

Research Article

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## Opioid Poisoning in Children: A Report of 90 Cases

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**Introduction:** The opioid overdose epidemic is a worrying and considerable public health problem in many countries. A few studies have been done in children about opioid poisoning. The aim of this study was to explain the clinical symptoms and laboratory findings of opioid poisoning and the associated complications among children.

**Material and Methods:** This prospective cross-sectional study was conducted on 100 children under 14 years of age who were poisoned with opium, tramadol, buprenorphine, methadone, and diphenoxylate and admitted to Loghman-Hakim Hospital, a major center for poisoning treatment in Tehran, Iran, from April 2011 to April 2012. The exclusion criteria were a history of musculoskeletal diseases, concurrent ingestion of other drugs, intramuscular injection, and a history of trauma. The clinical presentation and renal and electrolytes complications were recorded.

**Results:** Finally, 90 out of 100 admitted children were eligible to be included in the study, 64 boys and 26 girls (median age: 40.3 ± 32 months, range: 1 month to 11 years old). The minimum duration of admission was 1 day and the maximum was 29 days with a mean of 2 days. The major opioid substance was methadone. The most common symptom was decreased consciousness followed by bradypnea. The incidence of opioid-induced rhabdomyolysis was 2.2% but none of them were complicated with acute renal failure or electrolyte disturbance.

**Conclusions:** Concerning this study, we recommend attention to muscle enzymes elevation and preventive spade work for its complications in children poisoned with opioids.

**Keywords:** Opium; Poisoning; Rhabdomyolysis; Acute Kidney Injury; child.

**Running Title:** Opioid Poisoning in Children: A Report of 90 Cases

### Introduction

Poisoning, either through inhalation, ingestion, injection or absorption of a toxic substance, injures and/or destroys cells and results in inadvertent mortality and morbidity, particularly among children [1]. In 2004, acute poisoning caused more than 45 000 deaths in children and adolescents, about 13% of all fatal accidental poisonings worldwide.

In 16 high-income and middle-income countries, poisoning is the fourth most important cause of unwitting injury after road traffic injuries, fires, and drowning. Fatal poisoning rates in low-income and middle-income countries are four times more than other countries. The highest rates of fatal poisoning are observed in children less than one year and in adolescents that are about fifteen years. Common

poisoning agents in middle-income and low-income countries are fuels such as kerosene and paraffin, pharmaceuticals, and cleaning agent [2]. The opioid overdose epidemic is a worrying and considerable public health problem in many countries. Among poisoning agents in children and adults, opioids are reported to be a major etiology. Opioid ingestion can induce high morbidity and mortality even disproportionate with dose [3-6]. An opioid epidemic with adverse consequences is escalating due to many factors such as increasing the prevalence of chronic pain with prescription of overdoses of opioid pain relievers, increasing the health care costs, and increasing adult illicit drug abusers [7]. An inevitable consequence of increasing adult drug prescriptions is an increase in pediatric poisonings and exposure, particularly for opioids and among children aged 0 to 5 years [8]. Considering the limited number of studies conducted on opioid ingestion and its disastrous consequence among children, the present study was conducted to examine the clinical symptoms and laboratory findings of opioid poisoning including tramadol, buprenorphine, methadone, and dipheoxylate and the associated complications in children.

**Material and Methods**

This prospective cross-sectional study was conducted on all children under 14 years of age that were poisoned with opium, tramadol, buprenorphine, methadone, and dipheoxylate and were admitted to Loghman-Hakim Hospital, a major center for poisoning treatment in Tehran, Iran, from April 2011 to April 2012. Opioid ingestion was confirmed through patient's history, physical examination, and urinary test for opium. The exclusion criteria were a history of musculoskeletal diseases, concurrent ingestion of other drugs, intramuscular injection and a history of trauma. Finally, 90 out of 100 admitted children were eligible to be included in the study. Laboratory tests including serum creatine phosphokinase (CPK) using the Hitachi Japan 711 device, blood urea nitrogen (BUN), creatinine (Cr), lactate dehydrogenase (LDH), sodium (Na), potassium (K), blood sugar (BS), phosphate (PO4) and calcium (Ca), uric acid and urinalysis were performed. CPK was rechecked 24 hours later to examine a possible delay in CPK rise. We considered the CPK level suggestive of rhabdomyolysis (RM) when it was more than 1000 either in the first or the second sample. The

