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Case Presentation
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Acute Abdominal Pain in a Diabetic Patient Receiving SGLT2i: Is it an Endocrine or Surgical Emergency?

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Abstract

Sodium/Glucose Cotransporter-2 Inhibitors (SGLT2i) have been associated with increased risk for ketoacidosis, but it is considered a rare event and its real incidence is still unknown. We here report the case of a severe ketoacidosis (pH 6.9) caused by empagliflozin during an emergency laparoscopic cholecystectomy, to make aware of this drug's adverse effect and to suggest a perioperative management.

Clinical features: A 73-years-old man presented at our ER with abdominal pain, nausea, vomiting, and constipation. In his past: a silent myocardial infarction, hypertension, T2DM for 10 years. He was in therapy with empagliflozin 5 mg in association with metformin 1000 mg, insulin glargine 24 UI, bisoprolol 1.25 mg, cardio-aspirin, atorvastatin 40 mg. He introduced empagliflozin one month before the hospital admission.

He underwent video-laparoscopic surgery for acute cholecystitis without intraoperative complications. At the end of surgery, since an arterial blood gas analysis showed a marked metabolic acidosis (pH 6.9), the patient was maintained intubated and admitted to the ICU where he was extubated 12 h later, when the blood pH had returned towards normal levels. After diabetological consultation, he was discharged with subcutaneous insulin (Glargine and Lispro) and metformin without empagliflozin.

Conclusion: A blood gas analysis is rarely performed in patients with acute abdominal pain, but it is necessary in diabetic patients treated with SGLT2i because euDKA is a severe complication. This case illustrates that an adequate preoperative evaluation of diabetic patients in therapy with these drugs is necessary in order to correctly manage their intake before surgery and to diagnose early a condition of euDKA.

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Introduction

The Sodium/Glucose Cotransporter-2 Inhibitors (SGLT2i) are a recently introduced class of oral antidiabetics approved with the indication of type-2 diabetes (T2DM) treatment, alone or in association. Despite their well-established use, safety of this class of drugs is still a major concerning.

In May 2015 the European Medicine Agency, following a search in the EudraVigilance database which brought to the light a conspicuous number (101) of diabetic ketoacidosis SGLT2i associated reported cases, issued a safety warning for this class of agents and in June requested a benefit-risk assessment by the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC then concluded that SGLT2i associated DKA is a rare event but should be always considered in a patient presenting with non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness [1]. Also, a recent meta-analysis of randomized controlled trials concluded that no signal of increased risk for ketoacidosis was observed for SGLT2 inhibitors as a class or as individual molecule [2]. However, the risk of ketoacidosis appears higher when considering data not sourced from clinical trials but coming from real life in fact in a retrospective database analysis, Fralick et al. demonstrated that SGLT2i are associated with a doubled risk of hospitalization for diabetic ketoacidosis compared with DPP4i [3]. Several predisposing factors of SGLT2-associated diabetic ketoacidosis in T2DM can be identified. These include surgery, infection and omission or significant dose reduction of insulin.

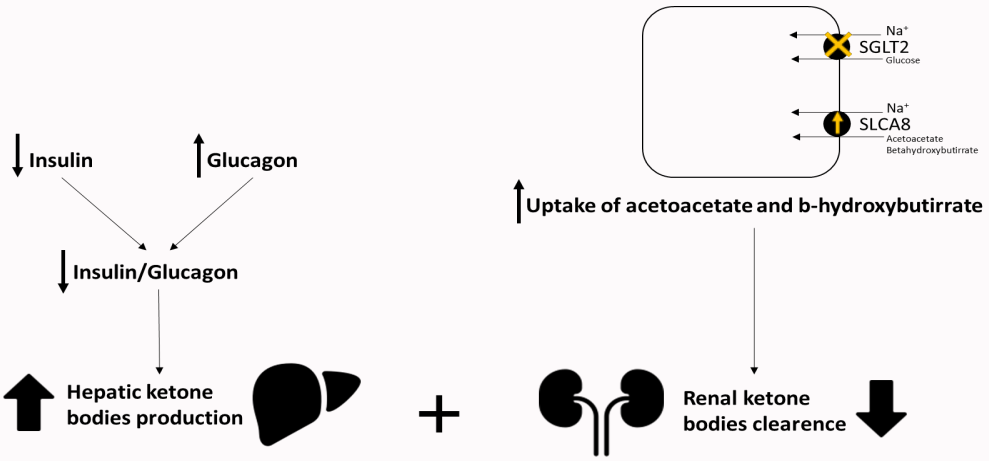

Figure 1: Mechanism of ketoacidosis induced by SGLT2i.

