

Research Article

J Ped. Nephrology 2016;4(2):65-69

<http://journals.sbmu.ac.ir/jpn>

DOI:

Reliability of Urine Strip Test For Confirmation of Methadone Poisoning in Children

How to Cite This Article: Farnaghi F, Pournasiri Z, Vakili A. Reliability of Urine Strip Test For Confirmation of Methadone Poisoning in Children. J Ped. Nephrology 2016;4(2):65-69.

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Received: Feb-2016

Revised: Feb-2016

Accepted: Mar-2016

Introduction: Methadone is a drug with biologic effects similar to morphine which acts via interacting with major classes of receptors κ and μ . It has a half-life of 25 to 50 hours. Ingestion of this substance causes serious symptoms such as bradycardia, apnea, decreased level of consciousness, and death. Rapid diagnosis and treatment is life-saving. The methadone urine test is an easy to perform test which could detect the substance rapidly. This study was conducted to determine the reliability of the positive methadone urine test in the first and second days of poisoning in children below the age of 13 who have been poisoned with it.

Materials and Methods: A total of 50 children below 13 years of age were enrolled in the study from April 2013 to April 2014. They were referred to Loghman Hakim Hospital with a history of incidental methadone ingestion and clinical symptoms congruent with methadone poisoning such as apnea, drowsiness, decreased level of consciousness, and bradycardia and miosis. Methadone urine strip test was performed on the first and second days. Five parameters (age, gender, dose of ingested methadone, urine SG, and urine pH) were tested and recorded for each patient.

Results: This test is an accruable test for the detection of methadone (P value<0.05). Findings suggested that as little as 2 mg of methadone administration could lead to a positive urine test. The highest frequency of positive test was observed when the test was given between 6 to 12 hours after methadone ingestion and the lowest frequency was obtained in the first 6 hours after poisoning. It is suggested that the test result can be false negative if it is carried out in less than 6 hours after methadone consumption.

Conclusions: According to the results of this study, the methadone urine drug screen test has high accuracy for detection of methadone in the urine. In addition, if the initial test result is negative in the first 24 hours, we recommend that the test should be repeated 24 hours after the ingestion; thus, two negative results in the first 48 hours of ingestion can rule out methadone poisoning by a probability of 98.5%.

Keywords: Poisoning; Urine Test; Methadone; Child.

Running Title: Urine Strip Test For Confirmation of Methadone Poisoning

Introduction

Methadone is a synthetic narcotic drug which shows morphine-like characteristics. In addition, it affects κ and μ receptors as an agonist and can lead to drowsiness, reduced consciousness, apnea, miotic pupils, bradypnea, cyanosis, long QTC, vomiting, bradycardia, and eventually death [1-3].

Due to the high prevalence of opioid addiction and the use of methadone as a substitute, as well as the lack of knowledge about its danger in the general population, poisoning with this substance is increasing, especially in children.

Methadone has a half-life of 25-50 hours [4] and a dose of 1mg/kg can cause apnea and even death.

Drugs that affect cytochrome p450 can interfere with the methadone metabolism [5, 6].

There has been limited research addressing the toxicokinetics and toxicodynamics of methadone in children [7] which have produced elusive knowledge about the toxicity of this substance in this group of population. However, in some studies, 10 mg methadone has been reported to be lethal in children [8, 9].

Due to the high prevalence of methadone poisoning in children and its serious side effects, as well as access to the suitable antidote, well-timed detection and treatment is important for rescuing the patients.

Rapid detection of methadone in the urine is one of the most practical tests [10, 11]. There are several compromising factors such as the administration of other drugs, systemic diseases such as diabetes, liver and kidney disorders, and acidic or alkaline pH and high or low SG of urine [12, 13]. The appropriate range of pH and SG should be 4-8 and 1005-1025, respectively [14, 15].

The main goal of this study was to calculate the percentage of the positive methadone urine test on the first and second days of poisoning and the correlations between the dose of ingested methadone and a positive test.

