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CASE REPORT

Methadone Toxicity with Electrocardiographic Sodium Channel Blockade Changes in a Pediatric Patient Post-cardiopulmonary Arrest: a Case Report

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Abstract

Background: Cardiopulmonary arrest in the pediatric population due to methadone toxicity is not commonly reported. Severe methadone toxicity often involves respiratory depression with reports of orthostatic hypotension, due to vasodilation, and QTc prolongation.
Case presentation: A pair of toddler siblings presented in cardiopulmonary arrest due to methadone ingestion. They were successfully resuscitated with no significant neurobehavioral deficits despite a suspected prolonged "downtime." After return of spontaneous circulation, the older sibling, a four-year old male, had electrocardiographs (ECGs) that were suggestive of sodium channel blockade. These changes were reversed following bicarbonate therapy. The two-year old child's ECGs did not show such changes.
Discussion: There is no prior clinical literature on sodium channel blockade in methadone toxicity. The older sibling's ECG findings and response to bicarbonate therapy appeared to be consistent with sodium channel blockade. There have been preclinical data that suggest methadone cardiotoxicity may involve cardiac sodium channels. Pharmacogenetic variations could also explain how these effects may selectively manifest.
Conclusion: Physicians should be aware of the possible toxicologic causes of cardiopulmonary arrest in the pediatric population. Pharmacogenetic variations may contribute to different clinical manifestations in methadone cardiotoxicity.

Keywords: Electrocardiography; Heart Arrest; Pediatrics; Toxicology

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INTRODUCTION

Cardiopulmonary arrest in the pediatric population due to methadone toxicity is not commonly reported. (1) Severe methadone toxicity often involves respiratory depression with reports of orthostatic hypotension, due to peripheral vasodilation, and QTc prolongation. (2) With the rare exception of prescription methadone use for chronic pain in children, such as for cancer-related pain, toxic ingestions in the young pediatric population are attributed to unintentional ingestions of recreational drugs or child abuse. (3-5)

CASE PRESENTATION

Case report of a pair of toddler siblings

Two siblings, a two-year old girl and a four-year old boy, were brought to our pediatric emergency department by their parents via private transport. Both children were in acute cardiopulmonary collapse at triage. A medical code was immediately activated and advanced pediatric life support was initiated. There were no obvious signs of trauma, therefore a toxicological cause for their presentation was strongly suspected. The parents were noted to be poor historians and claimed to be unable to recall the timeline precisely. It was claimed that the siblings were left unsupervised at home for an hour and were found by the father unconscious with undigested food noted in both children's mouths. The father claimed he tried to clear their mouths of the food and assumed that they were tired and "sleeping". When the parents realized that they were unresponsive, they called their family friend who arrived ten minutes later and brought the children to the hospital. Based on the history given, one hour and forty-five minutes elapsed between the time they were found unconscious at home and when they arrived in hospital.

Upon arrival, chest compressions were immediately started, and the children were attended by two teams. There were no recordable vital signs and both children were in asystole and had non-reactive, pin-point pupils. They were successfully intubated at the resuscitation bay.

The older sibling had return of spontaneous circulation (ROSC) after three doses of adrenaline but remained hypotensive. The first blood gas and point-of-care micro-electrolytes with glucose showed pH 6.807, pCO2110.2mmHg, pO2 42mmHg, BEecf -17mmol/L, HCO3

