Hypoglycemia due to Methadone Mimicks Insulinoma

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Introduction

Hypoglycemia is rare in patients without diabetes mellitus. We describe a case of a patient with end-stage renal disease (ESRD) and 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 a prior hospital admission for severe fasting hypoglycemia. Workup at that time was negative for a hyperinsulinemic disorder (Table 1), including an endoscopic ultrasound negative for pancreatic lesion suggestive of insulinoma. He was started on octreotide at 100mcg every 8 hours. He was lost to endocrine follow up.

On present admission, 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. After medication review, the patient's long-standing methadone was discontinued and transitioned to buprenorphine. He then remained euglycemic, and methadone was deemed the culprit for his recurrent asymptomatic hypoglycemia (Figure 1).

	Ref. 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

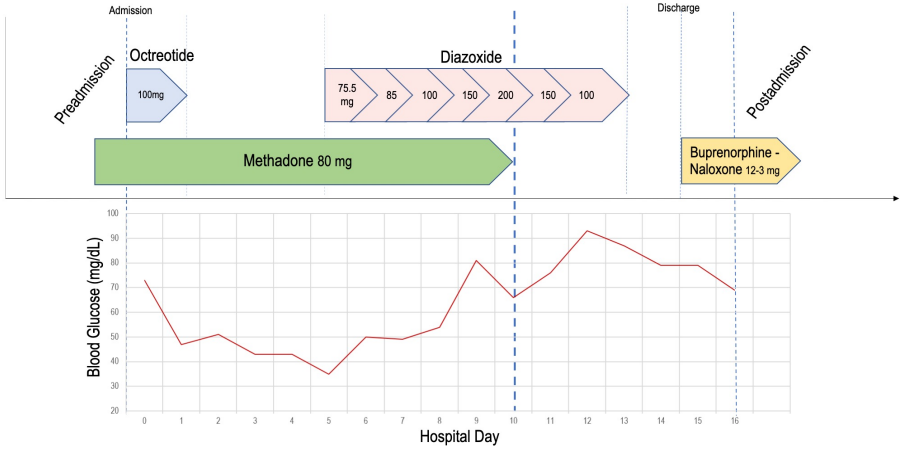

Figure 1: Timeline showing pertinent medications with doses (top) and nadir blood glucose during each day of patient's hospitalization (below).

Discussion

The evaluation of hypoglycemia is complicated by ESRD, which decreases clearance of pancreatic peptides. Causes of hypoglycemia can be separated into disorders with depressed insulin, or with elevated levels of insulin. The latter scenario should prompt evaluation for overproduction of 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 investigations for a hyperinsulinemic disorder during two hospitalizations. While a case report has reported an insulinoma in a patient with CKD, this pathology is very rare [4]. Another case report describes hypoglycemia in a patient with ESRD thought to be due to endogenous hyperinsulinism, but was eventually shown to be due to methadone [5]. Our report supports this finding; despite biochemical evidence of endogenous hyperinsulinism, our patient's hypoglycemia was in fact caused by methadone.

References:

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