Journal of Research in Pharmacy Practice

Brief Communication

Methadone toxicity in a poisoning referral center

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Received: March 2013
Accepted: May 2013

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ABSTRACT

Objective: Methadone poisoning can occur accidentally or intentionally for suicide or homicide purposes. The aim of this study was to evaluate the epidemiological and clinical manifestations of Methadone poisoning.

Methods: A descriptive analytical study was performed from 2010 to 2012 in the poisoning emergency and clinical toxicology departments of Noor hospital affiliated with Isfahan University of Medical Sciences (Isfahan, Iran). All patients with Methadone poisoning within this period of time were investigated. Different variables were recorded in a checklist.

Findings: A total of 385 patients were studied. About 85.7% had ingested only Methadone and 14.3% had ingested other medications with Methadone. Mean ± standard deviation of the age was 32.1 ± 15 years (range: 1-90). Most of the patients were male (76.4%). Nearly 40% of the patients were narcotic addicts, 25.5% were addicts under surveillance of Methadone maintenance therapy centers and 34.5% were non-addicts. Intentional poisoning was observed in most of the patients (57.7%). Most of the patients had a low level of consciousness on admission (58.2%). Respiratory depression and hypotension was observed in 35.6% and 12.7% of the cases as the most common symptoms. Regarding vital signs, there was a significant difference in respiratory rate on admission among different evaluated groups ($P = 0.02$). Length of hospital stay was 18.79 ± 0.72 h (range: 4-240 h, median: 15 h). About 57 patients (25.8%) from the intentionally poisoned patients and 19 patients (12.3%) from the unintentionally poisoned patients had a history of psychiatric disorder ($P = 0.001$). Most of the patients survived without complications.

Conclusion: Addiction, age, gender, attempt to suicide and a history of psychiatric disorder were of the most important factors effective in Methadone poisoning, which should be considered in the public training and prevention of poisoning.

Keywords: Methadone; overdose; poisoning; toxicity

INTRODUCTION

Neurobiological evidence and medical experiences show that opium dependence is a common problem. Agonist maintenance therapy is one of the present therapies for opioid dependency. One of these opioid agonists used to treat addiction is Methadone. Despite the effectiveness of this agonist, comprehensive care facilities for the people under this treatment are not still enough.

Although Methadone is not a new medicine, its use to reduce pain and treat addiction has increased rapidly. Pharmacological characteristics of Methadone indicate lethal and dangerous effects of Methadone poisoning. Methadone poisoning can occur accidentally (resulting from overdose due to abuse of narcotic substance or accidentally by children or elderly) or intentionally for suicide or homicide purposes.[1] Classical symptoms of poisoning include central nervous system (CNS) depression, respiratory depression and miosis that due to the long-lasting effects of Methadone may last for several days.[2] Respiratory depression is a symptom of serious poisoning with Methadone which is observed in 50% of people with

Access this article online

Website: www.jrpp.net

DOI: 10.4103/2279-042X.122387

CNS depression.[3] Methadone poisoning may rarely have other symptoms. Nearly 25% of death cases with methadone poisoning have been reported in the first 14 days starting on methadone maintenance treatment with opioids.[4]

Methadone poisoning is a common poisoning observed in poisoning emergency and clinical toxicology department of Noor hospital (Isfahan, Iran). This may be due to the large number of addicted patients under Methadone maintenance therapy (MMT) protocol and also Methadone availability to other family members. Pharmacy companies usually prepare Methadone for the purpose of MMT as a solution with a fruit taste. In this way, the good taste of Methadone makes it attractive for the children.[5] Because of easily availability of Methadone in our country, and increasing MMT centers for addicted patients, there is a need for epidemiological study on this poisoning to improve both the quality of care and imposing better program on prevention methods. Therefore, the epidemiological and clinical manifestations of Methadone poisoning in the mentioned hospital have been investigated.

METHODS

A descriptive analytical study was performed from 2010 to 2012 in the poisoning referral center of Noor hospital, Isfahan, Iran. All patients poisoned with Methadone who was hospitalized in the poisoning ward and intensive care unit during the abovementioned period were investigated. Patients who had been discharged by their own consent were excluded from the study. Patients who consumed Methadone in concomitant with other medications, which may affect on the level of consciousness or vital signs, were excluded.

After admission of patients to the hospital, blood pressure, heart rate, respiratory rate, and body temperature were recorded. Different variables including gender, age, route of poisoning, clinical symptoms on admission, time interval from ingestion to admission, average dose of Naloxone used, history of psychiatric disorder, kind of exposure (under MMT program, accidental, intentional), co-ingestion of other medication, hospitalization time and outcome (survived without complication, survived with complication including aspiration pneumonia and pulmonary edema and death) were investigated and recorded in a checklist. Data was analyzed by statistical package for the social sciences for windows (SPSS, Chicago, IL, USA) version 20.0. ANOVA, Chi-square, or Fisher Exact Test was used. *P* value less than 0.05 was considered to be significant.

