Zolpidem-Induced Sleep-Eating Resulting in Significant Hyperglycemia in a Subject With Type 1 Diabetes Discovered Via Continuous Glucose Monitoring

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PRESENTATION

The subject is a 36-year-old single white man diagnosed with type 1 diabetes in 1992 at the age of 24. He is of average build (68.9 kg, BMI 22.4 kg/m^2) and works as a social worker. He began using an insulin pump in 2001. His A1C was 8.3% in October 2005, at which time he was enrolled in a clinical study designed to optimize basal insulin dosing using continuous glucose monitoring (CGM).[1]

It was noted at routine follow-up visits when the CGM device was downloaded for review that

the patient had large excursions in glucose levels between midnight and 8:00 a.m., with glucose levels as high as 350–400 mg/dl (Figure 1A). There did not seem to be any clear explanation for this, and the patient had no recollection of being awake or eating during these times.

On further investigation and review of the patient's medications, it was discovered that he had been on zolpidem since July 2003. He was being treated concomitantly for depression with duloxetine, which was ultimately discontinued during the clinical study because of frequent heart palpitations.

It was then suggested that zolpidem-induced sleep-eating may be responsible for the large excursions in blood glucose level. The patient later disclosed that he had found bowls in the kitchen sink in the morning that he did not remember using. The dishes appeared to have been used for cereal. This led to the belief that, because of the zolpidem, the patient had been eating in the middle of the night but not recalling these events.

Subsequent CGM uploads, after discontinuation of the zolpidem, showed resolution of overnight hyperglycemia (Figure 1B).

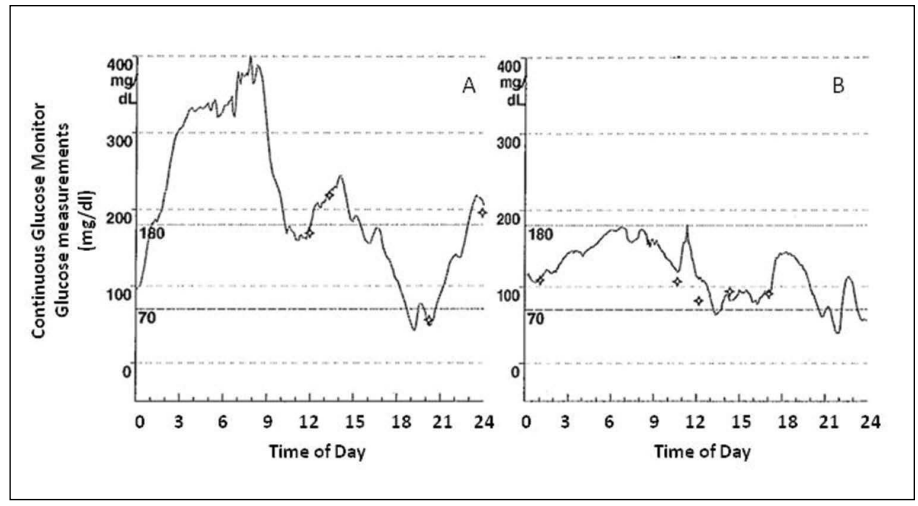

Figure 1. CGM downloads showing A*) large glucose excursions at night while on zolpidem and* B*) resolution of these excursions after discontinuation of zolpidem.*

QUESTIONS

1. What adverse effects could a medication such as zolpidem have for patients with type 1 diabetes?
2. When dealing with patients with poorly controlled diabetes, what other medications or medical conditions should be considered when taking a detailed history?

COMMENTARY

Zolpidem, a non-benzodiazepine sedative hypnotic, among other medications approved by the Food and Drug Administration for treatment of insomnia, has recently gained notoriety for its involvement in complex behaviors including sleep-eating, sleep-driving, sleep-cooking, and sleep-conversations (including telephone calls and texting).[2] Some case studies suggest that having a concurrent diagnosis, such as restless leg syndrome or personality or mood disorders may place patients at higher risk for these sleep behaviors.[3] Thus, extra caution may be worthwhile when considering zolpidem for a patient with diabetes.

