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CASE REPORT

Methadone-induced hypoglycemia: A case report

Ramin Malboosbaf, Neda Hatami*, Zohreh Maghsoomi

Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran

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***Correspondence**
Neda Hatami
Tel.: +98-21-86701
Fax: 009888945173
E-mail address:
melodyhatami36@gmail.com

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ABSTRACT

Hypoglycemia is rare in patients without diabetes mellitus. Methadone is a synthetic μ-opioid receptor agonist used for cancer or non-cancer pain and the treatment of opioid dependence. Here, we report a case of a 31-year-old man who presented with recurrent hypoglycemic events that resolved on discontinuation of methadone. Thus, if hypoglycemia occurs while a patient takes methadone, the amount should be reduced or replaced with another opioid before a full investigation for inappropriate hyperinsulinism is initiated.

INTRODUCTION

Hypoglycemia is rare in individuals without diabetes. Non-diabetic hypoglycemia causes include sepsis, adrenal insufficiency, liver failure, insulin-secreting tumors, non-islet cell tumor hypoglycemia, insulin antibodies, exogenous insulin use and medication side-effects. We describe a case of methadone-induced hypoglycemia who presented with recurrent hypoglycemic events that resolved with the discontinuation of methadone.

CASE REPORT

A 31-year old man presented with symptoms of dizziness and sweating that resolved after eating food or sweet candies that had started 2 months earlier. One time, he experienced decreased consciousness level, and the emergency team detected his blood sugar to be 25 mg/dL. With 50% dextrose, he became conscious and did not remember this event. He was admitted to the hospital to evaluate the cause of hypoglycemia. He did not have diabetes, nor did any of his family members. He denied using drugs, but only a fixed dose of 25 mg methadone to treat opioid addiction for approximately 2 months. The patient had never consumed alcohol. The 72-h fasting test was carried out, but he did not become symptomatic until the end of the test. Nevertheless, a blood sample was taken from the patient at the end of the trial. The results were as follows: blood sugar with glucometer 60 mg/dL, simultaneous blood sugar 25 mg/dL, insulin 0.4 mIU/mL (n2.6–25 mIU/mL), C-peptide 0.23 ng/mL (1.1–4.4 ng/mL) and cortisol 21.5 mcg/dL (6.2–20 mcg/dL), sulfonylurea in urine was negative. Liver, renal and thyroid function tests were in the normal range.

This pattern favored non-islet cell tumor hypoglycemia or adrenal insufficiency, but as cortisol was normal, the latter was excluded. To rule out malignancies that can cause non-islet cell tumor hypoglycemia, chest and abdominopelvic computed tomography scans were carried out with no abnormalities. A suggestion was made to discontinue the patient's long-standing methadone. The last dose of methadone was used approximately 3 h before blood sampling at the end of the 72-h fasting test; unexpectedly, hypoglycemia was confirmed despite the patient being asymptomatic. Methadone was discontinued, and bupropion 75 mg once daily was started. His hypoglycemic episodes resolved within a day of stopping the methadone. The patient remained euglycemic after methadone discontinuation, and methadone has been deemed the culprit for his recurrent hypoglycemia. At outpatient follow up, he reported no further hypoglycemic episodes.

DISCUSSION

Methadone is a synthetic μ-opioid receptor agonist used for cancer or non-cancer pain and the treatment of opioid dependence[1]. The mechanisms of hypoglycemia by methadone are not clear; direct action on the pancreas (possibly mediated through μ-opioid receptors) or suppressing counter-regulatory hormones or the central nervous system mediated (through the serotonergic pathway) might be responsible, although additional

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investigation is required. Other opioids that are active on the μ-opioid receptor – fentanyl, oxycodone and levorphanol – did not cause hypoglycemia, suggesting that the mechanism for the methadone effect is more than just activation of the μ-opioid receptor[2]. Lux *et al.*[3] showed that intrathecal morphine could reduce liver glycogen stores and hypoglycemia in mice. Other studies in mice showed that methadone and tramadol have serotonergic effects, and could induce hypoglycemia by increasing insulin levels[4,5]. In the present case, the possibility of opioid stimulating insulin release is low, considering the low serum insulin level. The probable explanation can be reduced liver glycogen stores versus serotonergic action.

In a study by Faskowits *et al.*[2], mice were studied to investigate the effect of methadone and other μ-opioids on blood sugar. Hypoglycemia by methadone was dose-dependent, but other μ-opioids, such as morphine and fentanyl, did not have the same effect on blood glucose. Toce *et al.*[6] reported hypoglycemia in an 11-month-old boy after acute accidental methadone exposure. Another retrospective cohort study showed that methadone was significantly associated with hypoglycemia, particularly at doses >40 mg/day[7]. For any methadone exposure, the average per-day rate of hypoglycemia was 6.9%. This rate increases with increasing doses of methadone; for doses of 0–15, 15–40, 40–80 and >80 mg, the per-day rate of hypoglycemia was 3.9, 4.2, 7.4 and 8.0% respectively[7]. The effect appears comparable for both intravenous and oral administration of methadone[7]. The association is time-dependent and occurs approximately 24 h after starting methadone therapy[7]. Some studies showed a rapid increase in methadone dose accompanied by hypoglycemia[8,9].

Otalora *et al.*[1] reported new-onset hypoglycemia in a 54-year-old man with end-stage renal disease who was frequently on methadone because of chronic back pain (50 mg in the morning and 15 mg at bedtime). After ruling out other causes, including insulinoma, methadone-induced hypoglycemia was diagnosed. Adjustments in methadone doses showed an improvement in hypoglycemic episodes. Makunts *et al.* showed that tramadol and methadone were associated with hypoglycemia, However, alternative opioids or non-opioid pain medications, serotonin-norepinephrine reuptake inhibitor (e.g., duloxetine) and N-methyl-D-aspartate receptor antagonists (e.g., dextromethorphan) were not associated with hypoglycemia[10].

We switched methadone to bupropion. Bupropion is an antidepressant, and its use as a smoking cessation aid has shown some benefits. The patient remained euglycemic after stopping methadone, and methadone was thought to be the culprit for his recurrent hypoglycemia.

To the best of our knowledge, this was the first time that switching to bupropion has resolved methadone-induced hypoglycemia. It can be useful to check glucose levels in patients using methadone, especially those on high doses. Insulinomas are rare, and evaluation might require the patient to be hospitalized for a supervised fasting test and then undergo localization studies. Thus, if hypoglycemia occurs while a patient takes methadone, the dose should be reduced or replaced with another opioid before a full investigation for inappropriate hyperinsulinism is initiated.

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: Written informed consent was obtained from the patient.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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