

Predictive Factors of Treatment Outcomes for Hospital Care in Children with Acute Methadone Poisoning

Yasamin Atighi¹, Nastaran Eizadi-Mood², Marjan Mansourian³, Amin Zamani⁴, Ali Saffaei¹, Ali Mohammad Sabzghabae²

¹Pharmacy Students' Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran

²Isfahan Clinical Toxicology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

³Department of Epidemiology and Biostatistics, Isfahan University of Medical Sciences, Isfahan, Iran

⁴Medical Students' Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran

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INTRODUCTION

Methadone is an agonist of opium μ -receptor which is used for the prevention of opiate withdrawal symptoms in detoxification and maintenance therapy for opioid dependents. Other uses are for severe chronic pain relief and intractable cough in advanced lung cancer.^[1]

In Iran, methadone is used for methadone maintenance therapy (MMT) and pain relief in tablet and syrup dosage forms.^[2] Each milliliter of syrup contains 5-mg methadone, and 1 mg/kg of it can cause toxicity, apnea, and even death for children.^[3] Pharmaceutical companies usually produce methadone syrup with fruit flavor in the purpose of MMT, but this flavor can attract children.^[4]

Keeping of this drug in water or juice bottle can cause a higher risk of children methadone toxicity.^[5]

By methadone consumption, the child may show symptoms including nausea, malaise, drowsiness, apnea, coma, and even death. The classical triad of opium toxicity consists of pinpoint pupils, respiratory depression, and unconsciousness, which may be presented in methadone toxicity as well.^[6,7] Another side effect of methadone toxicity is QT-interval elongation.^[8]

Address for correspondence:

Prof. Ali Mohammad Sabzghabae,
E-mail: sabzghaba@pharm.mui.ac.ir

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ABSTRACT

Objective: The trend of methadone toxicity in children and adolescents seems to be increasing in Iran since it is used as a legal measure of the treatment for opioids addiction in methadone maintenance therapy clinics. In the present study, we describe the clinical and demographical characteristics of acute methadone toxicity in a cohort of pediatric poisoned patients in Isfahan, Iran and discussed the predictive factors for their treatment outcomes. **Methods:** In this 4-year cross-sectional study which was performed from 2013 to 2016 in a referral university hospital (Isfahan, Iran), medical records of the demographic and admission time clinical characteristics of all in-patients aged <18 years with acute methadone poisoning were abstracted and analyzed. According to the outcomes of hospital care and treatment, patients were divided as survived without medical complication and patients survived with at least one medical complication or death. **Findings:** A total number of 157 (79 male) children and adolescents with a mean age of 105.4 ± 6.1 months were hospitalized and included in the study. A total of 145 (92.4%) patients survived and discharged from the hospital without any medical complication. Pupil size, respiratory rate, and level of consciousness were predictive factors for the outcome of death or medical complications. **Conclusion:** It seems that methadone poisoning in children and adolescents is more commonly accidental in school-aged boys (6–12 years old) and it occurs mostly with the syrup dosage form, especially when one of the parents or people who live with the child has an addiction history and if the patients' house located in lower socioeconomic class area of Isfahan city (Iran).

KEYWORDS: Acute poisoning, adolescents, children, Methadone overdose

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The trend of methadone toxicity in children and adolescents seems to be increasing in Iran since it is used as a legal measure of treatment for opioids addiction in MMT clinics. In the present study, we describe the clinical and demographical characteristics of acute methadone toxicity in a cohort of pediatric poisoned patients in Isfahan, Iran and discussed the predictive factors for their treatment outcomes.

METHODS

In this cross-sectional chart review study, medical records of children with acute methadone intoxication who were referred to the Department of Clinical Toxicology of Noor and Ali-Asghar (PBUH) University Hospital during the period 2013–2016 were screened, abstracted, and analyzed.

All children and adolescents aged <18 years, with clinical manifestations of acute methadone toxicity, who were referred to the aforementioned hospital as in-patients were included. Exclusion criteria included inaccessibility to complete records due to inaccessibility of patient's parents' addresses or phone numbers or lack of parent's cooperation.

The research protocol of this study was approved by the board of human study of Isfahan University of Medical Sciences.

