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Case Report

Empagliflozin-associated euglycemic ketoacidosis

Ivona Vranić[1], Ivan Stanković[1,2], Miloš Panić[1], Predrag Miličević[1], Aleksandar N. Nešković[1,2]

[1]Clinical Hospital Centre Zemun, Department of Cardiology, Vukova 9, Belgrade, Serbia, [2]Faculty of Medicine, Belgrade University, Dr Subotića 8, Belgrade, Serbia

Abstract We present a case of euglycemic ketoacidosis in a 69-year-old patient with diabetes mellitus type 2 treated with insulin and empagliflozin who was hospitalised for high-intermediate risk pulmonary thromboembolism. After initial clinical improvement with conservative therapy, on the fifth day of hospitalisation the patient became dyspnoeic (Kussmaul type), with nausea and fatigue, but without other significant physical, electrocardiographic or echocardiographic findings. Laboratory results revealed metabolic acidosis with increased anion gap and significant ketonuria, but without marked hyperglycemia. We suspected the occurrence of euglycemic ketoacidosis, stopped empagliflozin and proceeded with treatment protocol for diabetic ketoacidosis. After 36 hours the patient was stabilised with normal acid-base status, but glycosuria was observed the following seven days, as a prolonged effect of empagliflozin.

Key words empagliflozin, SGLT2 inhibitor, euglycemic ketoacidosis

Introduction

Sodium glucose cotransporter 2 inhibitors (SGLT2 inhibitors) represent an important therapeutic group that is widely used owing to their anti-diabetic, cardiovascular and renoprotective effects, a favourable safety profile and no need for dose titration[1,2]. Side effects are rare, with genitourinary infections (3-10%) and volume depletion (9.4%) being most commonly observed[3,4]. Euglycemic ketoacidosis is described as a rare adverse effect of SGLT2 inhibitors that can develop in circumstances of absolute or relative lack of insulin, during acute infections, surgery, pregnancy, fasting, dehydration, strenuous physical exertion or high alcohol consumption[5]. All of these scenarios can cause relative insulin deficiency and insulin glucagon ratio inversion leading to ketoacidosis[6]. Euglycemic ketoacidosis is a rare, life-threatening condition, that can be difficult to diagnose, thus leading to a delay in treatment. It is therefore important to recognise the conditions that might trigger this metabolic disorder in order to prompt early diagnosis and treatment[7]. We present a case of euglycemic ketoacidosis in patient with type 2 diabetes treated with insulin and empagliflozin who was hospitalised for high-intermediate risk pulmonary thromboembolism.

Case presentation

A 69-year-old woman presented to emergency room with progressive dyspnoea, malaise, fever and chest pain. She reported arterial hypertension, hyperlidipemia and diabetes mellitus type 2 (on insulin therapy and empagliflozin) in her medical history. One month prior to current admission, she had a cardiac surgery (a coronary artery bypass grafting) for unstable angina pectoris. After uncomplicated surgery with unremarkable perioperative period, the patient was inactive at home. On the day of admission to our department, the patient was conscious but adynamic, subfebrile and dyspnoeic with oxygen saturation of arterial blood of 87% on room air. Physical examination revealed no breath sounds in the basal portion of the left lung and occasional bilateral late inspiratory crackles. An electrocardiogram revealed sinus tachycardia and negative T-waves in the lateral leads, while echocardiographic examination showed the signs of right ventricular overload, including a dilated right ventricle, McConnell's sign and early systolic notching in pulmonary artery Doppler flow signal. Chest X ray showed signs of congestion and a large left sided pleural effusion (Figure 1), while computed tomography pulmonary angiography showed the signs of massive pulmonary thromboembolism, unilateral left pleural effusion with subsequent atelectasis (Figure 2). The patient was hemodynamically stable and was started on low-weight molecular heparin and also dual antibiotic therapy because of clinical and laboratory markers of infection (C-reactive protein 130 mg/L, fibrinogen 7.1 g/L). After the initial clinical improvement, on the fifth day of hospitalisation, the patient became dyspnoeic (with Kussmaul breathing), nauseous and lethargic. Laboratory results showed metabolic acidosis with increased anion gap (pH 7.19, bicarbonate 6.1 mmol/L, anion gap 31 mmol/L) and marked ketonuria with only slightly elevated blood glucose levels (9.5 mmol/L). Since the findings were consistent with an euglycemic ketoacidosis, empagliflozin was immediately stopped and protocol for diabetic

Address for correspondence: Ivona Vranić, Clinical Hospital Centre Zemun, Department of Cardiology, Vukova 9, 11080 Belgrade, Phone: +381 62 260 803, e-mail: ivona-26@hotmail.com

ketoacidosis initiated. The acid-base balance and patient clinical status gradually improved and eventually normalized in the ensuing 36 hours (Figure 3). Although empagliflozin was immediately stopped, its prolonged effect (glycosuria and ketonuria) was observed over the next 7 days, but without acidosis. The patient was recovered and discharged from hospital 3 weeks later.

