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Case Report

A Case of Ketoacidosis Caused by Tirzepatide in Non-diabetic Individual

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Abstract

Background: A new agonist for the glucagon-like peptide 1/glucose-dependent insulinotropic peptide (GLP-1/GIP) receptor is trizepatide. It was just approved to help non-diabetic persons lose weight and treat their diabetes. ***Case description:*** Due to the potential for starving ketoacidosis and insulin resistance, we report case of ketoacidosis following administration of trizepatide in an obese non-diabetic patient. ***Conclusion:*** Trizepatide, a dual-acting GLP-1 and GIP receptor agonist, can cause ketoacidosis in patients who are obese but not diabetic.

Keywords: ***Ketoacidosis, tirzepatide, obesity***

Introduction

Elevated levels of ketoacids (acetoacetate and beta-hydroxybutyrate) and anion gap metabolic acidosis are typically used to diagnose ketoacidosis [1]. Free fatty acids (FFAs) metabolized by extrahepatic tissues, primarily the brain, power the livers production of keto acids, which include beta-hydroxybutyric acid and acetoacetic acid. The liver turns FFAs into keto acids because increased synthesis necessitates a high concentration of FFAs. This conversion is frequently seen in diabetic patients as a result of high glucagon and inadequate insulin. Once weekly subcutaneous injections of tirzepatide [2], a new agonist of the glucagon-like peptide 1/glucose dependent insulinotropic peptide (GLP1/GIP) receptor, are delivered. For both individuals with and without diabetes mellitus [3], it is a recognized and successful treatment for obesity. After three weeks of tirzepatide medication, we report the case of an obese non-diabetic patient who developed ketoacidosis.

Case Presentation

A forty-year-old woman who was not known to have diabetes mellitus or hypertension and had no significant past medical history was admitted to the ICU from the ER with the chief complaints severe vomiting up to 10 times a day white in color that have lead to inability to tolerate orally. There was no history of fever, cough, dysuria, headache, or chest pain. has been trying to lose weight for the last three months with tirzepatide injections, starting with 2.5 mg and gradually increase by herself until 2 weeks prior she reached a dose of 10 mg. over the counter. She reported a loss of 12kg in 3 weeks. At home, she took antiemetic without any improvement. On admission, she was dehydrated with a heart rate of 61 beats per minute, a blood pressure of 145/74mmHg, an oxygen saturation of 100% on room air and a BMI of 23 kg/m2. The laboratory test results are shown in Table 1. Blood gas analysis revealed a pH of 7.19 (normal value 7.35 to 7.45), a partial pressure of carbon dioxide of 25 mmHg (normal 38 to 42 mmHg), a partial pressure of oxygen of 70 mmHg (75 to 100 mmHg), and a bicarbonate concentration of 9 mmHg (normal 21–28 mmol/l). The anion gap was 15 (normal value <12). Her urine ketone (+4).

Blood glucose levels were normal (4.9 mmol); Additional endocrine investigations showed a suppressed C-peptide level of 0.48 nmol/L (normal range: 0.84–1.43), an HbA1C of 4.6%—confirming non-diabetic status—and negative anti-islet cell antibodies, effectively ruling out autoimmune diabetes.

On assessment

GCS 15/15

Chest: Equal bilateral breath sound, abdominal: epigastric tenderness

No peripheral edema

As an inpatient, she was treated with 0.9 saline (1L) for 30 min, followed by D5 0.45 (150 mL/hour) and start on DKA protocol.

Blood glucose: Levels were between 7 and 8 mmol/L

Ondansetron was given every six hours orally for vomiting, and pantoprazole IV.

The anion gap was closed, acidosis was corrected, and the patient was advised against taking tarazepide.

Item	Value	Reference range
White blood count (*109/L)	10.1	3.3-10.8
Hemoglobin (G/L)	14.5	12-16
Platelet count (mmol/l)	422	150-450
Sodium (Mmol/L)	135	135-145
Potassium (Mmol/L)	4.69	3.5-5.1
Bicarbonate (Mmol/L)	8	22-29
Blood urea nitrogen (Mmol/L)	3.4	2.1-6.4
Corrected calcium (Mmol/L)	2.2	2.11-2.57
Phosphprus (Mmol/L)	0.9	0.84-1.43
Magnesium (Mmol/L)	0.67	0.71-0.96
Total bilirubin (Umol/L)	8	0-21
Gamma glutamyl Transpeptidase (U/L)	20	7-64
Aspartate amnio transferase (U/L)	20	8-43
Creatinine (Umol/L)	62	50-98
Glucose (Mmol/L)	9	3.9-7.8
HbA1C	4.6 %	4-5.6
Amylase (U/L)	30	25-125
Lipase (U/L)	28	8-78
Lactate (mmol/l)	0.79	
C-Peptide (Nmol/L)	0.48	0.84-1.43
Glutamate Decarboxylase Gad (IU/mL)	3	Less than 70

This test was developed and its analytical performance characteristics were determined by Quest Diagnostics. It has not been cleared or approved by the FDA; however, the assay has been validated pursuant to CLIA regulations and is intended for clinical use.