According to the objectives of the study, medical and demographic data of eligible patients and the type of pharmaceutical dosage form of the ingested methadone (syrup or tablet) were abstracted for further analysis. These were consisted of admission time vital signs including systolic blood pressure and diastolic blood pressure (SBP and DBP, respectively), pulse rate (PR), respiratory rate (RR), oxygen saturation (O₂ sat), blood sugar (BS), pupil size (miotic, normal, or mydriatic), and level of consciousness (conscious, lethargic, stupor, coma, and agitation) and also their demographics including patients' age, gender, duration of hospitalization, type of intoxication (accidental or intentional), patient's geographical place of residency (East, West, South, or Northern region of Isfahan city), father's occupation, parents' profile of addiction, and number of family member.

In case of incomplete data, the authors called the parents of patients to obtain missed or needed demographic details of family and the children. If authors were not able to find persuade parents, in case of lacking more than 20% of the needed information, the case was excluded from the final analysis.

The outcomes of the patients' treatment and hospital care were considered as (a) survived without complication and (b) survived with complication or death.

Data were analyzed using Statistical Package for the Social Science, SPSS software (IBM Corp., Released 2013. IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY, USA: IBM Corp.). The statistical tests used for data analysis were Mann–Whitney U-test, Chi-square test, or Fisher's exact test where appropriate. To investigate the factors affecting outcomes, backward stepwise binary logistic regression test was used. A $P < 0.05$ considered as statistically significant.

RESULTS

During the study period, 157 children poisoned with methadone (79 male, 50.3%) were evaluated. The mean age of the children was 105.4 ± 6.1 months. A total of 145 (92.4%) patients survived without complication while 12 (7.6%) patients survived with complication or died (two patients died). We could not have an estimation of the average dose of methadone ingested because of the dubiety of unreliable medical history which was provided by the parents and not recorded accurately in patients' medical chart.

A total of 129 (82.2%) acutely poisoned patients ingested syrup of methadone, while 25 (15.9%) children used methadone tablet. Among these children, 102 (65%) poisoned accidentally and 51 (32.5%) intentionally. Father or mother of 122 (77.7%) patients was an addict to opium or one of its derivatives. Even though most of the children were inhabitants of the lower socioeconomic class parts of the Eastern Isfahan city, we have not found a statistical difference between the patients' geographical location of inhabitation and the amount of drug ingested ($P = 0.77$). Job career of most of the fathers was simple laborers followed by lower grade governments' employees, and in only six cases, their fathers were unemployed fathers. Most patients had a five-member family (53 patients) followed by 41 patients who had a four-member family. Relation of complication with the number of family member is shown in Figure 1. The number of the family member was not statistically related to the amount of ingested methadone ($P = 0.596$).

We have assessed and compared the medical condition and outcomes of treatment of the studied patients in two groups, Group A who survived and discharged without any complication and Group B who died or survived with at list one medical complication [Table 1]. Clinical characteristics of the patients (including PR, blood pressure, O₂ sat, and BS) at the time of hospital admission in both groups of with and without complication in case of treatment outcomes were not statistically different. The only two notable findings of difference between the two groups were the patient's pupil size and status (mydriatic, normal, or miotic) and their RR [Table 1].

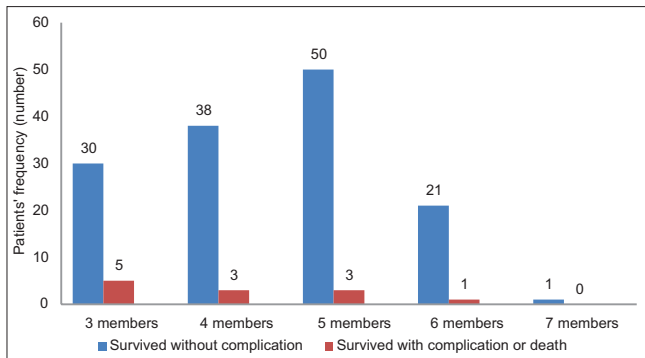


Figure 1: The distribution of family members of the poisoned children with or without medical complications

The hospital stay of Group A was significantly less than Group B (18.2 ± 0.87 h vs. 41.9 ± 13.6 h, $P < 0.001$). Age, gender, history of addiction in one or both parents, type of methadone dosage form, and type of intoxication (accidental or intentional) of the two groups of poisoned children are compared and presented in Table 2.

