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Methadone-Associated Severe Hypoglycemia and Secondary Adrenal Insufficiency in a Patient with Opioid Use Disorder

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Gustavo Da Silva Borba [1], Garrett J. Cherry [1], Chloe Arima [2], Mahwash Siddiqui [3]

1. Internal Medicine, Mount Sinai Hospital Chicago, Chicago, USA 2. Endocrinology, CHICAGO MEDICAL SCHOOL AT ROSALIND FRANKLIN UNIVERSITY OF MEDICINE AND SCIENCE, Chicago, USA 3. Endocrinology, Diabetes and Metabolism, Mount Sinai Hospital Chicago, Chicago, USA

Corresponding author: Gustavo Da Silva Borba, gustavo.dasilvaborba@sinai.org

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Abstract

INTRODUCTION

Methadone is an important therapy for opioid use disorder (OUD); however, its endocrine complications remain under-recognized. We report severe, persistent hypoglycemia associated with high-dose methadone occurring with secondary adrenal insufficiency, highlighting methadone's dual impact on glucose regulation and the hypothalamic-pituitary-adrenal (HPA) axis.

CASE DESCRIPTION

A 55-year-old man with OUD, type 2 diabetes mellitus, chronic obstructive pulmonary disease, hypertension, and hyperlipidemia was admitted for COPD exacerbation complicated by acute hypoxic hypercapnic respiratory failure requiring mechanical ventilation. Methadone was initiated for opioid withdrawal at 20 mg daily and titrated to 80 mg twice daily (160 mg/day total). He developed new-onset, persistent hypoglycemia with nadir glucose of 56 mg/dL despite continuous enteral nutrition (2,620 kcal/day) and intravenous dextrose (D20 at 50 mL/hour).

Endocrine evaluation revealed inappropriately low morning cortisol (2.2 µg/dL, repeat 4.9 µg/dL) and ACTH (15 pg/mL), consistent with secondary adrenal insufficiency. Intravenous hydrocortisone (50 mg every 8 hours) stabilized glucose levels, allowing dextrose discontinuation. Methadone was subsequently reduced, and steroids were tapered to physiologic replacement dose.

CONCLUSION

Methadone-associated hypoglycemia shows increased risk at doses ⩾40 mg/day with threefold higher odds at doses >80 mg/day. The FDA notes cases may be dose-dependent, particularly in patients with diabetes. Proposed mechanisms include effects on insulin secretion and impaired counter-regulatory responses, with reports of hypoketotic, hyperinsulinemic hypoglycemia. Concurrently, Chronic opioid exposure suppresses the HPA axis, with secondary adrenal insufficiency reported in 9–29% of long-term users. The coexistence of impaired cortisol-mediated counter-regulation and methadone-related glucose lowering represents a clinically significant and potentially dangerous metabolic state. This case underscores the importance of vigilant glucose monitoring and adrenal evaluation in patients receiving high-dose methadone, particularly those with underlying glycemic disorders, and highlights an under-recognized endocrine complication in populations with high OUD prevalence.