Materials and Methods

The participants were 50 children under 13 years old referred to Loghman Hakim Hospital from April 2013 to April 2014 with a history of methadone ingestion and commensurate clinical symptoms of methadone poisoning such as apnea, miosis, drowsiness, decreased level of consciousness, and bradycardia. They entered the study after their parents gave informed consent. The patients who denied methadone ingestion with a history of multiple drug ingestion or a systemic underlying disease such as diabetes, liver and kidney disorders, or an inappropriate range of urine pH (<4 & >8) and SG (<1.005 & >1.025) were excluded from the study. For each patient, a questionnaire was filled to collect the data of the age, gender, clinical symptoms, time of methadone ingestion, and other recent co-administered drugs. Urine samples were taken on admission and 24 hours later. The urine specimen was collected in a clean and dry container. Urine samples exhibiting visible precipitates were initially centrifuged, filtered, and allowed to settle to obtain a clear supernatant for testing. This procedure was carried out by a methadone specific strip test

manufactured by Hannan Teb Pars Co. The MTD One Step Methadone Test Strip (Urine) is a lateral flow chromatographic immunoassay for the detection of methadone in the human urine at a cut-off concentration of 300ng/ml. The pouch was brought to the room temperature before opening and the test strip was removed from the sealed pouch with arrows pointing toward the urine sample; the test strip was immersed vertically in the urine specimen until the specimen starts to migrate. The countdown was then started for the red line to appear. The result was read after 5 to 10 minutes. **POSITIVE RESULT:** One red line appears in the control region (C). No line appears in the test region (T). **NEGATIVE RESULT:** Two lines appear: one red line in the control region (C), and another red or pink line in the test region (T). The Methadone Test Strip is an immunoassay based on the principle of competitive binding. Drugs that may be present in the urine sample compete against the drug conjugate for binding sites on the antibody. During testing, a urine specimen migrates upward by capillary action. Methadone, if present in the urine specimen at concentrations below 300 ng/mL, will not saturate the binding sites of antibody-coated particles in the test. The antibody-coated particles will then be captured by immobilized methadone-protein conjugate and a colored line will show up in the test line region. The colored line will not form in the test line region if the methadone level exceeds 300 ng/mL because it will saturate all the binding sites of anti-methadone antibodies. A drug-positive urine specimen will not generate a colored line in the test line region because of drug competition, while a drug-negative urine specimen or a specimen containing a drug concentration less than the cut-off will generate a line in the test line region. To serve as a procedural control, a colored line will always appear at the control line region indicating that proper volume of sample has been added. A total of 100 samples were collected prospectively.

Five parameters including age, gender, dose of methadone administration, urine SG, and urine pH were assessed in the study.

Statistical analysis

The frequency of the positive test on the first, second, or both days was reported. The correlation between the positivity rate on the first and/or the second day and the dose of ingested methadone was analyzed, and the relationship of apnea with the first- and second-day positive test was also investigated using the student's t-test,

²
 χ^2 and Fisher's exact test. Analyses were done with the Statistical Package for Social Sciences (version 18.0 SPSS Inc., Chicago, USA) software, and $p < 0.05$ was considered statistically significant.

Results

Demographic characteristics

Fifty children including 27 boys and 23 girls with a mean age and SD of 15.7 ± 32.8 (minimum 8 months and maximum 155 months) were studied in this research.

Six percent of the patients were under 12 months age, 10% were 13-24 years, 30% were in 25-36, 12% in 37-48, 4% in 49-60, 12% in 61-72, 2% in 73-84, 10% in 85-96, 6% in 97-108, 6% in 109-120, and 2% in 145-156 months group. Twenty-eight cases (55%) of poisonings occurred in the age group 1-5 years old.

Dose of methadone:

Thirty-one patients of all 50 were poisoned with known amounts of methadone with a minimum of 2 mg and a maximum of 50 mg, and 19 subjects ingested unknown amounts of this substance.