RESULTS

A total of 385 patients poisoned with Methadone were investigated during the study period. About 330 patients (85.7%) had ingested only Methadone and 55 patients (14.3%) had ingested other medications with Methadone. These medications are drugs such as acetaminophen, antibiotic, etc., which do not affect on the level of consciousness or vital signs.

Average age of patients was 32.1 ± 15 years with the range of 1-90 [Table 1]. About 154 patients (40%) were narcotic addicts, 98 patients (25.5%) were under surveillance of MMT centers and 133 patients (34.5%) were non addicts. Distribution of the above-mentioned variables in terms of different groups of patients is shown in Table 1.

The average interval between Methadone ingestion and the first medical care was 7.3 ± 8.4 h with the range of 1-96 h. Treatments offered to the patients included gastric lavage performed for 49 patients (12.7%), activated charcoal administration for 60 patients (15.6%) and prescription of Naloxone for 253 patients. Average dose of naloxone used during hospitalization was 1.86 ± 0.21 mg with domain around 0.05-14 mg. Length of hospital stay was 18.79 ± 0.72 h (range: 4-240 h, median 15 h).

From all patients, 20.5% had a history of psychiatric disorder, which the difference was not significant (P = 0.22) with respect to different groups (24% addicts, 21.4% addicts under MMT, and 15.8% non-addicts). Totally, 57 (25.8%) of the intentionally poisoned patients and 19 (12.3%) of the unintentionally poisoned patients had a history of psychiatric disorder (P = 0.001).

The results regarding outcome have been shown in Table 1. Most of the patients survived without complications. The frequency distributions of clinical symptoms on admission with regard to the patients' outcome are shown in Table 2. Most of the patients were lethargic on admission (58.2%). Respiratory depression and hypotension were observed in 35.6% and 12.7% of the cases, respectively. Regarding vital signs, there was a significant difference among different groups only in respiratory rate [Table 1].

DISCUSSION

The general purpose of this study was to determine epidemiological and clinical characteristics of the patients poisoned with Methadone. According to the results obtained from this study, 60% of the Methadone poisoned patients were in the age group of 20-39 years which is compatible with other studies.[2,6-8] Most of the poisoning cases were narcotic

Table 1: Demographic characteristics, poisoning characteristics, vital signs on admission, intervention during hospitalization, and outcome of methadone intoxicated patients based on three study groups

Variable	Addict (*N*=154)	Addict under MMT (*N*=98)	Non addict (*N*=133)	*P* value
Age (year)	34.9±13	36.8±14.6	25.5±15.1	<0.001
Sex				
Male	86 (87.8)	70 (52.6)	138 (89.6)	<0.001
Female	12 (12.2)	63 (47.4)	16 (10.4)	
Kind of poisoning				
Intentional	42 (44.7)	53 (40.2)	127 (85.2)	<0.001
Unintentional	52 (55.3)	79 (59.8)	22 (14.8)	
Route of exposure				
Ingestion	92 (93.9)	131 (98.5)	149 (96.8)	0.16
Injection	0 (0)	1 (0.8)	1 (0.6)	
Unknown	6 (6.1)	1 (0.8)	4 (2.6)	
Vital signs on admission				
Heart rate (per minute)	83.8±16.8	85.9±16.4	85.9±19.8	0.55
Respiratory rate (per minute)	13.9±4.8	15.1±5.3	15.4±4.5	0.02
Body temperature (°C)	36.97±0.5	36.5±2.6	36.88±0.97	0.07
Systolic blood pressure (mmHg)	110.3±16.5	109.3±16.6	107.8±17.1	0.47
Diastolic blood pressure (mmHg)	68.9±10.8	68.1±14.9	67.1±13.5	0.52
Intervention during hospitalization				
Oxygen 100%				
Yes	112 (72.7)	68 (69.4)	69 (51.9)	0.001
No	42 (27.3)	30 (30.6)	64 (48.1)	
Mechanical ventilation				
Yes	8 (5.2)	6 (6.1)	6 (4.5)	0.92
No	146 (94.8)	92 (93.9)	127 (95.5)	
Outcome				
Survived without complication	137 (89)	93 (94.9)	124 (93.2)	0.07
Pulmonary edema	3 (1.9)	0 (0)	0 (0)	
Aspiration pneumonia	13 (8.4)	2 (2)	6 (4.5)	
Death	1 (0.6)	3 (3.1)	3 (2.3)	

The results are presented as mean±SD or *N* (%) where applicable. MMT=Methadone maintenance therapy, SD=Standard deviation

addicts. In this manner, the most important factors in poisoning with Methadone is its availability, namely the addicts receive it through MMT centers or buy it from the free markets. Moreover, in this way, the addict makes it accessible to his/her other family members. Therefore, limitation of access to Methadone and prevention of its sale in the free market can be an appropriate approach to prevent and reduce Methadone poisoning. On the other hand, some studies indicated incidence of Methadone poisoning symptoms at the same time of starting abstinence of addiction.[9,10]

