Hypoglycemia due to Methadone Masquerading as Insulinoma

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Introduction

Hypoglycemia is rare in patients without diabetes mellitus. Nondiabetic causes of hypoglycemia include sepsis, adrenal insufficiency, liver failure, insulin secreting tumors, insulin antibodies, exogenous insulin use, and medication side effect. We describe a case of a patient with end-stage renal disease (ESRD) and a history of polysubstance use disorder who presented with recurrent hypoglycemic events that resolved with discontinuation of methadone.

Case Report

A 74-year-old man with a history of symptomatic hypoglycemia, cirrhosis, ESRD on hemodialysis, and polysubstance use disorder on methadone presented following a syncopal episode at home, where point-of-care blood glucose was 27 mg/dL.

He had previously been admitted to the hospital for severe fasting hypoglycemia. Workup during that admission was negative for insulin-like growth factor 2 (IGF2), proinsulin, and insulin antibodies. Endoscopic ultrasound did not reveal evidence of any pancreatic lesion suggestive of insulinoma. He was started on octreotide at 100mcg every 8 hours, but was lost to endocrine follow up several times, and eventually stopped taking octreotide.

Once admitted to hospital in the current presentation, he was restarted on octreotide at 100 mcg daily. Home methadone dose of 80 mg daily was continued. Hypoglycemic episodes were captured and correlated with hyperinsulinemia. (Table 1)

He continued to have asymptomatic hypoglycemia despite treatment. A suggestion was made to discontinue the patient's long-standing methadone. The patient remained euglycemic after discontinuation, and methadone was deemed the culprit for his recurrent asymptomatic hypoglycemia.
He was transitioned to buprenorphine and remained euglycemic without anti-hypoglycemic agents. He continues to remain euglycemic 10 months following discharge. (Figure 1)

	Reference range	1/4/2018	7/21/2020	7/23/2020
Serum Glucose (mg/dL)	*70 - 99*	**40**	**43**	**35**
Free Insulin (uIU/mL)	*3 - 19*	8.1	12	9
Total Insulin (uIU/mL)	*3 - 19*	-	14	10
Proinsulin (pmol/L)	*<=8.0*	**9.2**	**29.1**	**23.3**
C-peptide (ng/mL)	*1.1 - 4.4*	**7.0**	**10.0**	**8.7**
Beta Hydroxybutyric Acid (mmol/L)	*<0.27*	<0.02	-	-
Cortisol (mcg/dL)	*4.8 - 19.5*	13.2	10.1	-
Insulin-like growth factor 2 (ng/mL)	*180 - 580*	447	-	-
Insulin antibody (units/mL)	<0.4	<0.4	-	-

Table 1: Hypoglycemia labs correlated to hypoglycemic episodes during 2 hospital admissions

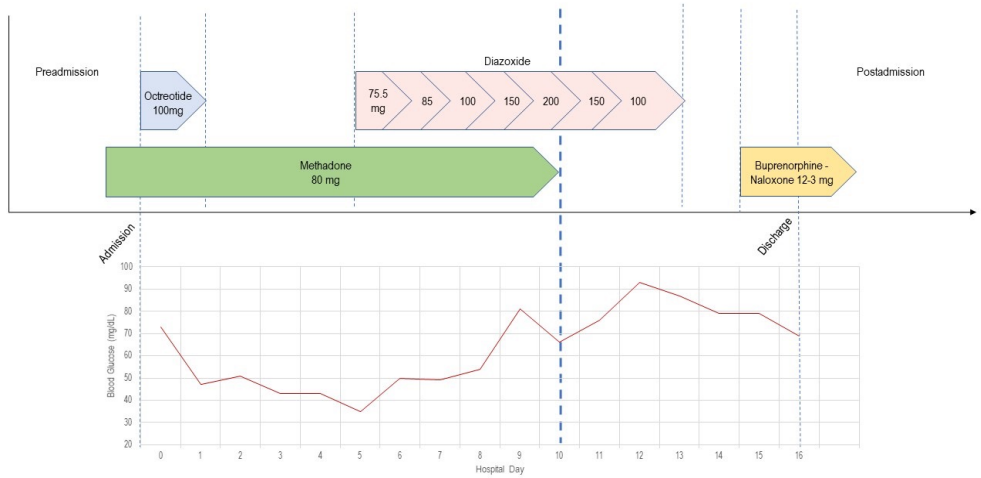

Figure 1: Timeline showing pertinent medications with doses (top) and nadir blood glucose during each day of patient's hospitalization (below).

Discussion

The evaluation of hypoglycemia in patients without diabetes mellitus is complicated by ESRD, which decreases clearance of pancreatic peptides. Contributing causes of hypoglycemia can be separated into disorders with appropriately depressed plasma insulin, and inappropriately elevated levels of plasma insulin. The latter scenario should prompt evaluation for overproduction of endogenous insulin or exogenous hyperinsulinism due to medication effects [1].

Methadone has been shown to cause hypoglycemia. High dose (>10 mg/kg) systemic administration of methadone in a mouse model has been shown to lower blood glucose in a dose-dependent manner [2]. These findings were reproduced in humans, where an increased risk of hypoglycemia with methadone use at an odds ratio of 2.2, as well as a linear relationship between risk of hypoglycemia and increasing methadone dose was demonstrated[3].

Our patient had an extensive work up to assess for an endogenous hyperinsulinemic disorder during two hospitalizations. While a single case report has been published reporting insulinoma in a patient with CKD, this pathology is very rare [4]. Alternately, a sole case report notes a patient with ESRD presenting with hypoglycemia, whose clinical picture appeared to be due to endogenous hyperinsulinism but was eventually shown to be due to methadone [5]. Our report further supports this finding; despite biochemical evidence of endogenous hyperinsulinism in the setting of ESRD, our patient's persistent hypoglycemia was in fact caused by methadone.

References:

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