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A case report of methadone-associated hypoglycemia in an 11-month-old male

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Abstract

Background—Methadone is a synthetic μ -opioid receptor agonist that is used in the management of pain, neonatal abstinence withdrawal syndrome, and opioid dependence. Overdose can cause miosis, respiratory depression, and central nervous system depression. Rarely, hypoglycemia has been reported. We present the case of an 11-month-old male who developed hypoketotic, hyperinsulinemic, hypoglycemia after an acute, unintentional methadone exposure.

Case details—The patient was a previously healthy 11-month-old male who presented in respiratory failure. He was intubated and transferred to a large tertiary care center where his physical exam was notable for miosis. His labs were notable for a blood glucose of 17 mg/dL, an elevated insulin level, and suppressed serum beta-hydroxybutyrate. The patient was given a dextrose bolus with improvement in blood glucose. Administration of IV naloxone improved his miosis and mental status. A quantitative methadone level was sent upon arrival and was 123 ng/mL. Testing for ethanol, salicylates, sulfonyleureas, and metabolic causes of hypoglycemia was negative. A fasting study showed euglycemia with suppression of insulin and appropriate ketosis.

Case discussion—We present the case of an 11-month-old male who developed hypoketotic, hyperinsulinemic, hypoglycemia after an acute, unintentional methadone exposure. Alternative explanations for hypoketotic hypoglycemia were rule out. Methadone-induced hypoglycemia has been reported in cancer patients receiving methadone for pain, but a mechanism has not been identified. Based on this case, we believe that the patient's hypoglycemia was the result of methadone-induced insulin secretion.

Conclusion—This case proposes that hyperinsulinism is the mechanism responsible for methadone-associated hypoglycemia. Methadone exposure should be included in the differential diagnosis of new onset hypoglycemia.

Keywords

Pediatric; opioid; overdose; hyperinsulinism

Background

Methadone is a synthetic μ -opioid receptor agonist that is used in the management of pain, and as a maintenance strategy for treating opioid dependence. It has a high oral bioavailability (approximately 80%), a long half-life ($t_{1/2} = 7\text{--}65$ hours), and an oral time to maximum plasma concentration of approximately 2 hours.[1] In overdose, methadone produces typical findings of opioid intoxication, namely respiratory and central nervous system depression.[2] Pediatric patients are especially vulnerable to the effects of methadone due to the delay in onset of respiratory depression.[3] Hypoglycemia may be another potentially dangerous side effect of methadone overdose. Methadone can elicit hypoglycemia during rapid dose escalation or in the case of acute, unintentional exposure, but to date no mechanism has been elucidated.[4–7]

We present the case of an 11-month-old male with an unintentional methadone exposure who subsequently developed hypoketotic, hyperinsulinemic hypoglycemia. Per our institution, the review of records for 3 or less patients to report as a case study or case series is not considered human subject research under the jurisdiction of the Institutional Review Board (IRB) and may proceed without IRB review.

Case Report

An otherwise healthy 11-month-old male presented to an outside hospital in respiratory failure. His parents reported two days of low-grade fevers and rhinorrhea, but baseline enteral intake. On the day of presentation, he developed “funny breathing” and progressive sleepiness over the course of the day. On arrival, he was noted to be unresponsive, cyanotic, and bradypneic, with a Glasgow Coma Score of 3. The patient weighted 11 kg, with initial heart rate of 115 beats per minute, a blood pressure of 82/54 mmHg, and a respiratory rate of less than 6 breaths per minute. Bag-mask ventilation was initiated and the patient was subsequently intubated without sedation. Initial glucose was 194 mg/dL. His last meal occurred 6 to 8 hours prior to presentation and consisted of 1.5 packages of oatmeal, fruit, and a 6 ounce bottle of formula. Due to the development of jaw clenching and upper extremity fasciculations that were concerning for seizure activity, he received a total of 4 mg intramuscular lorazepam, with resolution of abnormal movements. In addition, because of his tenuous hemodynamic status refractory to fluids, he was started on a dopamine infusion at 10 mcg/kg/min, received 1 mg intramuscular ceftriaxone, and transferred to a large, tertiary children’s hospital. During transport, patient received 150 mL of normal saline and remained on the dopamine infusion.