DISCUSSION

Methadone is used as an effective measure for the treatment and control of opioid addiction. Since the emergence of MMT clinics in private and governmental sectors in Iran, there is an apparent increase of accidental and intentional overdose or abuse of it which subsequently influences children's health who live in the same location. Unsafe home storage of methadone without tight and children-proof containers may contribute to the pediatric acute intoxication of younger family members, especially younger children.^[4,9,10]

To our best of knowledge, most of the previously published epidemiological studies on acute methadone toxicity in Iran were conducted on the adults' population.^[2,11] This may be rational because most of the adult cases of opioid overdose are normally found and placed in this age category. In the adult population, most of the referred acute cases of poisoning with methadone had the outcome treatment of discharge without further medical complication. For instance, in the study of Taheri *et al.*, 91.1% of the patients with acute methadone intoxication discharged from the hospital without a notable medical complication,^[2] and in the study of Aghabiklooei *et al.*, 18.3% of the patients had complications and 28 (8.7%) cases died.^[11]

Despite the facts that younger family members of methadone abusers are at a higher risk for accidental or intentional intoxication and the seriousness of clinical consequences for poisoning with methadone dosage forms in children, the number of reported studies with a demographic and clinical description of poisoning with

Table 1: Clinical characteristics of the studied children with acute methadone poisoning at the time hospital admission

| Variables | Survived without complication (n=145) | Survived with complication or death (n=12) | P |
|------------------------|---------------------------------------|--|---------|
| RR (per minute) | 19.19±0.43 | 15.8±2.5 | 0.043* |
| Oxygen saturation (%) | 92.6±0.8 | 95±0.7 | 0.39* |
| SBP (mmHg) | 104.1±1.60 | 106.2±11.57 | 0.75* |
| DBP (mmHg) | 60.89±1.92 | 57.1±11.4 | 0.61* |
| PR (per minute) | 102.8±1.57 | 106.5±6.68 | 0.521* |
| BS | 130.8±3.7 | 125.5±10.7 | 0.698* |
| Pupil size | | | 0.022** |
| Miotic | 81 (52.9) | 10 (83.3) | |
| Normal | 57 (37.3) | 1 (8.3) | |
| Mydriatic | 3 (2) | 1 (8.3) | |
| No data | 4 (3) | 0 | |
| Level of consciousness | | | 0.014** |
| Conscious | 73 (46.5) | 5 (41.7) | |
| Lethargic | 64 (40.8) | 4 (33.3) | |
| Stupor | 5 (3.2) | 0 | |
| Coma | 1 (0.6) | 1 (8.3) | |
| Agitation | 2 (1.3) | 2 (16.6) | |

Results are presented as mean±SE or n (%) where appropriate. *Mann–Whitney U-test, **Fisher's exact test. SE=Standard error of the mean, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, PR=Pulse rate, RR=Respiratory rate, BS=Blood sugar

Table 2: Comparison of different demographic characteristics of the studied children with acute methadone poisoning concerning the treatment outcomes

| Variables | Survived without complication (n=145) | Survived with complication or death (n=12) | P |
|---------------------------------|---------------------------------------|--|---------|
| Age (month) | 104.7±6.3 | 114.6±23.4 | 0.667* |
| Gender | | | 0.963** |
| Male | 73 (50.4) | 6 (50.0) | |
| Female | 72 (49.6) | 6 (50.0) | |
| Parent's addiction | | | 0.815§ |
| Yes | 111 (76.5) | 11 (8.6) | |
| No | 11 (7.7) | 1 (0.7) | |
| No data | 23 (15.9) | 0 | |
| The dosage form of methadone | | | 0.15§ |
| Syrup | 119 (77.3) | 10 (6.5) | |
| Tablet | 25 (16.2) | 0 | |
| Accidental/intentional toxicity | | | 0.524§ |
| Accidental | 95 (62.1) | 7 (4.6) | |
| Intentional | 46 (30.1) | 5 (3.3) | |

Results are presented as mean±SE or n (%) where appropriate. *Mann–Whitney U-test, **Chi-square test, §Fisher's exact test. SE=Standard error of the mean

methadone in the pediatric population is limited.^[5,12-16] Sharif *et al.* in a study conducted in Iran have reported

clinical complications in almost half (48.3%) of the children with acute methadone toxicity, which is in contrast to our study with a 7.6% of complication during treatment. This can be attributed to the difference between the time elapsed from poisoning and hospital admission in these studies and also the accessibility of a well-equipped medical ward and well-trained medical and nursing staff in our referral university medical center.