Moreover, Methadone poisoning occurs either with the intention of suicide or accidentally. In our study, 57.7% of the patients had intentionally used the drug. Somnolence, miosis, respiratory depression and hypotension are among the most common clinical symptoms of the patients poisoned with Methadone. The other studies have also shown that miosis is an important symptom of Methadone poisoning.[3] Also, CNS symptoms like somnolence are among the important symptoms of Methadone poisoning, which evidently are due to acetylcholine blockade in the reticular-activating system. Respiratory depression is also a serious symptom of Methadone poisoning observed in 50% of the patients.[3] In Caplehorn's study, the most common initial symptom of severe Methadone poisoning has been reported to be euphoria, slurred speech and ataxia.[10] In the study by Afshari *et al.*, it has been reported that Methadone poisoning causes a considerable drop in the systolic blood pressure. The difference in the admission clinical symptoms could be due to the difference in severity of poisoning cases.[11]

An investigation into the critical symptoms of the patients at the beginning of their entry in to the hospital showed that respiratory rate of the addict patients was significantly different from that of the non-addict poisoned patients, which may be due to unintentional ingestion and less severity of toxicity.

According to the results of this study, 25.8% of the intentionally poisoned patients and 12.3% of the unintentionally poisoned ones had a history of

Table 2: Clinical manifestations on admission in terms of different outcomes of methadone intoxicated patients

Variable	Survived without complications (*N*=354)	Survived with complications (*N*=24)	Death (*N*=7)	*P* value
Age (year)	31.8±0.79	37.5±3.14	32±4.9	0.19
Sex				
Male	267 (75.4)	22 (91.7)	5 (71.4)	0.18
Female	87 (24.6)	2 (8.3)	2 (28.6)	
Addiction				
Addict	137 (38.7)	16 (66.7)	1 (14.3)	0.03
Addict under MMT	93 (26.3)	2 (8.3)	3 (42.9)	
Non-addict	124 (35)	6 (25)	3 (42.9)	
P value	<0.05	<0.05	>0.05	
Clinical manifestations				
Pupil status				
Normal	117 (33.1)	4 (16.7)	1 (14.3)	0.004
Miosis	223 (64.4)	17 (70.8)	4 (57.1)	
Mydriasis	9 (2.5)	3 (12.5)	2 (28.6)	
P value	<0.05	<0.05	<0.05	
Level of consciousness				
Normal	62 (17.5)	1 (4.2)	0 (0)	<0.001
Somnolence	214 (60.5)	9 (37.5)	1 (14.3)	
Dizziness	55 (15.5)	7 (29.2)	1 (14.3)	
Stupor	19 (5.4)	4 (16.7)	1 (14.3)	
Coma	4 (1.1)	3 (12.5)	4 (57.1)	
P value	<0.05	<0.05	>0.05	
Respiratory rate (per minute)	14.8±0.24	14.3±1.27	9.4±4.2	0.04

The results are presented as mean±SE or *N* (%) where applicable. SE=Standard error, MMT=Methadone maintenance therapy

psychiatric disease. The other performed studies have shown that there was a significant relationship between addiction, mental disorder and suicide and that most of the addict patients committing suicide had a mental disorder background.[7,12] In our study, this fact was also obvious so that 24% of the addicts, 15.8% of the non-addicts and 21.4% of the quitting addicts had a mental disorder background. In the study of Mégarbane *et al*., tendencies to commit suicide have been reported in the Methadone poisoning patients more than the other cases.[13] Brands *et al*., have also shown that the psychiatric problems in the Methadone poisoned patients were considerably more than the other patients.[14] In Cowan's study, hospitalization rate of Methadone poisoned patients in the psychiatric unit has been significantly more than the normal ones.[15]

Considering the result of the treatment, 91.9% of the patients were improved without any complications, three patients (0.8%) suffered from severe pulmonary edema, 21 (5.5%) suffered from aspiration pneumonia and seven patients (1.8%) died. Although differences in the three groups weren't statistically significant, fatality rate of the addicts was considerably higher than that of the non addicts. We could not find a significant difference in the outcome in terms of gender. However in Jean-Paul Bernard study, most people who have died of Methadone poisoning have been men.[16] According to the results, addiction, pupils' size, level of consciousness and respiratory rate on admission had a significant impact on patient's outcome.

One important limitation in our study was different amounts of Methadone ingested by studied patients, which may definitely affect the clinical manifestations and also outcome. In conclusion, considering the Methadone toxicity this study showed that narcotics addiction, age, gender, attempt to suicide and a mental disorder background are of the most important factors effective in Methadone poisoning, which should be considered in the public training and prevention of poisoning with Methadone. Furthermore, considering high incidence rate of Methadone poisoning especially among the addicts, it should be taken some effective steps for more control of access to this drug and when patients suspected of Methadone poisoning refer to the hospitals.

AUTHORS' CONTRIBUTION

FT, AY, AMS, ZF, FG and NEM carried out the design and coordinated the study, participated in most

of the experiments and prepared the manuscript. MM provided assistance in the design of the study, coordinated and participated in manuscript preparation. All authors have read and approved the content of the manuscript.

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How to cite this article: Taheri F, Yaraghi A, Sabzghabaee 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.

Source of Support: This study was financially supported by Vice-chancellery for Research and Technology at Isfahan University of Medical Sciences, **Conflict of Interest:** None declared.