According to post-marketing data reported by EMA [1] of 66 reported cases with glucose levels, 42 were characterized by low glucose levels (≤ 250 mg/dL or ≤ 13.9 mmol/L) or described the case as euglycemic ketoacidosis, which is very difficult to diagnose in emergency departments and surgery because symptoms of ketoacidosis can simulate medical or surgical emergencies.

In this case report, we will present the case of a euglycemic diabetic ketoacidosis occurred in a patient in therapy with empagliflozin who underwent surgery.

Case Presentation

A 73-years-old man presented at our ER complaining of abdominal pain, nausea, vomiting, and constipation. His laboratory tests showed elevated white blood-cells 18.24×10^9/l, serum creatinine 1.27 mg/dl, total bilirubin 1.09 mg/dl, aspartate aminotransferase 70 U/l, C-reactive protein 34 mg/dl. He performed an abdominal X-ray and an abdominal CT which showed a thickened walls gallbladder without calculations and he was hospitalized with the diagnosis of acute cholecystitis. In his past medical history: silent myocardial infarction in 2017, hypertension, T2DM for 10 years. He was in therapy with empagliflozin 5 mg in association with metformin 1000 mg twice a day in the last month, insulin glargine 24 UI, bisoprolol 1.25 mg, cardio-aspirin, atorvastatin 40 mg. He introduced empagliflozin one month before the hospital admission.

He was reviewed by the anesthetist and then he underwent video laparoscopic surgery without any hemodynamic or cardiovascular intraoperative complications. At the end of surgery, after having uncovered his legs, mottled skin localized at both lower limbs was noticed, an arterial blood gas analysis was evidenced marked metabolic acidosis and the patient was sedated and admitted in intensive care unit.

The arterial blood gas analysis was consistent with marked metabolic acidosis: pH 6.9 (reference 7.35 to 7.45), pCO2 42.2 mmHg, pO2 242 mmHg, BE- 24.5 mmol/l, bicarbonate concentration 7.6 mmol/l, anion gap 27.9, glycemia 234 mg/dl, lactate 2.79 mmol/l, serum Na+ 132.9 mmol/l, serum K+ 5.1 mmol/l, serum Cl- 102 mmol/l, serum albumin 20 g/l. The elevated anion gap was suggestive for acid overload. The blood gas analysis was also analyzed according to the simplified Stewart approach proposed by Story et al. [4]. The non-lactic base excess was: 21.71 mEq/l. The impact of Strong Ion Difference (SID) was: -7.1 mEq/l. The impact of albumin deficit was: +5.5 mEq/l. The impact of unmeasured ions (UMAS) was -20.11 mEq/l. This approach confirms the overload of anions (e.g., acids).

Since the serious acidosis, the patient was maintained intubated and sedated. A volemic filling was performed with crystalloids, albumin, and bicarbonates. He was also assisted through artificial mechanical ventilation.

After being adequately hydrated and bicarbonate administration 7.5M 200 ml, with preserved diuresis and hemodynamic stability, a second ABG was performed with the evidence of pH 7.0, BE- 21.2 mmol/l, bicarbonate concentration 9.1 mmol/l, anion gap 27.1, glycemia 250 mg/dl, lactate 3.1 mmol/l. Having excluded intra-operative CO_2 reabsorption and because of the persistence of the severe metabolic acidosis, in the suspicion of embolic or compressive bowel ischemia, an abdominal CT scan with contrast was performed, which was within normal limits. The patient was admitted to the ICU, where he continued fluid replacement with crystalloids, sodium bicarbonate, and intravenous insulin, starting with a 3 UI bolus followed by a 3 UI/h infusion, invasive mechanical ventilation, active re-warming, calcium channel blocker for hypertension and antibiotic prophylaxis. After 12 h, blood pH returned towards normal levels. The patient was extubated and discharged from ICU on the first postoperative day. After diabetological consultation, he was subsequently discharged from the emergency department with subcutaneous insulin (glargine and lispro) and metformin without empagliflozin.

