Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 185-190 | ISSN:2251-6727

Accidental Methadone Intoxication in Young Children: The Urgency of Early Diagnosis, Screening, and Safe Storage

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(Received: 11 June 2024 Revised: 16 July 2024 Accepted: 10 August 2024)

KEYWORDS

Methadone, accidental poisoning, opioid dependence, toxicology screening, medication storage

ABSTRACT:

Accidental methadone intoxication is increasingly recognized as a critical public health concern, particularly in households where opioid medications are accessible. We report accidental poisoning cases involving two young siblings, who presented with severe central nervous system depression, respiratory compromise, and cardiac depression. Initially they were treated as paracetamol intoxication based on information from their mother. Routine drug screening was negative for both patients. However, it was later confirmed as methadone poisoning. Fortunately following intensive therapy, both siblings recovered well without neurological sequelae. The delayed diagnosis underscores the challenges in detecting methadone poisoning with standard toxicology screens, highlighting the need for specialized testing methods not universally available. This case also emphasizes the critical importance of safe medication storage and heightened awareness among caregivers, healthcare providers, and the community regarding the risks associated with methadone exposure in children, especially in environments where opioid maintenance therapies like Methadone Maintenance Therapy (MMT) are prevalent.

1. Introduction

According to the World Drug Report 2023, an estimated 36 million people globally used amphetamines, 22 million used cocaine, and 20 million used "ecstasy"-type substances. Furthermore, approximately 60 million individuals engaged in non-medical opioid use in 2021, with 31.5 million primarily consuming opioids, mainly heroin [1]. In Malaysia, opioids and amphetamine-type stimulants represent the majority of drug abuse cases. The National Anti-Drug Agency of Malaysia reported in 2018 that there were 17,474 new incidents and 7,793 recurrences of drug misuse, with opioids being the substance of choice for 7,746 individuals [2]. A national study conducted in 2021 revealed a lifetime prevalence of opioids use at 1%, equating to an estimated 109,502 individuals, while the current rate of opioids use was approximately 0.8%, affecting around 91,889 people [3].

Methadone, a synthetic opioid, is crucial in the management of opioids withdrawal and dependence, particularly through Methadone Maintenance Therapy (MMT). In Malaysia, MMT is one of the components of the Harm Reduction Program aimed at reducing the risk

Journal of Chemical Health Risks

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JCHR (2024) 14(5), 185-190 | ISSN:2251-6727

of human immunodeficiency virus (HIV) infection among individuals who inject illicit drugs. MMT is a comprehensive treatment strategy for opioids addiction that involves the oral administration of methadone to alleviate withdrawal symptoms and reduce cravings. This treatment is typically recommended for individuals with a confirmed diagnosis of opioids addiction and is provided through licensed clinics. The duration of MMT can vary, often extending beyond one year, and offers a safe, effective, and sustainable approach to managing opioids dependency [4,5].

Research has shown that methadone is effective in reducing withdrawal symptoms and cravings associated with opioids dependence [6]. A study by Ali et al (2018) demonstrated individuals receiving MMT experienced significant reduction in opioids use, along with improvements in their overall quality of life [7]. Furthermore, MMT has been associated with a reduction in the adverse effects of opiate addiction, including the risk of infections related to needle-sharing, thereby contributing to decreased transmission rates of HIV, hepatitis B and hepatitis C. Notable benefits of MMT include enhancements in employment, health status, social functioning, and a decline in crime, incarceration, and overall drug use [8].

Careful monitoring and gradual dose adjustments are crucial due to individual variations in response to treatment. Achieving optimal control can be challenging, as inadequate doses may lead patients to supplement with illicit substances, potentially obscuring the need for higher methadone doses [9]. Alarmingly, increased adoption of methadone in recent years has been accompanied by a rise in methadone poisoning, particularly among children, often resulting from take-home doses. Reports of neurotropic drug poisoning in children, including opioids, cannabinoids and cocaine, has become increasingly common [10,11]. This manuscript presents a case involving two young siblings who experienced methadone poisoning in Kota Bharu, Kelantan, Malaysia, highlighting the need for early clinical suspicion, increased awareness regarding safe medication storage and the risks associated with methadone exposure in vulnerable populations. The importance of methadone screening for early detection and management were also discussed.

