our referral poisoning emergency department.^[2] Methadone poisoning is normally caused by intentional or unintentional type of exposure because of lack of adequate knowledge and accurate monitoring; the analgesic effect of the drug

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is short whereas it has a long elimination half-life when used more than the recommended dosage. In addition, due to the easy availability of methadone for family members of addicts, it can be used for suicidal attempt or even unintentional ingestion by children.

In a cross-sectional study in our local forensic department, the number of addicts treated by methadone (MMT) dramatically increased from 2006 to 2014; and among all deaths caused by drugs, 24.4% of the decedents had methadone toxicity.^[2] Furthermore, the epidemiology of deaths from opioid toxicity in a poisoning referral center showed that the majority of deaths have been observed most in patients with methadone poisoning.^[3] Pulmonary edema is a mortal complication for acute methadone overdose which causes mortality in many patients. Considering the fact that methadone toxicity is common in our society, we evaluated the prevalence of pulmonary edema in the deceased cases with methadone poisoning and considered its possible relationship with different variables.

METHODS

In this cross-sectional study which was done in 2014, we have investigated the deceased patients with methadone toxicity who underwent autopsy at Isfahan forensic medicine department. The study protocol was approved by the vice-chancellery of Research and Technology, Isfahan University of Medical Sciences, Isfahan, Iran (Research Project Number 390600). Isfahan is the second largest city of Iran with an estimated population of 3.5 million inhabitants with about 100,000 drug addicts. The autopsy was completed by a full macroscopic and microscopic examination of all organs. In addition, biochemical indices of blood, urine, bile, and viscera at the time death (if available) were fully studied.

All variables including age, gender, and autopsy findings were recorded and analyzed. Demographic characteristics and medical complications of the patients were compared between the patients with or without pulmonary edema in the autopsy findings. Data were analyzed using SPSS software, version 18 (SPSS Inc., Chicago, IL, USA). Chi-square or Fisher's exact tests and independent *t*-test were used for analysis where applicable. To predict the possible associated factors (e.g., age, sex, history of addiction, heart failure) predicting the pulmonary edema, the binary logistic regression analysis was used. $P < 0.05$ was considered statistically significant.

RESULTS

The data from 64 deceased methadone poisoning cases were recorded and analyzed during the 1-year

study period. The mean (\pm standard deviation) age of these patients was 29.10 ± 1.32 years (range: 15–62). Forty-one (64.10%) cases were diagnosed with pulmonary edema. Pulmonary edema was observed more in single people than married ones [$P = 0.025$, Table 1].

Based on the results of the autopsy findings, liver complications have been observed in 39 patients (60.9%) and cardiac complications in four patients (6.3%). The frequency of all complications has been shown in Table 2. The liver and heart complications were not statistically significant between patients with and without pulmonary edema ($P > 0.05$).

The mean (\pm standard error [SE]) time between methadone ingestion and in-hospital admission was 17.3 ± 2.68 h with the range of 3–110 h. The average time (\pm SE) in cases with and without pulmonary edema was 18.1 ± 2.82 and 15.8 ± 3.29 h, respectively ($P = 0.4$). None of the variables (age, addiction history, gender, and complications) had predicting effect value on pulmonary edema in binary logistic regression analysis.

DISCUSSION

The main objective of this study was to determine the prevalence of pulmonary edema in deceased

Table 1: Demographic characteristics of the studied patients (n=64)

Variables	n	Without pulmonary edema	With pulmonary edema	P*
Age (years)				
<30	34 (53.1)	25 (61)	9 (39.1)	0.09
>30	30 (46.9)	16 (39)	14 (60.9)	
Gender				
Male	59 (92.2)	37 (90.2)	22 (95.7)	0.65
Female	5 (7.8)	4 (9.8)	1 (4.3)	
Married status				
Single	33 (51.6)	25 (61)	8 (34.8)	0.025
Married	25 (39.1)	11 (28.6)	14 (60.9)	
Divorced	6 (9.4)	5 (12.2)	1 (4.3)	
Education status				
None educated	2 (3.1)	0	2 (8.7)	0.39
Primary	15 (23.4)	9 (22)	6 (26.1)	
Junior	39 (60.9)	27 (65.9)	12 (52.2)	
Senior	3 (4.7)	2 (4.9)	1 (4.3)	
Academic	5 (7.8)	3 (7.3)	2 (8.7)	
Drug addiction				
Yes	50 (78.1)	30 (73.2)	20 (87)	0.12
No	14 (21.9)	11 (26.8)	3 (13)	
Other substance addiction				
Yes	42 (65.6)	27 (65.9)	15 (65.2)	0.96
No	22 (34.4)	14 (34.1)	8 (34.8)	

*Chi-squared test

Table 2: The frequency of liver, cardiac and pulmonary complications of deceased cases with methadone poisoning

Complication	Percentage
Liver	
None	39.1
Cirrhosis	3.1
Hepatitis	32.8
Steatorrhea	10.9
More than 1 in the above complications	14.1
Heart	
None	93.8
Myocarditis	4.7
Hypertrophic, myositis	1.5
Pulmonary	
None	18.8
Pulmonary edema	64.1
Other pulmonary complications	17.1

cases of methadone poisoning. Nearly 64.1% of the studied cases had pulmonary edema. A previous study has shown that methadone toxicity causes many problems including respiratory depression, aspiration pneumonia, pulmonary edema, and cardiac problems.^[6] However, the exact pathophysiology of pulmonary edema is not known yet, the observations suggest that the primary defect in the alveolar vascular causes leakage of vessel and reduction of the total albumin.^[7,8]

