MEGA JOURNAL OF CASE REPORTS

OPEN ACCESS

Case Presentation

Compiled Date: August 06, 2024

Status Epilepticus Secondary to Tirzepatide Induced Severe Hypoglycemia: A Case Report

Aarohi Parikh*, Anam Zara, Renu Thomas, Sara Shahid and Srinivas Panja

Division of Endocrinology, Department of Internal Medicine, HCA Houston Healthcare, USA

***Corresponding author:** Aarohi Parikh, Division of Endocrinology, Department of Internal Medicine, HCA Houston Healthcare, Kingwood, TX, 77339, USA

Abstract

Introduction: Type II diabetes mellitus is becoming increasingly prevalent worldwide, and in the recent years a surge of new medications that offers enhanced glycemic control along with notable weight loss has been discovered. One such drug, tirzepatide, is a dual agonist acting on glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors. It is gaining global popularity for its substantial weight loss benefits and its generally limited adverse effects which are mostly gastrointestinal. However, severe hypoglycemia, though rare has been reported as a potential serious side effect.

Case description: We report a case of a young female in her late-twenties who experienced a significant reduction in oral intake while on tirzepatide, leading to severe hypoglycemia and subsequent status epilepticus. She was treated with 10% dextrose in water, and her plasma blood glucose levels normalized. She was extubated and made an uneventful recovery. Brain imaging, EEG, and extensive laboratory tests revealed no other underlying cause for her status epilepticus, which was attributed to severe hypoglycemia induced by tirzepatide.

Discussion/Conclusion: The efficacy of tirzepatide in reducing hemoglobin A1C levels and facilitating substantial weight loss has been demonstrated in the SURPASS and SUROUNT trials. The adverse effects were extensively explored, revealing tirzepatide ability to reduce oral intake and induce early satiety, which can indirectly lead to hypoglycemia as in our patient. She obtained tirzepatide from an unofficial

source not regulated by a physician. This resulted in improper dose escalation and inadequate routine monitoring, potentially leading to unstudied and severe adverse effects that were not encountered in the trials above.

Keywords: Tirzepatide; Severe Hypoglycemia; Status Epilepticus; SURPASS; SURMOUNT

Introduction

The International Diabetes Federation estimates that 537 million adults currently have Type 2 Diabetes Mellitus (T2DM), with this number expected to rise to 783 million by 2045 [1]. T2DM results from insulin resistance in the body's tissue, often due to central obesity, and impairs insulin secretion due to pancreatic beta cell dysfunction. Obesity leads to increasing levels of free fatty acids in the blood, hampering its absorption by the liver, muscles, and adipocytes [2]. This in return increases the activity of serine kinases in myocytes and adipocytes leading to the phosphorylation of insulin receptor substrates, resulting in insulin resistance due to reduction of glucose uptake by the pancreatic beta cells [3]. Treatment options for T2DM have evolved to include medications that target glycemic control plus provide additional weight loss benefits. Previously, weight loss approaches included lifestyles changes, bariatric surgery, and medications like orlistat, which resulted in modest weight loss of about 6 kg over the span of four years [4]. Recently, Glucagon-Like Peptide receptor agonist (GLP-1) have gained attention globally for their rapid ability to induce substantial weight loss in diabetics. One such medication, tirzepatide, combines GLP-1 and Glucose-dependent Insulinotropic Polypeptide receptors (GIP), and has shown promising results in trials with limited adverse effects [5].

Tirzepatide was tested in the SURPASS and SURMOUNT trials, both demonstrating improvements in blood glucose control and notable weight loss. Adverse effects mainly consisted of gastrointestinal symptoms including nausea, vomiting, and diarrhea in both trials. Severe hypoglycemia was rarely observed in the SURPASS trial and was not observed in the SURMOUNT trial [5]. Neither trial displayed an increased risk of seizures related to tirzepatide. This case report highlights a young female adult who experienced severe hypoglycemia secondary to reduced oral intake and appetite suppression using tirzepatide, inducing status epilepticus, a situation that had not been previously documented to our knowledge. It also displays a concern for the dangers of using higher doses of tirzepatide when unofficially obtained and not regulated or monitored through physician supervision.