Discussion

Euglycemic ketoacidosis is an acute, life-threatening emergency that requires prompt diagnosis and treatment with an incidence of 2.6 – 3.2% of all admissions with diabetic ketoacidosis[8]. It was first described by Munro et al. in 1973 in patients with diabetes mellitus type 1[9] and is characterised by ketoacidosis and mildly elevated serum glucose (less than 14 mmol/L)[10]. It is diagnosed by excluding other causes of metabolic acidosis with increased anion gap such as excessive alcohol consumption, methanol or polyethylene glycol ingestion, sepsis, lactic acidosis, drug overdose (salicylate or tricyclic antidepressants), ketosis due to prolonged starvation and/or strenuous physical exertion, as well as glycogen storage diseases[5,10,11]. Common causes of euglycemic ketoacidosis are use of SGLT2 inhibitors, pregnancy, and prolonged starvation[5].

SGLT2 inhibitors reduce serum glucose by inhibiting 80-90% glucose reabsorption in the proximal renal tubule, subsequently leading to osmotic diuresis[5]. In the conditions of stress (e.g. acute myocardial infarction, acute decompensated heart failure, acute infection, surgery, trauma, fasting, strenuous physical exertion) there is an excess of counterregulatory hormones (catecholamines, cortisol and glucagon), leading to a relative deficiency of insulin in diabetes type 2, an absolute insulin deficiency in diabetes type 1 and ketogenesis and ketoacidosis[6]. The lack of carbohydrates and dehydration associated with SGLT2 inhibitor use (trough glycosuria and osmotic diuresis) plays a pivotal role in the development of euglycemic ketoacidosis[6]. Additionally, SGLT2 inhibitors stimulate pancreatic alpha cells promoting glucagon secretion and reduce the excretion of ketone bodies in the proximal tubule, thus facilitating the occurrence of euglycemic ketoacidosis in stress situations[12,13].

This rare, but life-threatening side effect of SGLT2 inhibitors was the reason American Association of Clinical Endocrinologists and American College of Endocrinology recommended that SGLT2 inhibitors should be omitted 24 hours prior to elective surgery[14]. There are some published data about the

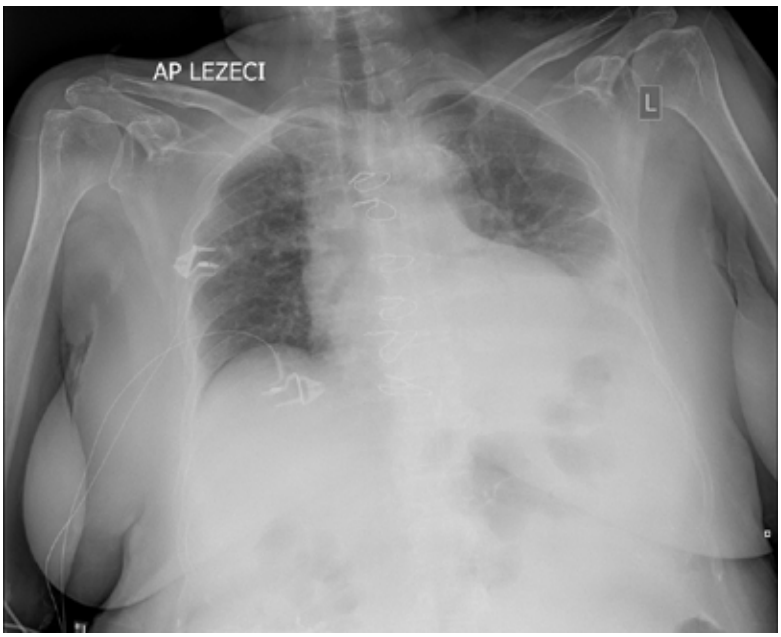

Figure 1. Chest X ray showing the signs of pulmonary congestion and a large left-sided pleural effusion

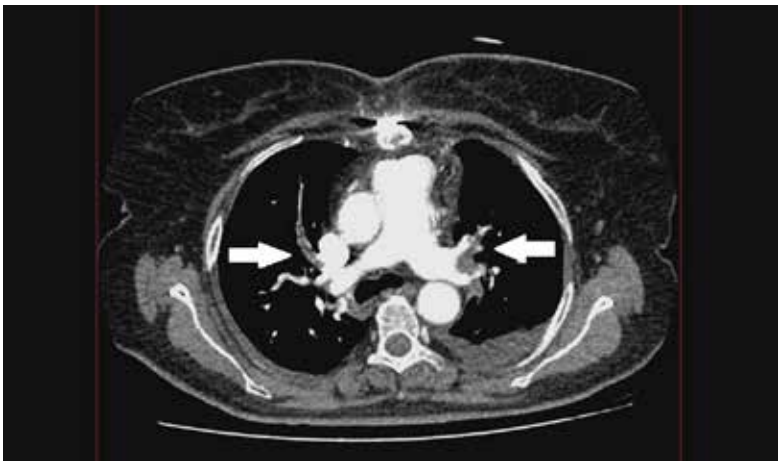

Figure 2. Computed tomography pulmonary angiography showing thrombi in both pulmonary artery branches and their lobar and segmental branches (arrows)