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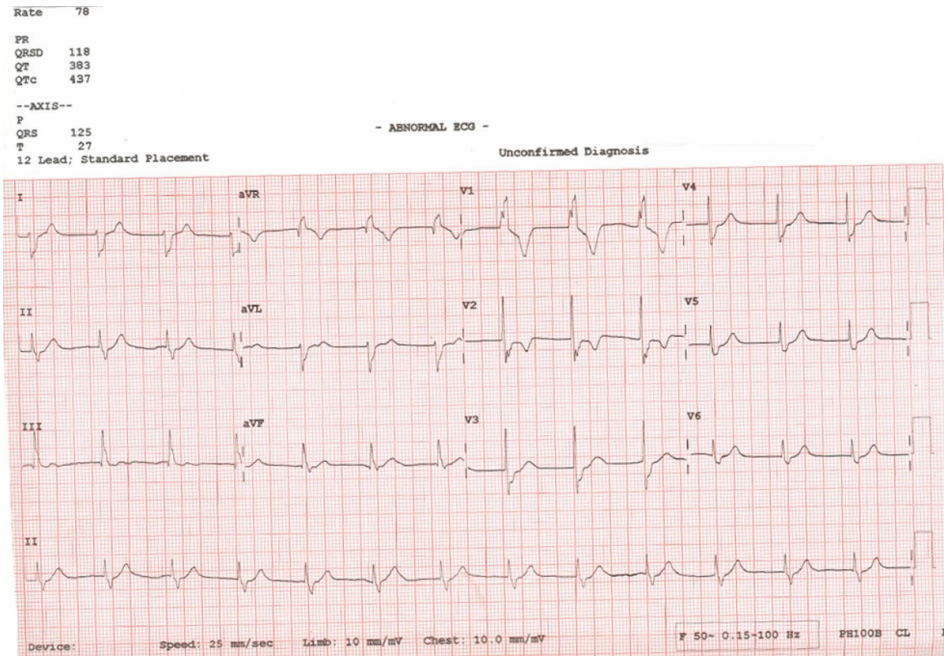
17.4 mmol/L, Na 141 mmol/L, K 4.8mmol/L, Ca 1.15 mmol/L, glucose 11.1 mmol/L, and Hct 38%. Blood and urine were sent for toxicology screening, given the unusual presentation.

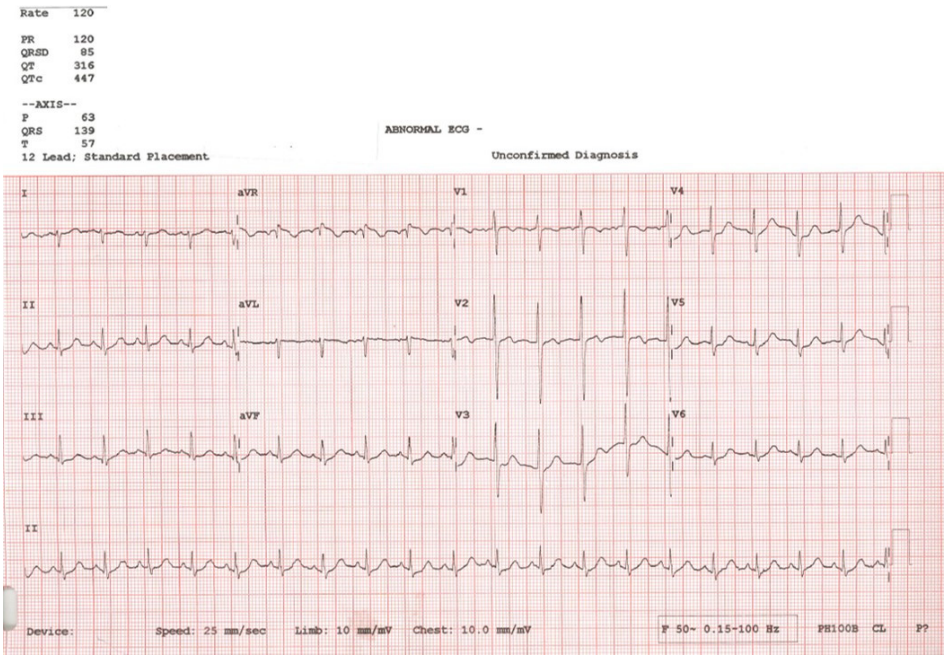
An electrocardiogram (ECG) done post ROSC on the four-year-old boy showed relative bradycardia with suggestions of sodium channel blockade (see Figure 1A). Calculated QT interval using the Barretz formula was 413.7 msec.

Intravenous (IV) sodium bicarbonate 1 mmol/kg was given and appeared to narrow the QRS complex. (Figure 1B). A total of 4 doses of sodium bicarbonate were given. The last ECG showed narrow QRS complex (<100msec) but the QTc interval had become prolonged at 455msec (calculated via Barretz formula). (Figure 1C).

