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Case Report

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Empagliflozin-Induced Delayed Onset Euglycemic Diabetic Ketoacidosis

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1. Background

A large anion gap metabolic acidosis, a comparatively low blood glucose level (less than 11.1 mmol/L), and evidence of ketosis are the hallmarks of euglycemic diabetic ketoacidosis (EDKA) [1]. EDKA can be brought on by a variety of factors, including excessive alcohol use, a reduction in caloric intake, infections, dehydration, severe sickness, and bariatric surgery. If the case is identified early and treated properly, the prognosis is typically quite good [2]. By blocking glucose reabsorption in the kidney's proximal tubule, sodium glucose cotransporter-2 (SGLT2) inhibitors reduce blood glucose levels while boosting glucose excretion in the urine One of the SGLT2 inhibitors, empagliflozin, has a half-life concentration of 5.6–13.1 hours, a peak plasma concentration of 1.33–3.0 hours after treatment, and a stable trough concentration after sixth day of administration [3,4]. Other research has demonstrated that the pharmacological effects of SGLT2 inhibitors can last longer than 10 days, as seen by the development of glucosuria following a 10-day medication cessation [5].

The most frequent adverse effect of SGLT2 inhibitors is an increased risk of urinary tract infections and female genital mycotic infections; EDKA is an uncommon but dangerous side effect Euglycemic status is found in 2.6% to 3.2% of admissions for diabetic ketoacidosis [6,2]. In individuals with type 2 diabetes, the incidence of DKA linked to SGLT2 inhibitor treatment was shown to be 0.16–0.76 occurrences per 1000 patient-years [2]. It has been suggested that SGLT2 causes DKA by lowering blood glucose levels through its mechanism of action, which entails binding to the kidney's proximal tubule and blocking glucose reabsorption into the circulation, Reduced blood glucose levels can promote lipolysis, which raises beta- oxidation and free fatty acid levels and results in the production of ketones [7]. Euglycemic diabetic ketoacidosis has also been linked to empagliflozin, dapagliflozin, and canagliflozin [1-9]. The majority of reports of EDKA in SGLT2 inhibitor-using patients focus on those who had been taking SGLT2 for a while before experiencing EDKA during their course of treatment [10-13].

Being the first case report to describe an EDKA state in a patient who stopped taking an empagliflozin SGLT2 inhibitor for 14 days, our intriguing case is unique. Our example is significant because it raises the possibility of a severe side effect from SGLT2 inhibitors, even after stopping the drug for two weeks.

2. Case Report

A 63-year-old man of Arabic heritage who had been suffering from type 2 diabetes mellitus, hypertension, and dyslipidemia for 15 years arrived at the emergency room complaining of weariness and lightheadedness for two days. He denies experiencing diarrhea, vomiting, or chest or abdominal pain. When he arrived, he was taking 1,000 mg of metformin once daily and 10 mg of empagliflozin once daily as antidiabetic drugs. Telmisartan 80 mg once daily and atorvastatin 20 mg once daily are additional drugs. There is no notable family history, and he does not have any pharmaceutical allergies. He had a laparoscopic gastric sleeve procedure to lose weight two weeks before to his presentation. Two weeks prior to his presentation, he stopped taking all of his anti-diabetic drugs on his own. The patient was found to be afebrile and vitally stable upon assessment. The results of the abdominal and general exams were unimpressive.

When the patient was brought to the emergency room, the following laboratory results were found: urine ketones (4+) mmol/l, urine glucose (3+) mmol/L, sodium 137 mmol/L (136–145 mmol/L), venous bicarbonate 7.9 mmol/L (22–26 mmol/L), chloride 97 mmol/L (98–107 mmol/L), and glucose 174 mg/dl (9.7 mmol/L). Venous samples were used to get all lab results (Table 1)., Sepsis was excluded by normal CRP, PCT and negative all septic workup like blood, urine and sputum cultures. Alcohol ketoacidosis as a cause of high anion gap metabolic acidosis was ruled out by normal Osm Gap (-9,0 mOsm/kg). After receiving a diagnosis of euglycemic DKA, the patient was admitted to the medical ward and treated with insulin and dextrose drips in accordance with the hospital's DKA protocol. The serum lactic acid level was 1.05 mmol/L while the patient was in the hospital.