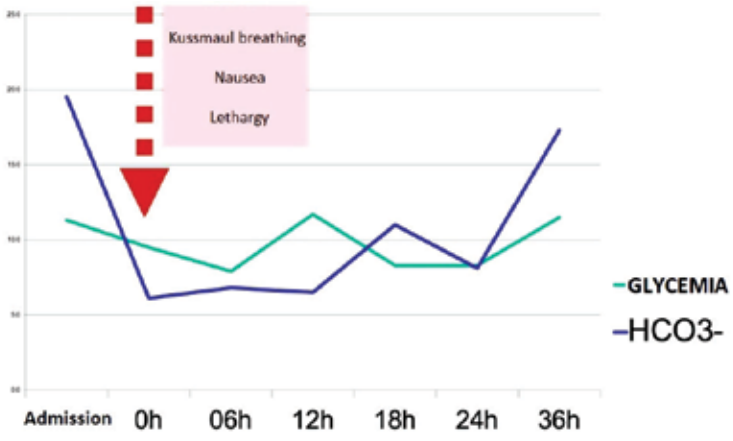

Figure 3. Temporal changes of bicarbonate and blood glucose levels from the occurrence of ketoacidosis (0h) and over the following 36 hours

possibility of prolonged SGLT2 inhibitors effect, that can last up to 8 to 10 days after drug discontinuation[15]. In some cases, even after drug omission 2-3 days prior to elective surgery, prolonged glycosuria with ketonemia was observed due to decelerated drug pharmacokinetics[16,17,18]. Given the long terminal half-lives of SGLT-2 inhibitors, the U.S. Food and Drug Administration recommends discontinuing canagliflozin, dapagliflozin, and empagliflozin at least three days before, and ertugliflozin at least four days before scheduled surgery[19]. In acidosis, SGLT2 inhibitors are highly bound to plasma proteins (80-90%), and their dissociation is possible only after acid-base normalisation, which is a necessary step in order for drug to be eliminated from the body[20].

In euglycemic ketoacidosis associated with SGLT2 inhibitors, immediate drug discontinuation is required followed by correction of hypovolemia and electrolytes, as well as insulin and glucose replacement[21]. Since drug prolonged effect has been observed, longer acid-base and electrolyte status follow-up is advisable.

SGLT2 inhibitors are used in treatment of diabetes mellitus, chronic heart failure and chronic kidney disease. In comparison to numerous beneficial effects, there is a fairly low occurrence of side effects (urinary tract infections, genital mycotic infections, dehydration, ketoacidosis), most of which are preventable. While the EMPEROR-PERSERVED study reported 4 cases (0.1 %) of ketoacidosis, there was no observed cases of ketoacidosis in the EMPEROR- REDUCED trial (22, 23). Furthermore, in a study investigating the effects of dapagliflozin in heart failure with reduced ejection fraction (DAPA-HF), only two cases (0.1 %) of diabetic ketoacidosis were observed (24). Additional 2 cases (0,1%) of diabetic ketoacidosis were reported in DELIVER study which investigated the effects of dapagliflozin in heart failure with preserved ejection fraction (25).

To prevent euglycemic ketoacidosis, temporary SGLT2 inhibitor discontinuation should be considered in acute illnesses, metabolic disturbances and infections.

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Sažetak

Euglikemijska ketoacidoza povezana sa empagliflozіom: prikaz slučaja

Ivona Vranić[1], Ivan Stanković[1,2], Miloš Panić[1], Predrag Miličević[1], Aleksandar N. Nešković[1,2]

[1]Kliničko-bolnički centar Zemun, Odeljenej kardiologije, Vukova 9, Belgrade, Serbia
[2]Medicinski fakultet, Univerzitet u Beogradu, Dr Subotića 8, Belgrade, Serbia

Prikazujemo slučaj euglikemijske ketoacidoze u bolesnice stare 69 godina, sa poznatim dijabetesom melitusom tip 2 na terapiji insulinom i empagliflozinom, koja je hospitalizovana zbog tromboembolije pluća visokog-intermedijarnog rizika. Ubrzo po prijemu, na primenjenu terapiju stanje pacijentkinje se stabilizuje, ali petog dana hospitalizacije dolazi do razvoja otežanog disanja Kussmaul-ovog tipa, mučnine i malaksalosti, bez drugih promena u fizikalnom, elektrokardiografskom i ehokardiografskom nalazu. U laboratorijskim analizama je registrovana metabolička acidoza sa povišenim anjonskim zjapom, izražena ketonurija bez značajne hiperglikemije. Postavljena je sumnja na euglikemijsku ketoacidozu, nakon čega je obustavljen empagliflozin i ordinirana terapija za dijabetesnu ketoacidozu. Nakon 36 sati dolazi do normalizacije acido-baznog statusa i stabilizacije stanja pacijentkinje, ali se odložen efekat empagliflozina u vidu glikozurije prati tokom narednih nedelju dana.

***Ključne reči**: empagliflozin, SGLT2 inhibitor, euglikemijska ketoacidoza*