

## Methadone Toxicity: A Pediatric Case Report

Rachel S. Segal and Derek J. Zhorne\*

Department of Pediatrics, Stead Family Children's Hospital, University of Iowa, United States

\*Corresponding author: Derek J. Zhorne, Department of Pediatrics, Stead Family Children's Hospital, University of Iowa, United States, E-mail: derek-zhorne@uiowa.edu

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### Abstract

Pediatric morbidity and mortality from methadone toxicity has increased in recent years. Multiple publications serve to highlight the danger of methadone ingestion for pediatric patients as there is notable overlap between toxic and fatal levels of methadone for children. This case report presents a 4-year-old male who was admitted to the pediatric intensive care unit due to emesis, altered mental status and acute hypoxemic respiratory failure. Methadone was identified on serum drug screening and no alternative explanation for patient's clinical presentation was found. This case report highlights importance of additional drug testing and consideration of methadone toxicity whenever a patient presents with miosis, central nervous system depression and respiratory depression as it may require testing beyond the standard urine drug screen to identify the correct drug exposure.

**Keywords:** Methadone; Pediatric morbidity; Mortality

### Introduction

Pediatric morbidity and mortality related to methadone toxicity has risen over time [1]. A synthetic diphenylpropylamine that is well absorbed from the gastrointestinal tract, methadone is effective in treating both nociceptive and neuropathic pain and has found use in the treatment of opioid dependence [2]. It is a highly lipophilic drug with a large volume of distribution and highly variable elimination half-life ranging from 15-55 hours. This allows for once daily dosing but also contributes to prolonged clinical effects that have been reported to last up to 72 hours in some patients after a single oral dose [2-4]. Signs and symptoms of methadone toxicity include miosis, vomiting, CNS depression that ranges from altered mental status to a comatose state, respiratory depression, apnea, cardiac arrhythmias or cardiovascular collapse [4,5]. Children are especially vulnerable to the effects of methadone as small doses may cause dramatic symptomatology. In this report, we describe the case of a 4-year-old male with no significant past medical history who presented with methadone toxicity.

### Case Presentation

A previously healthy 4-year old male presented to the local emergency room with acute onset of non-bilious emesis and lethargy. The patient had been staying at a maternal friend's house during the day where he was reportedly in good health. His mother picked him up around 15:00 and then dropped him off at his maternal grandmother's house while she left to run an errand. Upon returning around 17:30, the patient was seen sleeping on a couch. When his mother went to wake him up for dinner ~19:00, the patient was noted to be somnolent. He was unable to stand and then started having nonbilious, nonbloody emesis. He was taken to the local emergency room where his initial vital signs were notable for being afebrile, tachycardic (HR 131), tachypneic (RR 30) with normal BP and SpO<sub>2</sub> of 91% on room air. There is no documentation of his presenting physical exam although the transport phone call indicated that he was tremulous, ataxic and

had altered mental status upon arrival. In the ER, he became unresponsive with witnessed seizure-like activity that resolved after a dose of Ativan. He was subsequently intubated as he had further decline in his mental status and a venous blood gas was consistent with acute hypoxemic respiratory failure. Other labs obtained in the ER showed a normal complete blood count with differential, CRP, electrolytes, serum glucose, liver function tests and ammonia level. He had an undetectable acetaminophen level. A urinalysis was positive for amphetamines although there was insufficient sample for confirmatory testing. A chest x-ray and noncontrast head CT were both unremarkable. The patient was transferred via helicopter to the regional children's hospital and admitted to the Pediatric Intensive Care Unit (PICU).

Further history was obtained at that time. No one at the maternal grandmother's house saw the patient eat or drink anything prior to falling asleep. There was reportedly no ephedrine, propranolol, atenolol or carbidopa-containing medications at the maternal grandmother's home. The patient had met all developmental milestones appropriately but did not receive routine healthcare and had not seen a physician in > 2 years. He had never been hospitalized or required surgery. He did not take any medications. There was no known history of falls, trauma or previous seizure-like activity.

