

 Case Report

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Doxepin-Associated Hypoglycemia in an Ambulatory Nondiabetic Patient

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In the absence of diabetes, the diagnosis of hypoglycemia should only be considered for individuals who exhibit Whipple triad: symptoms consistent with hypoglycemia, confirmation of low glucose (<55 mg/dL) on blood testing, and resolution of these symptoms when the plasma glucose normalizes.¹ Hypoglycemia in healthy, nondiabetic individuals is uncommon and usually associated with endogenous hyperinsulinemia.¹ Most of these cases are secondary to insulinoma, noninsulinoma pancreatogenous hypoglycemia, post-gastric bypass hypoglycemia, or autoimmune hypoglycemia.¹ Insulin and sulfonylureas have been primarily implicated in cases of factitious hypoglycemia; however, other drugs have been identified in rare reports.¹ We present a case of postprandial hypoglycemia secondary to doxepin, a tricyclic antidepressant.

Case Report

A 43-year-old man with a history of posttraumatic stress disorder (per *DSM-5* criteria) presented to the endocrinology clinic in January 2022 for evaluation of symptoms suggestive of hypoglycemia (confusion, diaphoresis, tremulousness) occurring 2 hours after eating foods rich in simple carbohydrates. These symptoms improved with eating and had been present for many years but were worsening over the past 1 to 2 years. These symptoms were significantly interfering with the patient's life. He had no prior history of gastrointestinal surgery or regular alcohol intake. Current medications included citalopram 20 mg/d since 2007 and doxepin 50 mg/d since 2015.

His psychiatrist was consulted, and given rare reports of doxepin affecting blood glucose, doxepin was discontinued. While off doxepin, fasting laboratory tests (glucose, c-peptide, proinsulin) and a mixed meal test (59 g carbohydrates, 15 g fat, 22 g protein) were within normal limits. Factitious hypoglycemia was ruled out by a urine screen for oral hypoglycemic agents. The patient reported resolution of symptoms while off doxepin. A diagnostic, continuous glucose monitor (CGM) was then placed. In the first week of CGM use, the patient was off doxepin, and he remained asymptomatic. Doxepin was restarted in the second week, and his symptoms recurred. There was a 6.9 mg/dL decrease in mean glucose on doxepin therapy (Figure 1). Doxepin was once more discontinued, and the patient's symptoms again resolved.

Discussion

Antidepressant drugs have been occasionally associated with glucose dysregulation, both hypoglycemia and

hyperglycemia, in nondiabetic and diabetic individuals.^{2,3} The majority of reported cases of hypoglycemia associated with antidepressant use were in individuals with type 2 diabetes taking antihyperglycemic medications.⁴ Among the tricyclic antidepressants, imipramine, maprotiline, nortriptyline, and doxepin have been reported to cause rare hypoglycemic events.⁴ The only prior report of hypoglycemia secondary to doxepin was in a 71-year-old woman with type 2 diabetes also taking tolazamide (sulfonylurea) who had been on doxepin for 11 days prior to her presentation.⁵ This is the first reported case, to our knowledge, of doxepin causing postprandial hypoglycemia in an otherwise healthy nondiabetic individual. Symptomatic hypoglycemia related to fluoxetine use was previously reported in a nondiabetic male.⁶ Doxepin, fluoxetine, and other antidepressants with high serotonin transporter affinity appear more likely to increase insulin sensitivity.⁷

Doxepin has been shown to markedly enhance the action of insulin in albino rabbits on chronic doxepin (> 1 month), leading to profound hypoglycemia on oral glucose tolerance test.⁸ Acute administration of doxepin in 18-hour fasted albino rabbits led to significant hypoglycemia, peaking at 4 hours and lasting up to 10 hours. Hypoglycemic episodes were attenuated with chronic doxepin use by the seventh and 14th days, ending with hyperglycemia on the 21st day. Dysregulation of glucose resolved on the 29th day. Mixed results of doxepin on glucose regulation have been seen in obese mice.^{9,10}

It is important for clinicians to be aware of the potential impact of antidepressants on glucose regulation. This is especially vital given that symptomatic hypoglycemic episodes can adversely impact mental health,^{11,12} and severe hypoglycemia can be fatal.

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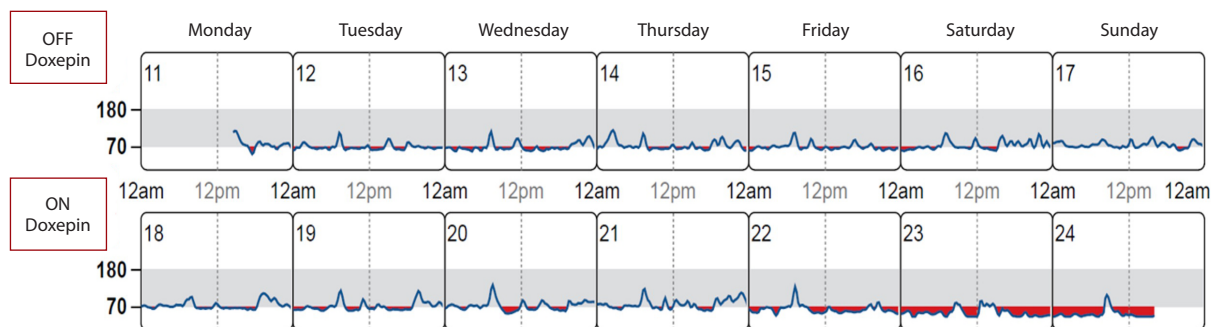
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Figure 1. Continuous Glucose Monitor Report^a

^aHypoglycemic episodes (glucose < 70 mg/dL) represented in red.

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