The patient was intermittently hypotensive and bradycardic, requiring repeated adrenaline doses (total six

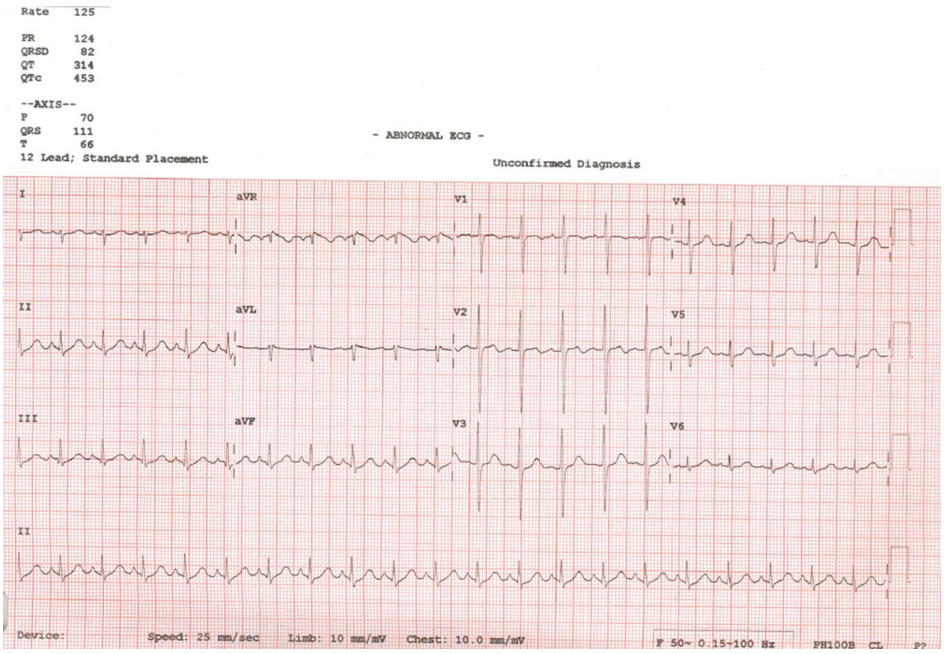


1A: Initial ECG post- ROSC



1B: After 2 doses of intravenous sodium bicarbonate 1mmol/kg/dose with narrowing of QRS complex

Figure 1. ECGs of the elder sibling (four-year old boy) post return-of-circulation (ROSC)



1C: ECG after 4 doses of sodium bicarbonate

Figure 1. Continued.

doses) every five minutes and a continuous infusion for hemodynamic stabilization.

He became hyperthermic post-stabilization, with a rectal temperature of 38 degrees Celsius, and was cooled externally. Some tonic posturing was noted, and resolved after a midazolam 0.1mg/kg bolus was given IV, followed by continuous infusion.

The younger sibling had ROSC after only one dose of adrenaline. She was normotensive and normothermic, and remained stable post-ROSC. Her ECG showed sinus tachycardia (rate of 138 beats per minute) with normal QRS complexes and normal QTc interval.

Nasogastric (NG) tubes were inserted post-crash intubation and produced pinkish aspirates in both children. After their blood pressure stabilized, activated charcoal 1g/kg was instilled via NG tube for both children after clearing the stomach contents. The gastrointestinal decontamination was done because of concerns about continued gastrointestinal absorption of a possible toxicological substance. The gastric aspirates were sent for toxicological analysis and returned positive for methadone. No other substances were found in the gastric aspirates. Blood and urine were also positive for methadone. The children were sent to the intensive care unit post-stabilization.

The parents left the hospital during the resuscitation in the emergency department and a police case was started, and social workers activated. Further investigations revealed that the parents took illicit drugs. It was uncertain if the poisoning of the children was accidental or intentional. Both siblings had full neurological recovery on follow-up at6 months and were under state-run foster care at that time.

DISCUSSION

Published reviews on methadone overdoses in children mostly reported cardiotoxicity in the form of QTc prolongation. (1, 2) The initial ECG changes noted in the older sibling were unlikely related to the resuscitation drugs given (only epinephrine) (Figure 1A). This is the first case report to our knowledge, in which a pediatric patient with methadone-induced cardiac arrest had ECG changes indicating sodium channel blockade, which appeared to be successfully reversed by sodium bicarbonate in (Figures 1A to 1C).