Case Presentation

A 27-year-old female arrived at an urgent care after an episode of a seizure. She experienced tunnel vision and lightheadedness prior to the seizure, following limb shaking in her upper extremities and a post-ictal state. Her medical history included childhood seizures and seizure free interval of five years with discontinuation of levetiracetam at that time. She had started taking tirzepatide 15 mg daily for weight loss within the past two weeks, obtained from an unofficial source, leading to significant appetite reduction and skipping two meals daily (usually breakfast and lunch). In the emergency department once she was transferred, she was observed having status epilepticus and a point of care glucose was noted to be 55 mg/dL and a plasma blood glucose was also drawn at the time which

resulted to be 52 mg/dL approximately one hour later. She was treated with dextrose 10% in water, midazolam 8 mg, and intravenous levetiracetam 2 grams immediately. And was intubated for airway protection, sedated with a propofol drip, and admitted to the ICU for acute hypoxic respiratory failure secondary to the status epilepticus. Upon arrival to the ICU, the patient's vitals were within normal limits and her BMI was 32.4 kg/m^2. The physical examination was remarkable for pinpoint pupils at 3 mm bilaterally and she was arousable to pain stimuli, all other further examination was limited due to sedation from the propofol drip. Her plasma blood glucose after one bag of dextrose 10% in water rose to 79 mg/dL. Laboratory testing including a complete blood count, magnesium, phosphorus, lactic acid, creatine kinase, urine drug screen, and alcohol level were all unremarkable. Initial CT scan of the cervical spine and head indicated no acute issues including no cervical fractures, infarctions, and tumors.

Neurology was consulted and recommended administering intravenous levetiracetam 1,000 mg twice daily while gradually reducing the propofol drip rate. An EEG performed the next day showed no clear focal, lateralizing, or epileptiform activity. The patient was successfully extubated on the third day of hospitalization without complications, and an MRI brain with and without contrast showed no signs of recent infarction or significant signal abnormalities. The patient was discharged with oral levetiracetam 1,000 mg twice daily and continued to follow up with her neurologist and primary care physician. She was seizure free for six months after discharge and discontinued levetiracetam per her neurologist. Her primary care physician also reduced her tirzepatide dose from 15 mg to 5 mg weekly, achieving sufficient weight loss without appetite suppression and a BMI of 28 kg/m^2.

Discussion

Neurological symptoms of severe hypoglycemia typically appear when the plasma blood glucose levels decrease below 55 mg/dL and often causes seizures [6]. Other common causes of seizures in adults (aged 18 to 60) include traumatic brain injury, illicit substance use, alcohol withdrawal, brain tumors, infections, and metabolic disturbances (such as changes in electrolytes) [6]. In our patient, none of these causes were present, except for severe hypoglycemia, which was noted during the status epilepticus episode. A point of care glucose and a plasma blood glucose were both obtained during the episode. A plasma blood glucose is considered gold standard due to its accuracy, while a point of care glucose usually deviates by 10 to 15% from the plasma blood glucose [7]. Therefore, severe hypoglycemia occurring simultaneously with the episode is the most likely the cause of the status epilepticus because it was less than 55 mg/dL with neurological symptoms of lightheadedness and tunnel vision, and a history of significant decrease oral intake of only one meal daily while using tirzepatide proceeding this episode. Additionally, the patient had been seizure-free for about five years, making it highly unlikely that her seizures were triggered due to lack of not taking seizure medications daily. The mechanism of tirzepatide is based on the actions of two key gut incretin hormones, GLP-1 and GIP. These hormones are released in response to nutrient intake within the intestine, leading to insulin secretion from pancreatic beta cells. GLP-1 is produced by L cells in the distal ileum and colon[8]. Its receptor agonist improves glycemic control and

promotes weight loss in T2DM by stimulating insulin secretion and reducing appetite through delayed gastric emptying [5]. GIP is secreted by K cells in the duodenum and jejunum, primarily enhancing the insulinotropic effect in non-diabetic individuals and stimulates glucagon secretion during euglycemia and hypoglycemia [8]. Both GLP-1 and GIP work synergistically to promote insulin release and are quickly degraded by dipeptidyl peptidase-4 enzyme [5].

Tirzepatide exhibits a significantly higher affinity for GIP receptors compared to GLP-1 receptors, with approximately five times stronger binding affinity for native GIP, closely resembling the natural affinity observed during trials [5,8-10]. In preclinical trials, it was observed that tirzepatide binds to G protein coupled receptors on pancreatic beta cells, generating cyclic Adenosine Monophosphate (cAMP) production [11,12]. This binding diminishes the effects of GLP-1 through receptor internalization, while maintain a high affinity for GIP, thereby reducing the occurrence of hypoglycemia events [11,12]. This indicates that the drug mechanism itself does not induce hypoglycemia but rather from its adverse effects of stimulating reduction of appetite though delaying gastric emptying as mentioned above. Additionally, the unique fatty acid at the C20 position of tirzepatide allows for albumin binding extending the drug's half-life to approximately five days [11]. This extended half-life supports a once-weekly administration regimen. Once the preclinical trials were completed, the SURPASS trials were designed to further investigate tirzepatide. These trials demonstrated that tirzepatide was highly effective in reducing hemoglobin A1C levels and promoting weight loss in patients with T2DM, where used as monotherapy or in combination with other diabetic treatments [5,8,10-13]. The trials also highlighted favorable safety and tolerability, making tirzepatide a promising option for T2DM management [5,8,10-13]. After the SURPASS trials, researchers began exploring the potential of tirzepatide for obese patients without diabetes.