2. Case Report

Two siblings, an older 4-year-old brother (Patient 1) and a younger 2-year-old sister (Patient 2), were noted by their mother to have a low-grade fever accompanied by cough and runny nose for one week duration. They were otherwise active, playful and eating well. There was no history of vomiting, diarrhoea, seizure or abnormal behaviour.

On the day of admission, the fever became high grade and hence the mother administered medication that she believed to be paracetamol (5 mL for patient 1 and 4 mL for patient 2). The medication was in a bottle with missing label, pink in colour and had been in the refrigerator for 2-3 months. Patient 2 subsequently became lethargic, and her mother brought her to the local health clinic where she became unresponsive around 8.30 pm. She was referred to the Emergency Department, Hospital Universiti Sains Malaysia (ED HUSM). Meanwhile, patient 1, who went out for dinner with his father, developed vomiting, became cyanosed and unresponsive around 9 pm, and was rushed to ED HUSM.

Both siblings were born at term with normal birth weight. Their antenatal and postnatal courses were uneventful. Immunization schedules were completed, and developmental milestones were appropriate for age. They lived with both parents and a maternal uncle. The parents had no chronic illnesses and only took medications when ill, claiming to keep medications well out of children's reach.

Upon arrival at ED HUSM, both siblings were unconscious with Glasgow Coma Scale (GCS) score of 3/15 (E1V1M1), cyanosed, poorly perfused, and apnoeic. No bruising or external injuries were observed. Pupils were 2 mm bilaterally, reactive to light. The clinical features and blood test results were illustrated in Table 1 and Table 2, respectively. CT brain and chest X-ray of both siblings were normal. Urine toxicology screening was negative for opioids, benzodiazepines and barbiturates.

Based on the clinical history and examination, both siblings were suspected of substance poisoning. Immediate intervention in the Intensive Care Unit for both siblings involved intubation and the administration of appropriate fluid therapy, specifically normal saline

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(5), 185-190 | ISSN:2251-6727

boluses at a rate of 20-30 mL/kg, with meticulous monitoring of input and output.

Table 1: Vital signs of the patients.

Parameters	Patient 1	Remarks	Patient 2	Remarks
Age (years)	4		2	
Gender	male		female	
Temperature (°C)	37.8	N	38.7	↑
Blood pressure (mmHg)	56/41	↓↓	74/45	↓
Pulse rate (beats/min)	86	N	156	↑↑
Respiratory rate (breaths/min)	3	↓↓	3	↓↓
Pupils (mm)	2	N	2	N
SpO_2 on room air (%)	47	↓↓	86	↓

Abbreviations: ↑, mildly increased; ↑↑, markedly increased; ↓, mildly reduced; ↓↓, markedly reduced; N, normal; SpO_2, saturation of peripheral oxygen

Initial symptoms and signs for both siblings indicated a depressant toxidrome, characterized by a markedly depressed respiratory rate, cyanosis, significantly lowered GCS scores, and hypotension. However, initial screening for serum paracetamol levels were negative. Other routine urine toxicology screens were also negative for common depressant drugs of abuse.

Further history revealed that the pink liquid found in the refrigerator was methadone which belonged to the maternal uncle. He was recently released from prison and was undergoing MMT for addiction management. Analysis of the liquid medication using spectrophotometer was suggestive of methadone. Further thin-layer chromatography (using the opiate protocol with iodoplatinate spray) demonstrated a band at retention factor (Rf) value of 0.8, consistent with the Rf value of methadone [12].

Both patients progressed well with stabilization of vital signs. Patient 1 was extubated on the next day and patient 2 after three days. Both patients were administered a one-week course of ceftriaxone in view of high TWBC count, although blood cultures revealed no growth, indicating no secondary infections.