In the past 10 years, zolpidem has been the most prescribed drug in its class for the treatment of insomnia. Other drugs in this class include eszopiclone and zaleplon. In the 5 years after Ambien became generic, zolpidem dispensing by pharmacies throughout the Unites States increased by ~ 10 million, from 34.5 million to 44.6 million prescriptions dispensed in 2011.[4] The popularity of zolpidem is likely part of the reason that most case reports of drug-induced complex behaviors note zolpidem as the culprit.

According to the package insert, which was changed in 2007 after post-marketing studies and case reports began to show zolpidem to be associated with sleep-related complex behaviors, co-administration with fluoxetine and sertraline can increase half-life and peak concentrations of zolpidem.[5] This becomes important in patients with concomitant mood disorders who are being treated with commonly used antidepressants such as selective serotonin reuptake inhibitors. This increase in half-life and peak concentration may have contributed to our patient's sleep-eating, particularly because he was previously treated with duloxetine.

Nocturnal sleep-related eating disorders appear to occur more commonly among women, though these disorders have also been described in men.[6,7] The concurrent use of antidepressants and zolpidem, however, is not necessary to see the complex sleep behaviors described, including sleep-eating.

Although nighttime eating would not necessarily be risky for patients without diabetes who are taking zolpidem, patients with diabetes should exercise caution when taking the drug because of the risk of uncontrollable hyperglycemia. Hyperglycemia is a term that refers to elevated blood glucose levels, usually measured as > 200 mg/dl. It occurs in patients with type 1 diabetes as a result of insufficient insulin production that impedes

cellular intake of glucose from the bloodstream.

One possible dangerous side effect of hyperglycemia is ketoacidosis. Diabetic ketoacidosis occurs in the setting of absolute or relative insulin deficiency, leading to decreased hepatic glucose production and peripheral glucose utilization. This, in turn, leads to hyperglycemia and hyperosmolarity, with subsequent osmotic diuresis and dehydration. Further mechanisms stimulate the release of free fatty acids, which are oxidized to ketones. Ketones then build up in the blood and urine. In high levels, these ketones are poisonous, causing metabolic acidosis. Hyperglycemia can also lead to coma or, in prolonged, untreated cases, micro- and macrovascular disease.

This is the first published case report of a patient identified through CGM as having zolpidem-induced sleep-eating. CGM is a diabetes technology that allows real-time measurement of glucose in the interstitial fluid, which is closely related to blood glucose. For people with type 1 diabetes, traditional glucose monitoring involves four to six finger sticks daily. Even this high level of monitoring can miss both hypo- and hyperglycemic excursions that may occur when individuals are unaware or unable to check their blood glucose (e.g., when they are asleep).

Given the well-established fact that maintaining blood glucose in a near-normal range and avoiding significant hypo- or hyperglycemic episodes may help prevent complications of diabetes, it has become prudent to develop new technologies to achieve this. Using the glucose concentration in the interstitial fluid has been considered minimally invasive and a good option for an accurate and concealable means of estimating blood glucose measurements.[8]

Finally, this case report of documented hyperglycemia in a clinical trial draws to our attention the precautions that should be taken when prescribing zolpidem to patients with type 1 diabetes. Health care providers should review their patients' full medication list to anticipate potential interactions and adverse effects such as those evident in our patient. Special attention should be paid to patients with mental health disorders because different providers may be treating them with antidepressants, which have been shown to potentiate the effects of zolpidem, leading to higher risk of sleep behaviors. Even in patients not on antidepressants, one must be wary of the possibility for zolpidem-induced sleep-eating. We believe this could help in avoiding both the immediate complications and the long-term effects of hyperglycemia.

CLINICAL PEARLS

- Zolpidem is a commonly prescribed sleep aid that has been implicated in sleep-eating, among other activities.
- Precautions should be taken when prescribing zolpidem to patients with diabetes because of the risk of unrecognized hyperglycemia that may occur in the setting of sleep-eating.
- Although not yet widely available, CGM may be a useful tool for viewing the effects of newly prescribed drugs on the glucose levels of patients with diabetes.
- More research is needed to find out whether patients with diabetes who take medications such as zolpidem have higher A1C levels as a result of unrecognized hyperglycemia.

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