Five patients were poisoned with methadone tablets and the others were poisoned with syrup.

Assessment of clinical symptoms

The minimum and maximum time interval between methadone ingestion and visiting the hospital was 30 minutes and 12 hours, respectively.

The signs and symptoms were observed as follows: reduced consciousness including drowsiness (90%), vomiting (60%), respiratory depression (52%) and apnea (28%); one patient was asymptomatic.

Seizure occurred in one patient (2%) before the administration of Narcan (an opioid antagonist and antidote of methadone). Furthermore, 26% of the subjects suffered from cyanosis at the time of admission. The frequency of clinical symptoms on admission to the emergency department is shown in Figure 1 separately.

Positive and negative methadone urine tests on the first and second days are shown in Table 1.

Twelve (24%) patients had delayed positive tests on the second day. The relationship between the two tests was not statistically significant in Table 1 ($P = 0.08$, MC Nemar test)

Relationship between first-day urine test and dose of ingested methadone

Of 31 patients with a known amount of methadone administration, 20 subjects had positive and 11 showed negative results. In addition, the mean ingested dose in the positive

and negative urine test groups was 21.2 ± 17.2 and 18.7 ± 18.6 mg, respectively.

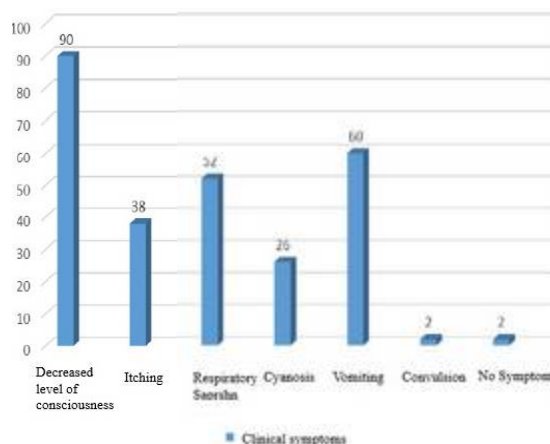


Fig 1. Clinical symptoms at the time of admission to emergency department

There was no statistically significant relationship between these two groups (T-test, $P = 0.71$).

Fifteen out of 19 patients with unknown amounts of methadone use had positive and four of them had negative tests on the first day.

Table 1. Urine tests on the first and second days

The first day \ The second day	The second day	
	+	-
+	31	4
-	12	3

Evaluation of relationship between second-day urine test and dose of methadone ingestion

Of 30 patients with known amounts of methadone ingestion, 25 had positive and 6 had negative test results on the second day. The mean dose of methadone ingestion was 23.6 ± 17.7 and 7.6 ± 6.7 mg in positive and negative cases, respectively. The correlation between the mean methadone dose and test positivity was significant (T-test, $P = 0.03$).

Eighteen out of 19 patients with unknown amounts of methadone administration had positive and one had negative tests on the second day; the difference between the two groups was not significant (Fischer's exact test, $P = 0.23$).

A total of 47 cases (94%) had at least a positive methadone urine test in the first 48 hours. Only three subjects had negative results and the parents of one of those children used methadone syrup instead of nasal drops by mistake.

Assessment of relationship between apnea and urine tests in two days

Apnea, which is an ominous symptom of methadone poisoning, was observed in 14 patients. Twelve out of 35 patients with positive test results and two out of 15 subjects with negative results on the first day had apnea.

There were no signs of apnea in three patients whose both tests were negative. There was no significant difference between the day of the apnea and the test result on the first and second days (Fischer's exact test, $P=0.18$). Figure 2 demonstrates the relationship of apnea with the first- and second-day urine tests.