Note: This analysis was outsourced to Quest Diagnostics Laboratories, Nichols Institute, San Juan Capistrano, CA.

Discussion

A major factor in the movement of free fatty acids (FFAs) from the body's adipose tissue is insulin resistance or insufficiency. The liver converts FFAs to keto acids when there is an excess of glucagon and insufficient insulin. Through the transport of FFAs into the mitochondria, which necessitates acylcarnitine transferase, excess glucagon promotes the synthesis of keto acids from FFAs. FFAs are metabolized to acetyl coenzyme A (acetylCoA) and then to keto acids after being transferred into mitochondria [4].

The enzyme acetylCoA carboxylase is necessary for the diversification of acetylCoA to fatty acid resynthesis. Increased synthesis of keto acids is the result of additional inhibition of the acetyl-CoA carboxylase enzyme by insulin shortage, excess glucagon, and excess catecholamines 5. GLP-1 receptor agonists [GLP-1RA], dual-acting GLP-1, and glucose-dependent insulinotropic polypeptide [GIP] receptor agonists are examples of glucagon-like peptide 1 (GLP-1)-based therapies that impact glucose control through a number of mechanisms, such as increasing glucose-dependent insulin secretion, decreasing gastric emptying, increasing satiety, and decreasing inappropriate glucagon secretion [6]. When compared to either medication alone, tirzepatide, a dual-acting agonist of the GLP-1 and GIP receptors, exhibits exceptional glycemic and weight-loss performance [5].

Its usage as a monotherapy and in conjunction with other medications, such as insulin, sulfonylureas, and metformin, has been investigated in individuals who have not responded well to diet and exercise [6,7]. The majority of GLP-1-based treatments have gastrointestinal side effects, especially the common ones of nausea, vomiting, and diarrhea. In studies 10, these illnesses routinely affect 10% to 50% of participants [8,9]. In a study contrasting semaglutide and tirzepatide, gastrointestinal side effects. The two groups experienced comparable side effects (diarrhea 11.5% to 16.4%, nausea 17.4 to 22.1%, and decreased appetite 5.3 to 8.9%) [10].111. ≥0.2% of the population experienced adverse effects that resulted in stopping tirzepatide or semaglutide; no cases of ketoacidosis were reported in the trial [11]. At least 5% of patients in the Tirzepatide Once Weekly for the Treatment of Obesity research experienced adverse effects, most of which were gastrointestinal in nature; no occurrence of ketoacidosis was observed. In one study, the FDA Adverse Event Reporting System (FAERS) database was used to evaluate the relationship between GLP-1RA and diabetic ketoacidosis/ketosis. In the FAERS database, there were 1,382 occurrences of diabetic ketoacidosis (1,491 cases of ketosis) linked to GLP-1RA during the first quarter (Q1) of 2004 and the fourth quarter (Q4) of 2019. After controlling for the effects of insulin and SGLT2, there was a little disproportionate reporting of diabetic ketoacidosis linked to total GLP-1RA (PRR 1.49, 95% CI 1.24-1.79, $p < 0.001$). When GLP-1RA and insulin were added for comparison, this disparity vanished. The disproportionate reporting of diabetic ketoacidosis linked to GLP-1RA when insulin was not taken with GLP-1RA

When 1RA and insulin were not coupled, a disproportionate number of cases of diabetic ketoacidosis linked to GLP-1RA were reported [11]. In obese non-diabetic patients taking dual-acting GLP-1 agonists for weight loss, ketoacidosis was not observed. This is the first instance of tirzepatide causing ketoacidosis. Starvation ketoacidosis is the most likely mechanism of ketoacidosis. The primary causes of starving ketoacidosis include inadequate dietary intake brought on by dual-acting GLP-1 agonists, vomiting, nausea, and diarrhea. Dual-acting GLP-1 agonists can also reduce calorie intake, delay stomach emptying, and suppress appetite. Patients who are obese and consume fewer than 500 calories per day are susceptible to ketosis [12].

The link between insulin resistance and metabolically harmful obesity [13] is another potential reason. Increased insulin resistance is brought on by an overabundance of free fatty acids in insulin-sensitive non-adipose tissues [14]. Since insulin withdrawal or dose reduction was found to represent a significant turning point in the development of diabetic ketoacidosis in patients treated with GLP-1RA, insulin resistance status may reflect relative insulin deficit status in obese patients with diabetes [11]. This case appears to be the first reported instance of tirzepatide-induced ketoacidosis in a non-diabetic patient within Saudi Arabia. The rarity of this presentation emphasizes the clinical importance of recognizing atypical metabolic responses to GLP-1/GIP agonists, especially when used without medical supervision.

Conclusion

We describe tirzepatide the first dual-acting agonist of the GLP-1 and GIP receptors, which causes ketoacidosis in obese non-diabetic subjects. In people with insulin reissuance, starvation ketosis is the most common cause. Physicians could be aware of this significant consequence, examine serum and urine ketone levels, be prepared to stop treatment, and be alert of early signs. Only under a doctor's supervision should trizepatide be prescribed; it should never be purchased over-the-counter.

Declarations

Data Availability

All data available on corresponding author upon a responsible request.

Funding Statment

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Conflicts of Interest

All the authors declare none.

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