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A Possible Case of Opioid-Induced Hypoglycemia and the Potential Role of Naloxone

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ABSTRACT
Literature has found that individuals with opioid use disorders have increased fasting insulin levels and that antagonism of the μ-receptor with naloxone blunted this hypoglycemic effect. We describe a 35-year-old woman with no history of diabetes who presented after being found unconscious where she was given naloxone and became awake and combative. Her blood glucose (BG) on presentation was 175 mg/dl, which declined to 40 mg/dl, and dextrose was administered. Subsequently, it declined to 42 mg/dl and was again given dextrose. Later her BG fell to 67 mg/dl and she was given dextrose and started on a dextrose infusion. She was then administered IV naloxone and 1 hr later the infusion was discontinued and she had no further hypoglycemic events. Clinicians should consider altering monitoring parameters in the setting of acute overdoses to include repeated glucose assessment to ensure early identification of hypoglycemia and the potential influence of naloxone.
Key words: emergency medicine, glucose, hypoglycemia, naloxone, overdose

PREVIOUS LITERATURE has found that individuals with heroin and methadone use disorders have altered responses to glucose administration due to a reduced insulin response compared with healthy control subjects (Ceriello et al., 1987). Further, they have found that these patients have increased fasting insulin levels and hence altered glucose metabolism. Animal models have shown that activation of μ-opioid receptors with morphine and methadone increases glucose utilization in peripheral tissues and may inhibit hepatic gluconeogenesis leading to lower serum glucose concentrations (Faskowitz, Kramskiy, & Pasternak, 2013; Lux, Brase, & Dewey, 1988; Lux, Han, Brase, & Dewey, 1989; Tzeng et al., 2003). These models have also found that

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antagonism of the μ-receptor with naloxone blunted this hypoglycemic effect (Faskowitz et al., 2013). We report on a patient with no history of glucose dysregulation who presented to the emergency department (ED) after an accidental opioid overdose resulting in hypoglycemia that was potentially masked by the administration of naloxone and subsequently treated with additional naloxone.

CASE REPORT

A 35-year-old woman (67.6 kg) with a history of intravenous (IV) drug use disorder with heroin presented to the ED after being found unconscious in her apartment. Emergency medical services (EMS) administered a total of 3 administrations of 1 mg of intramuscular naloxone after which the patient became awake and combative. EMS did not report a blood glucose prior to naloxone administration. On arrival she was awake and alert but not responding purposefully to questions with a Glasgow Coma Scale score of 14. Her skin was noted to have evidence consistent with IV drug use and skin "popping." Vital signs upon arrival were: blood pressure, 105/72 mmHg; heart rate, 119; respirations, 16; oxygen saturation 99% on room air; temperature, 37.6 °C. The initial electrocardiogram (ECG) showed sinus tachycardia 106 beats/min, QRS duration of 98 ms, and QT interval of 340 ms (Bazett's QTc 451 ms). No previous ECGs were available for comparison. Troponin was 0.03 ng/ml (NL: ≤0.09 ng/ml). Initial venous blood gas showed: pH, 7.24; P_{CO_2}, 55 mmHg; bicarbonate, 23 mEq/L; and lactate, 6.75 mmol/L. Creatinine kinase was 51 units/L (NL: 20–190 units/L). On arrival to the ED, her blood glucose was 175 mg/dl (normal [NL]: 70–100 mg/dl) (see Figure 1). Other laboratory values were as follows: sodium 139 mmol/L (NL: 135–145 mmol/L), potassium 4.1 mmol/L (NL: 3.5–4.9 mmol/L), creatinine 1.1 mg/dl (NL: 0.6–1.3 mg/dl), blood urea nitrogen 14.0 mg/dl (NL: 8.0–26.0 mg/dl), chloride 102.0 mmol/L (NL: 98.0–109.0 mmol/L), white blood cell count 23 K/mm^3 (NL: 4.8–10.8 K/mm^3), hemoglobin 10.6 g/dl (NL: 12.0–16.0 g/dl), hematocrit 33.6% (NL: 37.0%–47.0%), platelet count 444 K/mm^3 (NL: 140–440 K/mm^3). A computed tomography of the head was obtained and was found to be unremarkable. The patient was administered broad-spectrum antibiotics over concern of possible infection and blood cultures were obtained. Blood cultures remained negative upon leaving the hospital, chest x-ray was not suggestive of infection, and procalcitonin was undetectable, but the patient was found to have a respiratory viral panel positive for coronavirus HKU1.