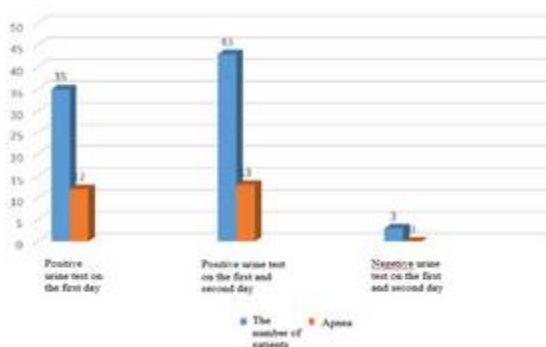


Fig 2. Relationship between apnea and methadone urine strip test

Assessment of test results on the first day regarding time interval between ingestion and urine test

The results of the first-day urine tests are shown in Figure 3 based on the time interval between methadone ingestion and strip test.

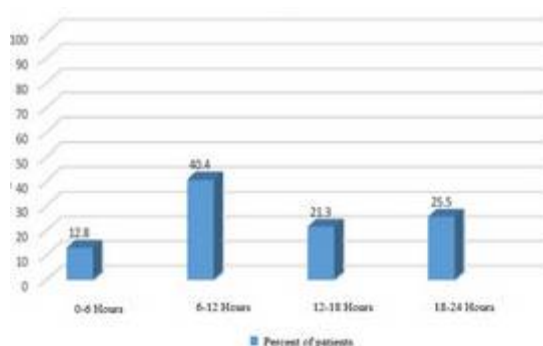


Fig 3. The prevalence of positive tests on the first day based on the time interval between methadone ingestion and strip test

Since the pH was in the normal range (4-8), this parameter was not considered as a confounding

factor. Only three patients had a SG of 1005; they also had positive urine tests.

Discussion

Urine drug screening tests (UDS) are reliable tests in daily practice when the implementation of rapid blood tests as a therapeutic aid is not available. They improve the assessment of poisoned patients. In the field of toxicology, assessment of substance use is a key element for diagnosis and medical management. Thanks to commercial kit UDS which could be performed at the patient's bedside to detect the type of the ingested drug in a few minutes.

One Scandinavian study compared the treatment strategy of using urine drug screening tests in emergency settings versus chromatography-tandem mass spectrometry as the reference. The sensitivity of UDS was 80% for opiates, and its specificity ranged from 82 to 100% for various classes of substances. In fact, the physicians usually underestimate the amount of psychoactive drug use and UDS should improve the clinical judgement [16].

In our study, three subjects had negative tests in both days (1.5% false negative).

Despite the high rate of false negative results, especially for benzodiazepines and cocaine, a false negative rate of 1.9% was reported for opioids in a study by Pesce et al [17]. According to the above mentioned study and our finding of 6% false negative, UDS is a helpful test, particularly in community office-based settings for office-based management of opioid dependence [18].

Fluoroquinolones and diphenhydramine can cause false-positive urine opiate screen tests [15, 20]. However, with excluding the patients with co-ingestion of other drugs, it was not considered as a confounding factor.

In a study by Ferrara et al. showed positive predictive values for opioids at levels exceeding 90% [19]. The study also showed that the predictability of chromatographic results was better than instrumental immunochemical tests, and that the latter was better than card on-site tests.

The results of this investigation demonstrated that the minimum amount of methadone needed for produce a positive urine test was 2 mg.

An important finding of this study, which has not been reported in other studies, is that negative urine stripe test in the first 24 hours after ingestion, especially in the first 6 hours, does not rule out poisoning.

The prevalence of positive tests was higher in patients with symptoms of apnea which could be an indication of the higher dose of methadone ingestion leading to poisoning.

The highest frequency of positive test results was observed when the test was applied between 6 to 12 hours after the ingestion and the lowest frequency was seen in the first 6 hours after the ingestion. Therefore, it could be suggested that the test should be repeated if it is carried out before 6 hours after methadone ingestion.

Conclusions

According to the results of this study, the methadone urine screening test has a high reliability for the detection of methadone in the urine. In addition, if the test result is negative in the first 24 hours, the test should be repeated after 24 hours. Two negative results in the first 48 hours can rule out methadone poisoning with a probability of 94%.

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