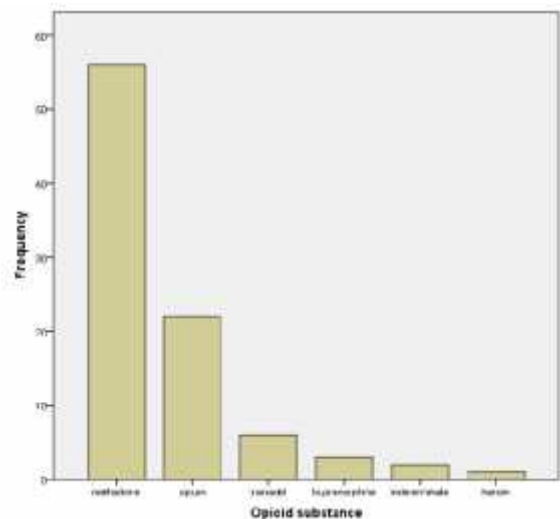
Ethics Committee of the University approved the study.

Statistical analysis: All analyses were performed using SPSS version 16 for Windows (SPSS Inc., Chicago, IL, USA). Comparison of the qualitative variables by presence or absence of RM was carried out using the Pearson's chi-square statistic or Fisher's exact test.

**Results**

Among 90 cases, 64 were boys and 26 were girls (median age: 40.3±32 months, range: 1 month to 11 years old).

The minimum duration of admission was 1 day and the maximum was 29 days with a mean of 2 days. The maximum delay for referring to the hospital was 22 hours with a mean of 5 hours. The major opioid substance was methadone. The distribution of opioid substances causing toxicity is indicated in Figure 1.



**Fig 1.** The distribution of opioid substances causing poisoning

**Table 1:** The frequency of clinical symptoms

| Symptom           | Presentation (percentile) |
|-------------------|---------------------------|
| Apnea             | 19(21.1)                  |
| Cyanosis          | 24(26.7)                  |
| Convulsion        | 4(4.4)                    |
| Consciousness     |                           |
| Awake             | 28(31.1)                  |
| Verbal responsive | 54(60)                    |
| Pain responsive   | 2(2.2)                    |
| Unresponsive      | 6(6.7)                    |
| Hypotension       | 11(12.2)                  |
| Bradypnea         | 37(41.1)                  |

The most common symptom was decreased consciousness followed by bradypnea (Table 1). Out of 90 patients 2 had RM (2.2%) whose clinical symptoms and lab data are presented in Table 2.

**Table 2.** Clinical symptoms and lab data of two patients with rhabdomyolysis

| Demographic data            | Case 1    | Case 2    |
|-----------------------------|-----------|-----------|
| <b>Sex</b>                  | F         | M         |
| <b>Age(month)</b>           | 42        | 36        |
| <b>Referral delay(hour)</b> | 2         | 22        |
| <b>Substance</b>            | methadone | methadone |
| <b>Bradypnea</b>            | +         | +         |
| <b>Cyanosis</b>             | -         | +         |
| <b>Convulsion</b>           | -         | -         |
| <b>Hypotension</b>          | -         | -         |
| <b>CPK(U/L)</b>             | 1000      | 2300      |
| <b>LDH(U/L)</b>             | 800       | 900       |
| <b>SGOT(U/L)</b>            | 106       | 113       |
| <b>SGPT(U/L)</b>            | 40        | 18        |
| <b>Myoglobinuria</b>        | -         | +         |
| <b>Ca(mg/dl)</b>            | 9         | 9.5       |
| <b>Po4(mg/dl)</b>           | 6         | 3.5       |
| <b>BS(mg/dl)</b>            | 66        | 446       |
| <b>Na(meq/l)</b>            | 138       | 135       |
| <b>K(meq/l)</b>             | 4.5       | 4         |
| <b>Cr(mg/dl)</b>            | 0.7       | 0.7       |
| <b>Uric acid(mg/dl)</b>     | 4.5       | 4.1       |
| <b>HCO3(meq/l)</b>          | 15        | 12        |

In our study, a few electrolyte disturbances were observed. Hyperkalemia was not observed because of the absence of severe muscle injury so that maximum CPK was 2000. We observed three cases of hypokalemia and 5 cases of hyponatremia due to gastroenteritis. One child with hypocalcaemia and four cases with hypophosphatemic rickets was reported. There was no report of hyperphosphatemia in two children with RM. Hyperglycemia >200 was observed only in one patient because of stress and decrease to normal levels after 24 hours. On the other hand, we remarked two cases of hypoglycemia due to prolonged fasting. One hyperuricemic case had dehydration. SGOT was more than two time of normal in three patients including two with RM. Metabolic acidosis was observed because of hypoxia.

## Discussion

Poisoning was two times more prevalent in boys than girls, probably due to their activeness. It was more common in 2-4 year olds, which is also the common age group for other types of poisoning, as well.