Upon arrival (2 hours and 20 minutes after initial presentation to outside hospital), the patient was persistently hypotensive with a blood pressure of 58 mmHg/33 mmHg. An epinephrine infusion was added at 0.1 mcg/kg/min and his hemodynamic status improved. Lab evaluation was notable for an initial glucose of 87 mg/dL; this value was recorded 145 minutes after the previous triage glucose measurement of 194 mg/dL. Repeat blood glucose level 36 minutes later, however, was 17 mg/dL. Insulin level at that time was elevated at 14.4 μ IU/mL, with suppressed serum beta-hydroxybutyrate (0.22 mmol/L). The patient was given

a 4 mL/kg bolus of 10% dextrose and his blood glucose level improved (53 mg/dL). Although on arrival the patient was noted to have 4 mm pupils, he later developed pinpoint pupils prompting two 0.1 mg/kg doses of IV naloxone (2.2 mg). Mental status and miosis improved and he was admitted to the medical intensive care unit (MICU) for further treatment. Fentanyl and midazolam were used for sedation while in the MICU. A naloxone infusion was started upon arrival to the MICU (range 8 – 15 mcg/kg/hr) and was discontinued 8.5 hours later.

Upon questioning, the mother and father reported having a history of intravenous drug abuse and were currently receiving methadone maintenance therapy with the father having a 5-day supply at home due to years of compliance. A quantitative methadone level sent from a blood sample collected from the patient at the time of arrival to the emergency department (ED) was 123 ng/mL by quantitative liquid chromatography-tandem mass spectrometry (lower limit of detection 10 ng/mL). Metabolic evaluation, including plasma amino acids and urine organic acids, was normal. Toxicologic testing for sulfonyleureas was negative. Serum and urine drug in-hospital screening, including acetaminophen, ethanol and salicylates, was otherwise negative except for positive urine benzodiazepines, which had been administered in the ED. Blood, urine, and cerebral spinal fluid cultures were negative. A respiratory culture grew *S. aureus* and *K. pneumonia* and patient remained on ceftriaxone for 7-days.

In the MICU, blood glucose levels remained within normal range without need for dextrose-containing IV fluids, although he was started on continuous enteral feeds with a glucose infusion rate of 5.1 mg/kg/min. The patient was extubated on hospital day 6 and transferred to the Neurology service on hospital day 9. He was eventually transitioned to intermittent bolus naso-gastric tube feeds without hypoglycemia. On hospital day 14, an 18-hour fasting challenge was performed and the patient maintained normal blood glucose levels throughout the period of fasting, with appropriate ketosis (Table 1). Notably, he had a robust serum cortisol level after 18 hours of fasting. On hospital day 15, he was discharged to a rehabilitation facility for further care.

Discussion

The differential diagnosis for hypoglycemia in the pediatric patient is broad and includes inborn errors of metabolism, endocrinopathies, and toxic exposures (Table 2). Hypoglycemia has been reported with therapeutic use of methadone in the cancer population.[6–8] In humans, a retrospective cohort study looking at cancer patients receiving opioids for pain control found an association between methadone and hypoglycemia, leading to the recommendation for routine blood glucose monitoring for patients starting methadone at 40 mg per day or greater.[8] In mice, intravenous methadone has been shown to lower blood glucose levels in a dose-dependent manner in doses greater than 10 mg/kg.[9] This effect is blunted by mutation of the μ -opioid receptor, suggesting a mechanistic role for the μ -opioid receptor to mediate opioid-induced insulin secretion. Chronic methadone treatment is protective against the development of diabetes in mice after multiple low doses of streptozotocin, who exhibit both preserved glucose tolerance and insulin secretion.[10] Previous work has demonstrated increased insulin secretion from cultured islet cells in

response to morphine administration, but application of naturally-occurring opioids, including leucine-enkephalin, methionine-enkephalin, and D-al²-leucine-enkephalin, suppressed insulin secretion.[11] This suggests receptor-specific effects on insulin secretion, as the μ -opioid receptor is more specific for morphine and other narcotics, whereas the δ -receptor binds enkephalins with greater affinity. Interestingly, naloxone, a pure opioid antagonist that competitively blocks the μ -, κ -, and δ -opioid receptors reversed both effects. [11] To our knowledge, the effect of methadone on islet cell insulin secretion, *in vivo*, has not been tested.