Approximately 30 min after arrival, the patient began to become less responsive and a blood glucose was obtained that was found to be low (40 mg/dl). Subsequently the patient was administered IV dextrose 50% in water (D50W) and upon recheck it had risen to 170 mg/dl. Approximately 1-hr following arrival, the patient was noted to be interactive and was following commands. At that time the patient's blood glucose was rechecked and was found to be 42 mg/dl and the patient received 12.5 g of IV D50W. Four hours after presentation, the patient's blood glucose had fallen to 67 mg/dl and the patient was given 7.5 g of IV D50W and a dextrose 5%–0.45% normal saline infusion at 125 ml/hr was initiated. Approximately 45 min after the start of the infusion, naloxone 0.4 mg IV was administered for mitigation of the patient's recurrent hypoglycemia. One hour later the patient's IV fluids were discontinued, and the patient suffered no further incidences of hypoglycemia (range: 93–101 mg/dl). The patient left against medical advice 48 hr after presentation.

After admission to the hospital, the patient reported injecting cocaine, using marijuana frequently, and taking diazepam frequently, although she stated that she had exhausted her supply of diazepam a week prior to presentation. She also reported taking hydrocodone-acetaminophen 10-325 mg four times in the 24 hr before presentation. Independent verification found that approximately

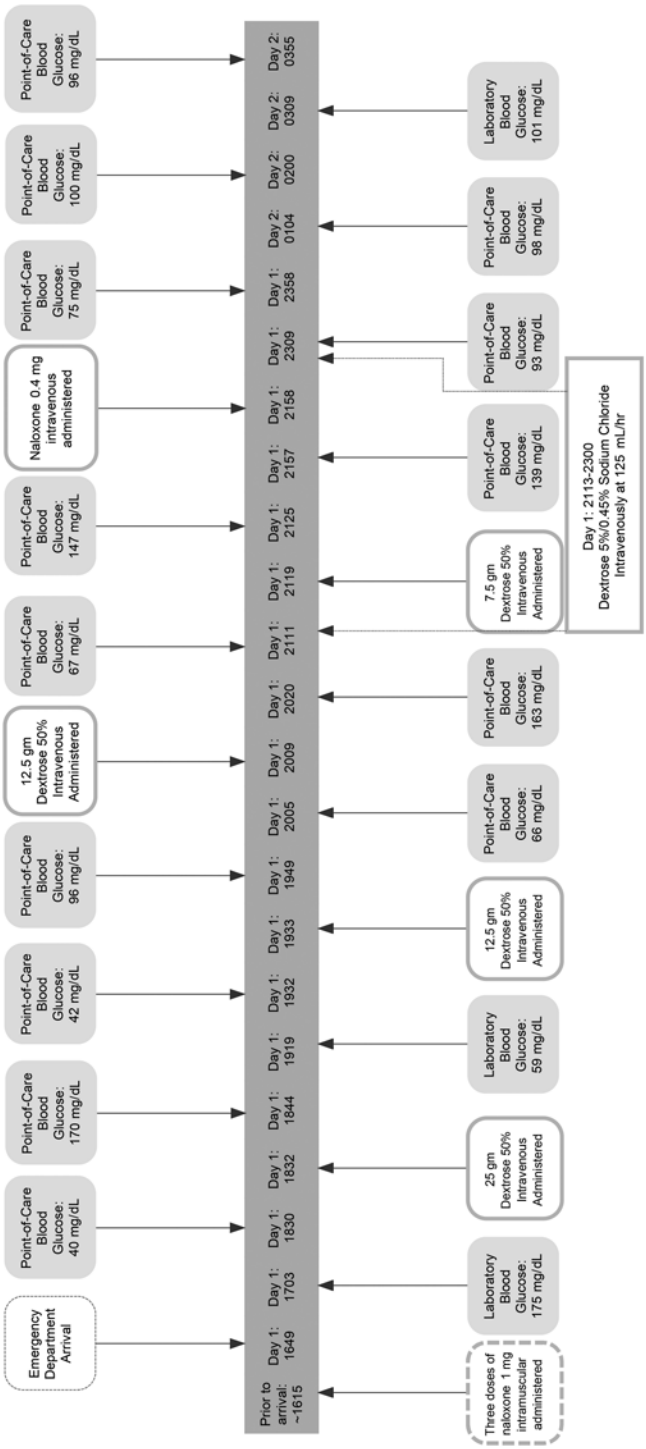

Figure 1. Blood glucose assessment and treatment timeline.

3 weeks prior to presentation she had filled 120 tablets of hydrocodone-acetaminophen 10–325 mg and 30 tablets of diazepam 2 mg. Subsequent toxicologic analysis on arrival was negative for acetaminophen (<3.0 mcg/ml), ethanol (<10 mg/dl), and salicylates (<5.0 mg/dl). Her urine drug screen on arrival was positive for opiates, benzodiazepines, and cocaine and negative for amphetamines, barbiturates, cannabinoids, phencyclidine, oxycodone, and methadone. The patient had no medical history of hypoglycemia, hyperglycemia, or diabetes. Her hemoglobin A_{1C} on admission was found to be 5.3% (NL: 4.3%–5.6%).