According to the results of this study, methadone was the most common type of opioid substance causing poisoning. Acute methadone overdose has become one of the most common poisonings in Iran and around the world [9]. The main reason is an increased number of methadone maintenance clinics in the past decade in Iran. Although according to a study on 893 drug-related deaths in Virginia, deaths due to methadone increased rapidly over the 7-year study period (1997 to 2003), none of the patients died in our study. This is possibly due to the fact that the exposure is accidental and consequently leads to low dose ingestion [10]. Most of the accidental poisoning cases occurred as a result of mistaking opioid syrup with cough medicine or water, particularly by children under 12 years old. Since it was in a liquid form, the exact mean ingested dose of the syrup was also unknown.

In our study, opioid-induced RM was observed in 2.2% of the children. However, few studies have investigated the incidence of rhabdomyolysis in opioid poisoned children.

The first historical report of RM goes back to the Old Testament in which the Jews developed RM after the ingestion of quail. The reason was considered to be consumption of hemlock herbs by these birds during their spring time migration around the Mediterranean sea [11]. The modern explanation of RM was developed by Fleischer in 1881 in which a new type of hemoglobinuria following muscle exertion was reported [12]. The etiology of RM is categorized in three groups: traumatic, non-traumatic exertion, non-traumatic non-exertion. The main causes of non-traumatic non-exertion, particularly in the peace time, are reported to be drugs and toxins. RM can be induced by about 200 different drugs which affect muscles either directly, e.g., statins, or indirectly, e.g., illegal drugs [13-17]. Drugs can induce primary RM or a secondary phenomenon following hypoxia, convulsion, or shock [18, 19]. RM is caused by sarcolemma injury of the skeletal muscles resulting in the leakage of its constituents into the blood and urine. These contents include myoglobin, creatine phosphokinase, aldolase, lactate dehydrogenase, potassium, and serum glutamic-oxaloacetic

transaminase (SGOT). Any drug or toxin that impairs skeletal muscle ATP production and increases energy requirements may cause RM. Direct drug -induced sarcolemmal injury is mediated by activation of phospholipase A. A drop in myoplasmic ATP paralleled with sustained elevations in cytosolic  $Ca^{2+}$  concentration represents a common signature of RM. Serious drug poisoning is frequently associated with RM. It has been reported that drug overdose is the major cause of RM (28% of the patients) [20] and acute chemical poisoning is the cause in 0.06% (93 of 143,830 patients admitted). The etiologies of RM in children are various and differ from those reported in adults. Perreault S et al reported that drugs caused only 6% of the cases of RM in children [21-23].

Among abused drugs and substances, amphetamine, cocaine, barbiturates, methadone, and ethanol can induce RM. In poisoned adults, the most common causes of RM are opioids and ethanol intoxication [21]. In a study on 475 hospitalized patients with RM, exogenous toxins were the most common cause of rhabdomyolysis, with illicit drugs, alcohol, and prescribed drugs including antipsychotics, statins, zidovudine, colchicine, selective serotonin reuptake inhibitors, and lithium responsible for 46% [22]. According to several studies from Iran, among illegal drugs, considering prohibition against ethanol, opioids were the main cause of RM (28% and 23%, respectively) [14, 23]. Different types of opioid intoxication with either natural opioids such as opium or synthetic opioids such as methadone, tramadol, dipheoxylate, buprenorphine may cause RM. We had 2 children with RM. Although apnea and cyanosis was present in one of them, the other one did not have any manifestations of apnea, cyanosis, or convulsion, suggesting the direct effect of opioids on the muscle cell. Although opioids have been introduced as the major cause of RM in poisoning (even up to 41%) in several studies [24], we believe low dose ingestion was the reason for the lower incidence of RM in our study.

Acute renal failure is one of the important complications of RM, which is caused by the accumulation of myoglobin in renal tubules. The prevalence of acute kidney injury following RM has been reported to be 16-46% among adult patients, but this rate has been about 5% in children in several studies [25]. None of the children in the present study developed ARF because CPK did not increase severely.

In opioid poisoning, different electrolyte disturbances such as hypo or hyperkalemia, hypernatremia, hypomagnesemia, and hypocalcaemia could also occur [26-32].

In this study, none of the electrolyte disturbances was related to intoxication directly. In general, the electrolytic disturbances were associated with the comorbid conditions rather than opioid ingestion including hypokalemia and hyponatremia in a few patients with gastroenteritis, and hypocalcaemia and hypophosphatemia in patients with rickets. This is probably due to the inadvertent and low consumption of opioids.

### Conclusion

Concerning this study, we recommend attention to muscle enzymes elevation and preventive spadework for its complications in children poisoned with opioids.

### Conflict of Interest

None declared

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