Investigation	Result	Normal Value
Serum glucose	9.7 mmol/L	3.9–6.1 mmol/L
Serum sodium	137 mmol/L	136–145 mmol/L
Serum chloride	97 mmol/L	(98– 107 mmol/L)
Serum potassium	3.91 mmol/L	3.5–5.2 mmol/L
Venous bicarbonate	7.9 mmol/L	22-26 mmol/L
Urinary ketones	(4+)	Negative
Urinary glucose	(3+)	Negative
Serum lactic acid	1.05 mmol/L	0.5–2.2 mmol/L
Serum creatinine	72 umol/L	64-102 umol/L
White blood cell count	7.10 10"9/l	4.0-10.0 10"9 /l
Hemoglobin	132 g/L	130-170 g/L
procalcitonin	0,05 ng/ml	(<0,5 ng/ml)
C-reactive protein CRP	3 mg/L	0-5 mg/L
Troponin	0.00 ng/ml	negative
Cal.osmolality	279.8 mOsm/kg	275-295

Table 1: Investigations

The patient was discharged after being hospitalized for six days. Insulin glargine (U100) 20 units once daily was one of his discharge prescriptions. After two weeks, when his prior oral antidiabetic medications were resumed, the patient returned for follow-up at the Diabetology clinic.

3. Discussion

High anion gap metabolic acidosis combined with hyperglycemia and evidence of ketosis is known as diabetic ketoacidosis. The hallmarks of euglycemic diabetic ketoacidosis are slightly raised blood glucose levels, less than 200 mg/dl (11.1 mmol/L) [14]. In all, euglycemic diabetic ketoacidosis accounts for 2.6% to 3.2% of hospitalized cases [2]. Because SGLT2 inhibitors are known to be prone to DKA, the Food and Drug Administration even issued a warning regarding this side effect in May 2015 [15]. Numerous explanations have been identified by studies as to why using medicines that inhibit SGLT2 may result in DKA. Empagliflozin and dapagliflozin may raise glucagon levels via acting on the pancreatic alpha cell, which would encourage hepatic ketogenesis and ketone production. This is one of the postulated explanations [15]. Recent insulin use, pregnancy, heavy alcohol use, chronic liver illness, glycogen storage disease, and reduced caloric intake are additional risk factors for euglycemic DKA [16,17]. The pharmacological effects of empagliflozin may last for more than 10 days, as seen by the development of a high level of 10 days after quitting the medication, and the drug's peak plasma concentration may occur 1.33–3.0 hours after administration [4,5]. Up to 9–10 days after ceasing treatment, SGLT2 inhibitors may result in glucosuria [5]. Although it's unclear when SGLT2 inhibitors should be stopped and resumed, it's recommended to do so for at least 9–10 days [5].

The emergence of EDKA in individuals already using SGLT2 inhibitors has been covered in numerous case reports. A patient with type 2 diabetes mellitus who had stopped taking her Dapagliflozin SGLT2 inhibitor prescription two weeks before to the presentation was reported to have experienced EDKA by Iqbal et al. [18]. The fact that his case involved a delayed occurrence of EDKA after the patient was already off medication made it distinctive [18]. In our instance, a normal lactate level ruled out any chance of metformin- induced lactic acidosis and other causes of high anion gap metabolic acidosis. Additionally, all of the patient's septic workup, including blood cultures and inflammatory markers, came back negative, ruling out sepsis. Uremia was also ruled out with normal renal function testing. The patient denies ever drinking alcohol.

We therefore draw the conclusion that, in our instance, the patient experienced a major adverse event of this kind of antidiabetic medicine, EDKA, even though he had ceased taking his empagliflozin SGLT2 inhibitor medication two weeks before to his presentation. The case demonstrated that EDKA can also be a delayed adverse effect that happens after the patient quits taking medicine, rather than usually happening while the patient is taking the medication [18]. There are no clear guidelines on whether it is advisable to stop or continue using SGLT2 inhibitors after an episode of SGLT2 causes EDKA, however the majority of instances in the literature quit SGLT2 inhibitors indefinitely [1,9,12]. Two weeks after being discharged, our patient was reviewed and his SGLT2 inhibitor, empagliflozin, was resumed.

4. Conclusion

Despite stopping SGLT2 inhibitors for two weeks, this is an uncommon and intriguing instance of EDKA, which is a delayed significant adverse effect of this class of drugs. Given the extensive use of SGLT2 inhibitors, which have several demonstrated positive effects, medical professionals should be aware that EDKA may occur even when SGLT2 inhibitors are stopped.

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