Recent clinical guidelines on glucose management in type 2 diabetes have strongly recommended the use of SGLT2-inibitors as a second line therapy after metformin failure [5,6] (*Standard Italian per la cura del diabete mellito 2018* available at http://aemmedi.it/standard-di-cura/). This is true at international level but also at a national level. SGLT2-inibitors use was associated with strong effects on cardiovascular and kidney disease protection [7-9]. Some molecules belonging to the SGLT2-inibitors class have been shown to reduce the risk of major cardiovascular events, hospitalizations for heart failure, incidence and progression of microalbuminuria. Surprisingly, empagliflozin, the drug the patient of our clinical case took, was reported to reduce death from any cause [10]. These are high costly drugs but with very important clinical benefits. In Italy data of the nationwide AMD Annals initiative, involving 427. 124

people with type 2 diabetes treated for by 222 diabetes Centers reported that SGLT2-inibitors were used in 2016 by 4.0% of the entire sample (Annali AMD 2018 available at http://aemmedi.it/wpcontent/uploads/2018/11/Annali_AMD-_2018_prot.pdf). The last revision of Italian clinical guidelines for type 2 diabetes management reduced the number of glucose lowering drugs to be used as a second line therapy after metformin failure (*Standard Italian per la cura del diabete mellito 2018* available at http://aemmedi.it/standard-di-cura/). Among these drugs there are SGLT2-inibitors. Therefore, also for this reason we have to expect a greater number of subjects could be treated with this class of drug. Recent evidences show advantages for people with type 1 diabetes who take SGLT2-inibitors in terms of significant antihyperglycemic effect, which is achieved with reduction or stabilization of insulin dose and with a very low trend for hypoglycemia [11]. Realistically, in the next future these drugs could be prescribed also to people with type 1 diabetes.

As previously discussed, euDKA is an important concerning associated with SGLT2i use. Probably the patient started to have euDKA several days before surgery (an acid smell from the patient's breath had been felt by the wife two weeks ago) and the euDKA was worsened by surgical stress. In the suspicion of DKA we performed a urinary ketone test that was positive. We could not perform a blood ketone test because it is unfortunately not available in our emergency department. However, our case is in line with other reported cases [12], where surgery seems to be a precipitant factor associated with the incidence of euDKA.

A combined action of enhanced hepatic production and a reduced renal clearance of ketone bodies could lies at the basis of SGLT2i induced diabetic ketoacidosis. As observed by Ferrannini, glycosuria induced by the inhibition of SGT2, produces a marked glycemic excursion and a reduction in insulin secretion with an increase in glucagon response and a consequent 25% reduction in the glucagon/insulin ratio [13]. On the other hand, the reduction in Na-glucose reabsorption increases luminal Na concentrations in proximal renal tubule where monocarboxylate transporter-1 (SLC5A8) which is responsible for Na mediated uptake of acetoacetate and beta-hydroxybutyrate is expressed [14]. The increase in luminal Na concentrations may increase SLCA8 mediated reabsorption of filtered ketone bodies (Figure 1). The metabolic stress of surgery, in addition to prolonged fasting, increases the risk of SGLT2-induced ketoacidosis. Euglycemic ketoacidosis is reported in the postoperative period from one day to one month after surgery [15].

The case was reported to the National Pharmacovigilance Network with code RNF 497529, and the Pharmacovigilance evaluated the causal link based on the Naranjo algorithm (the probability that a specific adverse event is linked to a drug) as: Probable.

For this reason, health care professionals need to have a high index of suspicion for symptoms and signs of ketoacidosis even beyond patient hospital discharge.

Furthermore, in order to balance the risk of perioperative hyperglycemia and postoperative euDKA, in case of elective surgery, it is recommended to discontinue SGLT2i 2 days before surgery [16] although it may be appropriate to stop the drug 3 to 5 days (or a week) before major surgery [15].

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