Table 2: Laboratory blood tests findings for the patients. Both patients showed severe metabolic acidosis.

Parameters	Patient 1	Patient 2
Venous blood gases		
pH	7.19	6.92
pCO_2 (mmHg)	36.3	133
pO_2 (mmHg)	40.1	77.5
HCO_3 (mEq/L)	13.8	16.4
BE (mmol/L)	-13.4	-5.9
Full blood count		
Haemoglobin (g/dL)	11.0	11.2
Platelet count (x 10^9/L)	461	393
TWBC count (x 10^9/L)	14.1	27.3
Neutrophil (%)	43.8	32.3
Lymphocytes (%)	46.6	56.6
Renal function		
Urea (mmol/L)	4.3	3.9
Sodium (mmol/L)	134	136
Potassium (mmol/L)	3.0	5.1
Creatinine (µmol/L)	68	52
Calcium (mmol/L)	2.14	2.14

Abbreviations: BE, base excess; HCO_3, bicarbonate; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; TWBC, total white blood cell

Both siblings were discharged in good health. Follow-up visits at the outpatient clinic confirmed a complete recovery, with no evidence of permanent neurodevelopmental sequelae. The case emphasizes the need for vigilance regarding medication storage and potential toxic exposures in young children, as well as the importance of thorough history-taking in cases of suspected poisoning.

3. Discussion

Methadone is a synthetic opioid with a pKa of 9.2, characterized by rapid absorption and excellent oral bioavailability (70% to 90%). It has a long and highly variable plasma half-life, ranging from 15 to 52 hours, due to its slow and variable metabolism in the liver,

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(5), 185-190 | ISSN:2251-6727

primarily involving cytochrome P450 enzymes CYP3A4, CYP2B6, and CYP2D6, as well as its high lipid solubility. After oral ingestion, peak plasma concentrations are typically reached within 2 to 4 hours, with the peak clinical effect occurring approximately 1 to 2 hours later [13]. The major metabolite of methadone, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), is largely inactive and is excreted in urine and bile along with the parent compound.

The use of methadone has increased significantly in recent years due to its role in maintenance therapy for opioid addiction, as it has a lower potential for abuse compared to morphine [14]. Data from the Malaysian National Poison Centre indicated a rise in methadone-related toxicity cases from 2006 to 2013, particularly notable in 2010, and this trend continues today [15]. While methadone intoxications predominantly occur among individuals with a history of substance use disorder, fatalities have been reported in opioid-naïve populations, including children and the elderly [16,17]. This case exemplifies the dangers associated with methadone acquired through maintenance programs being mistakenly administered to children, a scenario that has been reported in other cases as well [18].

Both siblings presented with hypoxia, which was notably more severe in patient 1, who received a slightly higher dose. The hypoxia observed in both cases can be attributed to respiratory depression resulting from methadone overdose. Respiratory depression can lead to acidosis, which may become metabolic in nature, as evidenced by lowered bicarbonate levels and negative base excess, particularly in patient 1, possibly indicating lactic acidosis due to anaerobic metabolism during hypoxia. Both siblings exhibited hypotension, which was more pronounced in patient 1, a common consequence of opioid overdose related to histamine-induced vasodilation. In acidosis, the interplay between sympathetic activation and direct cardio depressant effects on myocytes can influence vascular and cardiac function, with age and local vascular tone also playing critical roles [18]. Patient 2 demonstrated significant cardiac compensation, indicated by an elevated heart rate, whereas patient 1 did not exhibit tachycardia. This difference may be due to the vasodilatory effects of elevated pCO_2 and severe respiratory acidosis in patient 2, which triggered compensatory tachycardia to maintain blood pressure [14]. Additionally, the slightly elevated serum potassium in patient 2 likely resulted from severe acidosis.