Among the demographic and clinical variables, pulmonary edema was observed more in patients older than 30 years and married ones. It may be explained that married patients are usually elder than single ones. In the study by Peles *et al.* on patients under the MMT, younger age, a partner, negative serology for hepatitis B, and nonbenzodiazepine abuse were the important factors affecting survival in the patients.^[4]

Based on our results, among the three major complications of methadone toxicity, pulmonary edema had the highest prevalence. This result is consistent with the findings of the other studies. In a study by Caplehorn and Drummer and Ridgway and Pountney, the most common signs of methadone toxicity were loss of consciousness and brown liquid discharge from mouth and nose due to pulmonary edema.^[8] It shows the necessity of medical attention to this issue with prompt treatments for the patients with pulmonary edema due to methadone toxicity.^[9,10]

The mean duration time from methadone ingestion to hospital admission was lower in patients with pulmonary edema, but there was no significant difference between the two groups. Other factors such as dosage and the accurate estimation of time of

methadone consumption have influence on patient's mortality time.^[11-13] The findings of this study and the comparison with a previous study show that a significant percentage of patients who died due to overdose of methadone were affected by pulmonary edema.^[2]

This study showed that 60.9% of the deceased patients had hepatic complications in autopsy findings. It was not clear whether the liver failure has been caused by chronic methadone toxicity or other substances such as heroin or stimulants. Cardiac toxicity in patients under MMT program has been described previously as QT interval prolongation.^[14] However, four cases in our study had cardiac toxicity in their autopsy findings.

We found that pulmonary edema is common in deceased cases due to acute methadone toxicity. We suggest prompt diagnostic tests and early intervention of pulmonary edema with intubation and mechanical ventilation for patients with methadone toxicity and clinical manifestations including tachycardia, tachypnea, and low arterial oxygen saturation. We also found liver and cardiac complications in some deceased cases which may suggest considering liver function tests as well as electrocardiography in methadone poisoning cases.

AUTHORS' CONTRIBUTION

Nastaran Eizadi-Mood, Ali Mohammad Sabzghabae, and Mahrang Hedayati contributed in designing and conducting the study. Hossein Madanai collected the data and Nastaran Eizadi-Mood did the data analysis. Ali Mohammad Sabzghabae rechecked the statistical analysis and prepared the manuscript. All authors have assisted in the preparation of the manuscript and have read and approved the content of the manuscript and are accountable for all aspects of the work.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Layson-Wolf C, Goode JV, Small RE. Clinical use of methadone. *J Pain Palliat Care Pharmacother* 2002;16:29-59.
2. Taheri F, Yaraghi A, Sabzghabae AM, Moudi M, Eizadi-Mood N, Gheshlaghi F, *et al.* Methadone toxicity in a poisoning referral center. *J Res Pharm Pract* 2013;2:130-4.
3. Eizadi-Mood N, Yaraghi A, Sharifian Z, Feizi A, Hedaiaty M, Sabzghabae AM. Clinical presentation and the outcome of therapy in a cohort of patients with methadone toxicity in Iran. *Mater Sociomed* 2015;27:276-9.
4. Peles E, Schreiber S, Adelson M. 15-Year survival and retention of patients in a general hospital-affiliated methadone maintenance treatment (MMT) center in Israel. *Drug Alcohol Depend* 2010;107:141-8.
5. Clausen T, Anchersen K, Waal H. Mortality prior to, during and after opioid maintenance treatment (OMT): A national prospective cross-registry study. *Drug Alcohol Depend* 2008;94:151-7.
6. Wolff K. Characterization of methadone overdose: Clinical considerations and the scientific evidence. *Ther Drug Monit* 2002;24:457-70.
7. Shartz M. Opiate and narcotics. *Clinical Management of Poisoning and Overdose*. Philadelphia: WB Saunders Company; 1998. p. 505-19.
8. Caplehorn JR, Drummer OH. Fatal methadone toxicity: Signs and circumstances, and the role of benzodiazepines. *Aust N Z J Public Health* 2002;26:358-62.
9. Ridgway ZA, Pountney AJ. Acute respiratory distress syndrome induced by oral methadone managed with non-invasive ventilation. *Emerg Med J* 2007;24:681.
10. Daugherty LE. Extracorporeal membrane oxygenation as rescue therapy for methadone-induced pulmonary edema. *Pediatr Emerg Care* 2011;27:633-4.
11. Presant S, Knight L, Klassen G. Methadone-induced pulmonary edema. *Can Med Assoc J* 1975;113:966-7.
12. LoVecchio F, Pizon A, Riley B, Sami A, D'Incognito C. Onset of symptoms after methadone overdose. *Am J Emerg Med* 2007;25:57-9.
13. Palmiere C, Brunel C, Sporkert F, Augsburg M. An unusual case of accidental poisoning: Fatal methadone inhalation. *J Forensic Sci* 2011;56:1072-5.
14. Gheshlaghi F, Eizadi-Mood N, Mardani A, Piri-Ardekani MR. Dose-dependent effects of methadone on QT interval in patients under methadone maintenance treatment. *Asia Pac J Med Toxicol* 2013;2:6-9.