Upon arrival to the PICU, he was placed on continuous EEG monitoring which was normal. A repeat urine drug screen was obtained at the time of admission to the PICU and resulted negative approximately 9 hours after the original positive urine test. A plasma drugs of abuse screen was sent approximately 12 hours after admission to the PICU and resulted positive for methadone and negative for amphetamine, barbiturates, benzodiazepines, buprenorphine, cocaine, opiates, phencyclidine, cannabinoids, oxycodone and methamphetamine. Subsequent testing via Quantitative Liquid Chromatography-Tandem Mass Spectrometry confirmed the presence of both methadone and its metabolite, ethylidene -1,5-dimethyl -3,3-diphenylpyrrolidine (EDDP). A DHS report was filed. He spiked an isolated fever to 38.8 degrees Celsius after admission and underwent an infectious work-up consisting of blood, urine and CSF cultures and was started on empiric antibiotics of vancomycin and ceftriaxone. His

CSF studies were not consistent with an infectious or inflammatory process and his antibiotics were stopped after 48 hours of negative cultures. His sedation and mechanical ventilation were weaned and he was extubated to room air on hospital day #2. The patient slowly returned to his baseline mental status and activity level over a 72 hour period.

## Discussion

This patient's presenting symptoms included ataxia, slurred speech, declining mental status and progressive respiratory failure which are consistent with methadone toxicity. The confirmed presence of both methadone and its metabolite, EDDP, in his serum at significantly elevated levels (184 ng/ml and 19 ng/ml, respectively) are indicative of methadone ingestion.

In 2000, Milroy and Forrest published a toxicological analysis of deaths involving methadone that included 5 cases involving children under 14 years of age. In those pediatric deaths, the serum methadone levels ranged from 200 – 489 ng/ml [3]. The largest review of pediatric methadone toxicity cases is a retrospective review from 2001 – 2012 in Tehran which included 453 cases of methadone toxicity of whom 3 patients (0.7%) died and 12 patients (2.7%) were intubated [6]. The authors noted that tachycardia, fever, an initial prolonged QTc interval and an elevated AST were all independently associated with intubation and death [6]. A systematic review of the literature by Alotai et al. identified 38 publications which included 62 cases of pediatric methadone toxicity. There were 29 children whose deaths were attributed to methadone toxicity and in those patients the serum methadone concentrations ranged from 60 – 1200 ng/ml (median: 385 ng/ml) compared to children who survived having concentrations which ranged from 30 – 360 ng/ml (median: 100 ng/ml) [1]. These publications serve to highlight the danger of methadone ingestion for pediatric patients as there is notable overlap between therapeutic adult serum methadone levels and fatal pediatric serum levels.

As illustrated by this case, it can be difficult to assess for and interpret drug testing in the pediatric population as samples may be collected from urine, blood, hair, sweat or saliva. The advantages and disadvantages of testing the various specimens are beyond the scope of this article. Currently however, urine remains the most popular clinical test because it is relatively inexpensive, easy to obtain and has the most published scientific data [7]. This patient's initial positive urine drug

screen prompted additional testing as urine toxicology tests can provide evidence of drug use at a single point of time, but cannot be used to determine the frequency or amount of drug that is consumed [8]. Our patient did have a hair sample sent for toxicology testing and it returned negative for methadone. The presence of methadone in the patient's serum sample but not in the hair sample is consistent with an acute methadone exposure with insufficient time for the drug to be incorporated in this hair at the time of sample collection.

## Conclusion

Pediatric morbidity and mortality related to methadone toxicity has increased over time. Children are at especially high risk for complications from methadone ingestion given that a very small amount of methadone may be fatal as there is significant overlap between toxic and fatal levels of methadone for children. Methadone toxicity should be considered whenever a pediatric patient presents with the combination of miosis, central nervous system depression and respiratory depression as it may require testing beyond the standard urine drug screen to identify the correct drug exposure.

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