It is important to note that the absence of miosis does not exclude the possibility of methadone poisoning, particularly in children. The classic triad of central nervous system (CNS) depression, respiratory depression, and miosis often seen in opioid toxicity may not be present in all cases [19]. Other manifestations, such as hypotension, bradycardia, hypothermia, pulmonary oedema, hypoglycaemia, and prolonged QT interval, may also occur. The lack of prominent symptoms, combined with difficulties in urine screening, can complicate the diagnosis. A higher index of suspicion, along with early administration of naloxone, may help mitigate respiratory depression and other symptoms [15]. It is advisable to consider a trial of naloxone, repeated as necessary due to its shorter duration of action compared to methadone. This is especially in situations where methadone testing facilities are unavailable, both for establishing a diagnosis and as a potential antidote. Based on our estimation, the methadone ingested by the patients was approximately 25 mg (5 mL x 5 mg/mL). For reference, adult drug users typically begin treatment with doses ranging from 20 to 30 mg, and significant toxicity or fatalities have been reported in children exposed to doses as low as 5 to 10 mg (~0.5 mg/kg body weight).

Poor prognostic factors associated with methadone related mortality includes delayed presentation to the hospital, severe loss of consciousness, acute toxicity in patients on chronic methadone therapy, the necessity for early endotracheal intubation, tachypnoea (indicating possible acute lung injury or aspiration pneumonitis), acute renal failure, and rhabdomyolysis. While our patients presented with very low GCS scores requiring intubation due to cyanosis, prompt referral and adequate management ultimately prevented permanent disability and death.

Despite the increasing incidence of methadone poisoning, awareness among healthcare providers remains low, and many laboratories do not include methadone as a standard, routine drug screening test. No common dipstick test specific to methadone is readily available. Detection using enzyme multiplied immunoassay technique (EMIT) requires specialized reagents, may not be cost-effective for smaller

Journal of Chemical Health Risks

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JCHR (2024) 14(5), 185-190 | ISSN:2251-6727

laboratories. While gas chromatography-mass spectrometry (GC-MS) is a sensitive detection method, it requires costly infrastructure, which may be inaccessible in rural settings. Consequently, many medical centres are unable to provide methadone screening or detection. On the other hand, colorimetric tests (e.g., Mandelin or Marquis tests) can be unreliable due to the presence of artificial colouring agents in methadone syrup, such as D&C Red 33 and FD&C Red 40.

Globally, methadone poisoning is on the rise, including in Malaysia, largely due to its widespread use in maintenance therapy for opioids addiction [16,17,20]. As with other drug abuse and intoxication cases, the actual numbers are likely underreported. Malaysian regulations dictate that methadone treatment should ideally be administered under Directly Observed Therapy (DOT) to ensure compliance and minimize the risk of diversion. However, certain facilities allow take-home doses for patients who consistently test negative for illicit substances over a period of at least six weeks. This practice aims to enhance treatment adherence and accommodate patients' practical needs, such as employment and travel. Balancing these benefits with the potential for misuse and diversion requires careful monitoring and adherence to established protocols to maintain the effectiveness and safety of MMT. Although guidelines suggest that methadone should be stored securely, however, there is no way to monitor them. Consequently, accidental poisonings, as seen in these cases, can occur. There is a critical need for enhanced patient education and the development of more accessible, efficient screening methods to reduce morbidity and mortality associated with methadone intoxication.

4. Conclusion

This case report highlights the growing public health concern of accidental methadone poisoning, particularly in children. The increasing use of methadone for opioid maintenance therapy raises the risk of exposure, necessitating greater awareness among healthcare providers and caregivers. The variable presentation of methadone toxicity and the limitations of standard toxicology screens complicate diagnosis, especially in paediatric patients lacking classic opioid symptoms like miosis. Additionally, this case emphasizes the need for safe medication storage and regulatory measures to prevent misuse. To protect vulnerable populations, more accessible methadone testing methods and education for healthcare professionals and the community are essential.

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Journal of Chemical Health Risks

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