DISCUSSION

Opioids continue to be one of the most common medications involved in drug overdose deaths and a frequent agent involved in ED presentations (Hedegaard, Bastian, Trinidad, Spencer, & Warner, 2018). As the use of opioids has grown over the last several years, research has been able to identify previously unrecognized and unintended consequences of opioid use. In one analysis of the Food and Drug Administration's Adverse Event Reporting System, the authors found that methadone was associated with a higher risk of hypoglycemia compared with other agents (Makunts, U, Atayee, & Abagyan, 2019). A similar association between methadone and hypoglycemia has been identified in patients being treated at a cancer center where they identified a dose–response relationship between the two (Flory, Wiesenthal, Thaler, Koranteng, & Moryl, 2016). This risk of hypoglycemia has also been demonstrated with the use of heroin, where it has been found to increase fasting insulin levels and alter glucose metabolism similar to methadone (Ceriello et al., 1987). Although the underlying mechanism of this effect is still unclear, the concept of reversing this effect through μ-receptor antagonism has been explored as a potential mitigation strategy. In one animal model, following the intrathecal administration of methadone, serum glucose levels were reduced by 32% at 60 min in a dose-dependent fashion (Faskowitz et al., 2013). Naloxone administration fully reversed this hypoglycemia at all doses, including the maximum dose administered. Pharmacodynamic studies of naloxone utilization in this particular scenario are limited, but in the setting of an opioid overdose, the duration of action of naloxone can range from 20 to 90 min depending on the type and dose of the opioid involved (Berkowitz, 1976; Evans, Hogg, Lunn, & Rosen, 1974; Olofsen et al., 2010; Yassen et al., 2007). If the mechanism of action of naloxone in reversing hypoglycemia in this setting is through μ-receptor antagonism, then presumably similar pharmacodynamics would be expected.

Our patient had no history of glucose derangements, had a normal hemoglobin A_{1C}, and had a glucose that stabilized prior to discharge. Although she admitted to hydrocodone-acetaminophen use prior to presentation, she had an undetectable acetaminophen concentration upon arrival. Her clinical response to naloxone by EMS and her positive screen for opiates however is consistent with her prior heroin use. Cocaine use has typically been associated with inducing hyperglycemia, not hypoglycemia, and although benzodiazepines have been implicated in causing hypoglycemia, it has been primarily associated with benzodiazepine overdoses with a Glasgow Coma Scale score of less than 10, which was inconsistent with our patient's presentation following naloxone administration (Nyenwe et al., 2007; Soroosh, Zakariaei, Azadeh, Tabaripour, & Banimostafavi, 2021; Warner, Greene, Buchsbaum, Cooper, & Robinson, 1998). Upon presentation to the ED, her blood glucose was elevated (176 mg/dl) and subsequently dropped to 40 mg/dl 30 min later. This could be in part explained by her receipt of 3 mg of naloxone by EMS, which could have corrected preexisting hypoglycemia prior to their arrival. Although her glucose was responsive to the administration of exogenous dextrose, the duration of each dose only achieved normoglycemia

only for around 60 min, complicating management, but was consistent with the known μ-receptor occupancy of naloxone. As a result of this short duration of activity, a continuous infusion of dextrose was initiated to limit both the necessity of frequent monitoring and the potential for unidentified glucose excursions. The administration of naloxone 5 hr into the admission was another attempt to address the patient's recurrent hypoglycemia that was more focused on the underlying etiology and was not utilized for recurrent opioid-induced respiratory suppression. Approximately 60 min after the administration of the naloxone, it became possible to discontinue the dextrose infusion and no further interventions were necessary. It is possible that the administration of naloxone at this time point happened to coincide with a waning of the μ-receptor occupancy by the opioid involved. It is notable however that the glucose level following the initial naloxone administrations is far in excess of any subsequently measured concentration and one in excess of her baseline levels as reflected by her hemoglobin A_{1C}, although her dietary intake prior to this event is unclear. It is unclear whether naloxone is the optimal treatment modality for hypoglycemia secondary to opioid use due to its apparent relatively short duration of action and further research is needed in this area. However, it does appear that more frequent monitoring of blood glucose concentrations is warranted in this clinical scenario to ensure that incidences of hypoglycemia do not go unidentified and untreated.

CONCLUSION

Although the exact mechanisms remain to be fully elucidated, opioids have the potential to cause hypoglycemia and in the setting of an acute overdose, this may both be obscured and treated with naloxone administration. Clinicians should consider altering monitoring parameters in the setting of acute overdoses, particularly involving heroin and methadone, to include repeated serum glucose assessment to ensure early identification of hypoglycemia.

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