Amongst the opioids, it is known that propoxyphene and dextropropoxyphene can cause QRS complex widening. (6) Propoxyphene cardiotoxicity seems to be based on local anesthetic-like action on sodium channels (7), and these effects have been reported to respond to sodium bicarbonate therapy. (8) However, experimental studies have shown that its toxicity could also be linked to effects on hERG potassium channels which typically affect the QTc interval. (9)

Most reviews and reports attribute methadone related cardiotoxicity to effects on potassium channels, leading to QTc prolongation. However, several experimental papers have also demonstrated that it blocks sodium channels. (10, 11)

Pharmacogenomic susceptibility has also been reported to produce opioid cardiotoxicity in patients who are ultra-rapid metabolizers. (12) Methadone metabolism primarily involves cytochrome P450 enzymes CYP3A4, CYP2B6, and CYP2D6. (13) CYP2B6 polymorphisms have also been postulated to affect individual susceptibility to methadone

toxicity. (14) Pharmacogenomic variations may not only predispose certain individuals to methadone cardiotoxicity but also impact how they manifest the toxicity. There may be a complex interplay of pharmacogenomics resulting in opioid-channel interaction and ion-selectivity and gating. It remains to be seen if there should be a more individualized approach rather than general, to manage methadone cardiotoxicity. More reports on this should be sought to shed light on this.

CONCLUSION

Physicians should be aware of possible toxicologic causes of cardiopulmonary arrest in the pediatric population. Pharmacogenetic variations may contribute to different clinical manifestations in methadone cardiotoxicity. Physicians should treat the manifestations accordingly, following the adage “treat the patient, not the poison”.

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REFERENCES

1. Paul ABM, Simms L, Mahesan AM. The Toxicology of Methadone-Related Death in Infants Under 1 Year: Three Case Series and Review of the Literature. *J Forensic Sci* 2017 ;62:1414-7.
2. Alinejad S, Kazemi T, Zamani N, Hoffman RS, Mehrpour O. A systematic review of the cardiotoxicity of methadone. *EXCLI J* 2015;14:577-600.
3. Lewington LE, Shaffer C, Ornstein AE. Pediatric methadone ingestions: An under-recognized form of child maltreatment? *Paediatr Child Health* 2014;19:139-40.
4. Ghaemi N, Alikhani S, Bagheri S, Sezavar M. A Cross Sectional Study of Opioid Poisoning in Children at a Tertiary Center. *Asia Pac J Med Toxicol* 2016; 5: 115-8.
5. Hamedi A, Ataei A, Balali M, Ghahremani S, Ghahremani S. A Cross Sectional Study on Pediatric Methadone Poisoning in Northeast of Iran. *Asia Pac J Med Toxicol* 2016; 5: 75-8.
6. Lund-Jacobsen H. Cardio-respiratory toxicity of propoxyphene and norpropoxyphene in conscious rabbits. *Acta Pharmacol Toxicol (Copenh)* 1978 ;42:171-8.
7. Whitcomb DC, Gilliam FR, Starmer CF, Grant AO. Marked QRS complex abnormalities and sodium channel blockade by propoxyphene reversed with lidocaine. *J Clin Invest* 1989;84:1629-36.
8. Stork CM, Redd JT, Fine K, Hoffman RS. Propoxyphene-induced wide QRS complex dysrhythmia responsive to sodium bicarbonate--a case report. *J Toxicol Clin1995*;33:179-83.
9. Ulens C, Daenens P, Tytgat J. Norpropoxyphene-induced cardiotoxicity is associated with changes in ion-selectivity and gating of HERG currents. *Cardiovasc Res* 1999 ;44:568-78.
10. Stoetzer C, Kistner K, Stüber T, Wirths M, Schulze V, Doll T, et al. Methadone is a local anaesthetic-like inhibitor of neuronal Na+ channels and blocks excitability of mouse peripheral nerves. *Br J Anaesth* 2015;114:110-20.
11. Schulze V, Stoetzer C, O'Reilly AO, Eberhardt E, Foadi N, Ahrens J, et al. The opioid methadone induces a local anaesthetic-like inhibition of the cardiac Na channel, Na(v)1.5. *Br J Pharmacol* 2014;171:427–37.
12. Elkalioubie A, Allorge D, Robriquet L, Wiart JF, Garat A, Broly F, et al. Near-fatal tramadol cardiotoxicity in a CYP2D6 ultrarapid metabolizer. *Eur J Clin Pharmacol* 2011;67:855-8.
13. Yiannakopoulou E. Pharmacogenomics and Opioid Analgesics: Clinical Implications. *Int J Genomics* 2015;2015:368979.
14. Kharasch ED, Regina KJ, Blood J, Friedel C. Methadone Pharmacogenetics: CYP2B6 Polymorphisms Determine Plasma Concentrations, Clearance, and Metabolism. *Anesthesiol* 2015;123:1142-53.