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ABSTRACT

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CASE REPORT

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Keywords: Diabetes type 2, Empagliflozin, Ketoacidosis

How to cite this article

Mitsiou E, Mandros C, Kotsa K, Koulis F, Christofidis C, Georgiadi S, Testa T, Anastasiou A, Efthymiou E, Potolidis E. SGLT2 inhibitor associated diabetic ketoacidosis. Int J Case Rep Images 2017;8(4):239–241.

Article ID: Z01201704CR10779EM

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Received: 27 November 2016

Accepted: 23 December 2016

Published: 01 April 2017

doi:10.5348/ijeri-201740-CR-10779

INTRODUCTION

SGLT2 inhibitors are sodium-glucose cotransporter 2 inhibitors (SGLT2) in the proximal renal tubules that reduce reabsorption of filtered glucose from the tubular lumen and lower the renal threshold for glucose (RTG). Therefore, SGLT2 is the main site of filtered glucose reabsorption. By inhibiting SGLT2, urine glucose excretion increases and plasma glucose concentration reduces [1]. The SGLT2 inhibitors are generally weak glucose-lowering agents, similar to efficacy to the DPP-4 inhibitors. Empagliflozin is one of the representatives of this category of glucose-lowering agents, which is used for the treatment of type 2 diabetes mellitus, usually in combination with metformin [2] or insulin [3], as an adjunct to exercise and diet to improve glycemic control. Common adverse reactions are hypoglycemia and urinary tract infections [4]. Since approval of the first-in-class drug in 2013, data have emerged suggesting that these drugs may increase the risk of diabetic ketoacidosis [5]. Moreover, in May 2015, the Food and Drug Association issued a warning that SGLT2 inhibitors can increase the incidence of diabetic ketoacidosis [6]. It also identified potential triggering factors such as illness, reduced food and fluid intake, reduced insulin doses, and history of alcohol intake. Our case will be one of the few cases of diabetic ketoacidosis reported in a patient with type 2 diabetes mellitus [7].

CASE REPORT

A 76-year-old female was admitted to our hospital because of increased fatigue and weakness during the last 10 days. At the same time, she started receiving medication for type 2 diabetes mellitus, which concluded metformin 850 (1x1) and empagliflozin 10 (1x1). She did

not receive any other medication. She reported just one fever wave up to 38°C, three days before the admission.

On examination she appeared confused and she had tachypnea. She did not show any signs of infection. The temperature was 36.9°C, the blood pressure 90/60 mmHg, the pulse 100 beats per minute, the respiratory rate 30 breaths per minute and the oxygen saturation 96%, while she was breathing ambient air. Blood tests revealed elevated hematocrit (52.8%), white blood cells (15200/ml) and CRP (100 mg/dl), whereas kidney function was normal (creatinine 1.0 mg/dl, urea 50 mg/dl). Serum electrolytes were also normal (serum potassium 4.9 mEq/l, serum sodium 137 mEq/l), serum calcium was 90 mEq/l and serum glucose was 202 mg/dl. Urinalysis revealed 4+ glucose, 1+ albumin, 4+ ketones by dipstick. Blood gas test revealed severe acidosis with pH 7.06, pCO₂ 24 mmHg, pO₂ 129 mmHg, lac 1.0 mmol/l, HCO₃ 9.6 mmol/l, base excess 20.7 mmol/l, SO₂ 99%. Urine culture was negative. Anion gap was calculated and appeared to be elevated at 36.4. HbA1c was 10.7%.

The patient was treated as having diabetic ketoacidosis due to type 1 diabetes mellitus. She aggressively received intravenous fluids and insulin and she was covered empirically with a broad spectrum antibiotic because of elevated CRP, even though she did not have any fever during her hospitalization. Urinalysis continued to show elevated glucose levels and ketones, until the day of discharge, on day-8. Blood gas tests stopped to show acidosis on the third day, but the base deficit remained high until the seventh day (HCO₃ 16.9 mmol/l, base excess 9.0 mmol/l). The test was normal on the day of discharge.

DISCUSSION

Empagliflozin is an SGLT2 inhibitor usually used in combination with metformin or insulin in order to further reduce serum glucose levels. Lately, apart from the common adverse reactions of hypoglycemia and urinary tract infections, cases of diabetic ketoacidosis come to light. Food and Drug administration issued a special warning about this adverse reaction, which include not only empagliflozin but also all drugs of this category. Based on the pharmacological characteristics of this type of drugs and the physiology of SGLT2, several possible mechanisms could be suggested for the development of diabetic ketoacidosis. Inhibition of SGLT2 causes a rapid increase in urinary volume excretion, which lasts more than 24 hours [8]. Also, the decrease in plasma glucose levels, that is caused by these drugs [9], lead to a decrease in plasma insulin levels and a significant increase in plasma glucagon concentrations, because of a diminished paracrine inhibition by insulin and a decreased SGLT2-mediated glucose transport into α -cells [10]. Therefore, SGLT2 inhibitors seem to be associated with euglycemic diabetic ketoacidosis, perhaps as a

consequence of their non-insulin dependent glucose clearance, hyperglucagonemia and volume depletion [8].

CONCLUSION

Patients who are treated with SGLT2 inhibitors should be closely monitored for this adverse reaction and clinicians should also be aware of it. Further research should be done in order to minimize the risk of ketoacidosis due to SGLT2 inhibitors.

Author Contributions

Evdoxia Mitsiou – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Charalampos Mandros – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Kalliopi Kotsa – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Frangiskos Koulis – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Charalampos Christofidis – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Sofia Georgiadi – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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Alexandros Anastasiou – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Evgenia Efthymiou – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Evangelos Potolidis – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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