We report a case of severe hypoketotic, hyperinsulinemic hypoglycemia after methadone exposure. Alternative explanations for hypoketotic hypoglycemia, namely sulfonylurea exposure, fatty oxidation disorders, and persistent hyperinsulinism, were negative. Other causes of hypoglycemia, like starvation or sepsis, would be expected to cause a hyperketotic hypoglycemia due to increased fatty acid oxidation. Administration of epinephrine would be protective against hypoglycemia through increased gluconeogenesis, glycogenolysis, and decreased glucose utilization. It is interesting to note that upon arrival to the presenting hospital, the patient was hyperglycemic, and only became hypoglycemic 3 hours later. One possible explanation for the delay in hypoglycemia is that methadone has a delayed time to peak concentration and clinical findings, like respiratory depression, can occur after peak analgesic effect.[3] It is conceivable that methadone-associated hypoglycemia is similarly delayed. With this in mind, a proposed mechanism of opioid-induced insulin secretion is suspected.

It is important to note that we were unable to rule out exogenous insulin administration being the cause of this patient's hypoglycemia, due to an inability to obtain a C-peptide level. Prior case reports of exogenous insulin overdose describe measured insulin levels several orders of magnitude higher than what we observed.[12,13] While this does not definitively rule out exogenous insulin administration, it supports our assertion of methadone-associated insulin secretion being the etiology of the patient's hypoglycemia.

Conclusion

Based on this case and the referenced literature, methadone exposure should be considered in the differential diagnosis of new onset hypoglycemia.

Abbreviations

ED	Emergency department
MICU	Medical intensive care unit

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Table 1

Metabolic regulation across 18-hour fast.

	Baseline	6 hours	12 hours	18 hours
Glucose	103 mg/dl	78 mg/dl	84 mg/dl	84 mg/dl
Insulin (normal range 3-12 μ IU/ml)	18.6 μ IU/ml	3.0 μ IU/ml	0.9 μ IU/ml	1.6 μ IU/ml
Beta-hydroxybutyrate	0.18 mmol/L	0.18 mmol/L	0.22 mmol/L	0.62 mmol/L
Ammonia (normal range 28-80 μ g/dl)	64 μ g/dl	68 μ g/dl	45 μ g/dl	71 μ g/dl
Free Fatty Acids (normal range 0.99 mmol/L)	0.29 mmol/L	0.18 mmol/L	0.36 mmol/L	1.02 mmol/L
Pyruvate				0.066 mmol/L
Lactate (normal range 0.5-2.2 mmol/L)				1.3 mmol/L
Cortisol (normal range 5-25 μ g/dl)				14.0 μ g/dl
Growth Hormone				0.92 ng/ml

Table 2

Causes of infantile and pediatric hypoglycemia.

<i>Inborn Errors of Metabolism</i>	
Disorders of carbohydrate metabolism	Glucose-6-phosphatase deficiency Glycogen synthetase deficiency Pyruvate carboxylase deficiency Galactosemia
Disorders of protein metabolism	Propionic academia Methylmalonic aciduria
Disorders of fatty acid metabolism	Medium-chain acyl-CoA deficiency (MCAD)
<i>Endocrinopathies</i>	
Hyperinsulinism	Persistent hyperinsulinemic hypoglycemia of infancy Insulinoma
Hormone deficiencies	Growth hormone deficiency Adrenal insufficiency
<i>Toxic Exposures</i>	
	Oral hypoglycemic agents (e.g., sulfonylureas) Unripened fruit from Ackee (<i>Blighia sapida</i>) tree β -adrenergic receptor antagonists (e.g., propranolol) Exogenous insulin administration Ethanol End-stage salicylate toxicity
<i>Other</i>	
	Sepsis Shock Burns