The SURMOUNT trials demonstrated that tirzepatide effectively induced weight loss in individuals with and without T2DM, those following a weight loss program, and those with cardiovascular risk factors [5,10,12]. The trials also showed that long-term weight management was achievable with a safety profile similar to the SURPASS trials. Adverse effects in both trials were mostly gastrointestinal, with nausea, vomiting, diarrhea, and constipation being common, especially during dose-escalation phases [14]. These symptoms typically lasted 4-5 days before diminishing. The risk of severe hypoglycemia was very low in SURPASS trials and absent in the SURMOUNT trials. Other noted adverse effects included hypersensitivity reactions, pancreatitis, and cholelithiasis [14].

During the two trials, dosing was escalated weekly under physician supervision. However, our patient started on the maximum dose of 15 mg subcutaneously per week without any dose escalation because tirzepatide was obtained unofficially, bypassing continuous monitoring for severe side effects. Once she started following up with her primary care physician, the dose was adjusted from 15 mg to 5 mg weekly for better control, allowing a seizure free interval of six months thus far and no severe reduction in appetite or oral intake.

Conclusion

As tirzepatide and similar drugs gain popularity for rapid weight loss, it is important to remember that not

all adverse effects have been fully explored. Our case highlights the potential dangers, including the risk of seizure induction and status epilepticus if severe hypoglycemia occurs from unregulated dosing at the maximum 15 mg weekly for tirzepatide. We extensive explored possible causes of her seizures and were unable to attribute them to any other cause besides the severe hypoglycemia noted to be 52 mg/dL during the seizure. Additionally, with the history of decreased oral intake with newly started tirzepatide, and no seizure history in the last five years, the status epilepticus was most likely secondary to the severe hypoglycemia induced by tirzepatide.

References

1. Annual Report 2022. International Diabetic Federation, 2022.
2. Brunton Stephen. Pathophysiology of Type 2 Diabetes: The Evolution of Our Understanding. J Fam Pract. 2016;65(4):supp_az_0416.
3. Petersen KF, Gerald IS. Etiology of insulin resistance. Am J Med. 2006;119(5):S10-6.
4. Torgerson JS, Jonathan H, Mark NB, Lars S. "XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients." Diabetes Care. 2004;27(1):155-61.
5. Forzano I, Varzideh F, Avvisato R, Jankauskas SS, Mone P, Santulli G. Tirzepatide: A Systematic Update. Int J Mol Sci. 2022;23(23):14631.
6. Imad H, Johan Z, Eva K. "Hypoglycemia and risk of seizures: a retrospective cross-sectional study." Seizure. 2015:25:147-9.
7. Garingarao CJP, Myrna BS, Cecilia AJ. "Accuracy of point-of-care blood glucose measurements in critically ill patients in shock." J Diabetes Sci Technol. 2014;8(5):937-44.
8. Karagiannis T, Ioannis A, Aris L, Stefano DP, David RM, Apostolos T, et al. "Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: a systematic review and meta-analysis." Diabetologia. 2022;65(8):1251-61.
9. Coskun T, Kyle WS, Corina L, Jorge AF, Shweta U, Krister BB, et al. "LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept." Mol Metab. 2018:18:3-14.
10. Sinha R, Dimitris P, Jack AS, Melanie JD. "Efficacy and Safety of Tirzepatide in Type 2 Diabetes and Obesity Management." J Obes Metab Syndr. 2023;32(1):25-45.
11. Christophe DB, Bailey C, Carol W, Andrea H, Allen SE, Jennifer P. "Tirzepatide for the treatment of adults with type 2 diabetes: An endocrine perspective." Diabetes Obes Metab. 2023;25(1):3-17.
12. Jensen TL, Brønden A, Karstoft K, Sonne DP, Christensen MB. The Body weight Reducing Effects of Tirzepatide in People with and without Type 2 Diabetes: A Review on Efficacy and Adverse Effects. Patient Prefer Adherence. 2024;18:373-82.

13. Nauck MA, D'Alessio DA. Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regrading glycaemic control and body weight reduction. Cardiovasc Diabetol. 2022;21(1):169.

14. Mishra R, Raj R, Elshimy G, Zapata I, Kannan L, Majety P, Edem D, Correa R. Adverse Events Related to Tirzepatide. J Endocr Soc. 2023;7(4):bvad016.

Citation of this Article

Parikh A, Zara A, Thomas R, Shahid S and Panja S. Epilepticus Secondary to Tirzepatide Induced Severe Hypoglycemia: A Case Report. Mega J Case Rep. 2024;7(8):2001-2006.

Copyright