In a case series reported by Farnaghi *et al.*,^[16] poisoning with methadone was accidental in almost all poisoned children which is in contrast to our findings in Isfahan with 65% of accidental poisoning and two other previously published studies which reported 57.7 and 30.3% of accidental poisoning with methadone in children in the same medical center.^[2,3] This trend of decrease in intentional methadone poisoning may be due to the recent restriction of methadone distribution in Iran and also using a safer dosage form containers with a more informative packaging.

In the present study, socioeconomic class of family members of the poisoned children was noted to be a potential variable related with accidental or intentional intoxication with methadone. We considered geographical location of patients' home, number of family members who live with each other in the same place, and the job career of the principal breadwinner of the family as proxies for indirect estimation of this status. According to our results, these demographic characteristics were not statistically significant predictors of methadone poisoning in children. This finding is in contrast to our previous report which we found both poor socioeconomic class and level of education as significant risk factors for committing intentional self-poisoning and suicide attempt in a general pediatric and adult population during a 2-year epidemiological study. In a similar study conducted in Spain, socioeconomic inequalities have presented as the cause of higher rate of drug abuse in a special population of patients.^[17] This may be due to the diversity of these characteristics between patients and also the referral nature of our medical center, which lets the admission of a heterogeneous population of poisoned patients.

In case of admission time clinical characteristics of the studied children, the RR was significantly lower in Group B (treatment with complication or death), but other vital signs (SBP, DBP, O₂ sat) and BS were not different, which is in contrast to our previously published finding in adult population with acute methadone intoxication.^[2,3] Mostly, nonintentional (accidental) nature of methadone poisonings in our studied children may contribute to explain the possible reason for this difference between the two populations of pediatric and adult patients. In our previous study on adults with methadone toxicity, most

of them were previously addicts who were on MMT with a natural craving of opioids and a tendency for overdose of methadone in larger doses, and their vital signs and clinical condition were influenced more than children in our present study, where their poisonings were mostly accidental and collateral in nature.

The association of patients' pupil size, level of consciousness, and RR with their hospital treatment outcomes is a common finding in previous studies on adult's patients with acute methadone toxicity.^[2,3,11,18] In the present study on children, most of the complicated patients with poor prognosis (Group B) had miotic pupil size, lower level of consciousness, and also lower rate of respiration at the time of admission comparing to children with no complication of treatment (Group A), which is consistent with previously reported results in the adult population.

In our study, the treatment outcomes for the patients were not in association with age, gender, addiction habits of the parents, number of family members who live in the same place, pharmaceutical dosage form (tablet/syrup) of methadone, and accidental/intentional cause of toxicity, which is consistent with the findings of Aghabiklooei *et al.*^[11]

Despite the fact that in our study, demographic details of the studied poisoned children had not a significant association with the treatment outcomes of hospital care and most of the acute poisoning cases of methadone toxicity were discharged from the hospital without any further medical complication, it seems that methadone poisoning in children is more commonly accidental in school-aged boys and is occurred mostly with the syrup dosage form, especially when one of the parents or people who live with the child has an addiction history, and if the patients' house is located in lower socioeconomic class area of Isfahan city. RR, size of the pupil, and level of consciousness of the pediatric patients at the admission time in hospital had predictive value for the outcomes of hospital care for these young patients.

AUTHORS' CONTRIBUTION

Nastaran Eizadi-Mood and Ali Mohammad Sabzghabae presented the idea and conceptualized the design of the study. Yasamin Atighi and Amin Zamani gathered and abstracted the data. Ali Saffaei, and Nastaran Eizadi-Mood analyzed the data. Yasamin Atighi, Amin Zamani and Ali Mohammad Sabzghabae drafted the manuscript. All authored revised and approved the final manuscript and are equally accountable for its content.

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Conflicts of interest

There are no conflicts of interest.

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