CASE REPORT

Euglycaemic ketoacidosis in a postoperative Whipple patient using canagliflozin

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SUMMARY

SGLT2 inhibitors are a new class of oral antihyperglycaemic agents that have garnered much attention for their attractive efficacy profile in glycaemic control along with the added benefit of weight loss. There has been increasing concern for the risk of euglycaemic (serum glucose 4–8 mmol/L) ketoacidosis with these agents. In the setting of a postoperative patient, the use of these drugs may exacerbate the normal physiological stresses of the body and increase the risk of developing euglycaemic ketoacidosis (euKDA). This case highlights a postoperative patient who was using an SGLT2 inhibitor and developed severe euKDA after a pancreaticoduodenectomy. The goal of this case report was to bring awareness to the possibility of this rare adverse event. In doing so, it may aid in preoperative planning of the diabetic patient and trigger appropriate management for those who develop euKDA.

BACKGROUND

SGLT2 inhibitors are a new class of oral antihyperglycaemic medication for type II diabetes, although they are sometimes used off-label in the setting of type I diabetes. The three SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) were first approved in Canada in 2014 as monotherapy for type II diabetes and their use has become increasingly popular. The product manufacturer notes that its limitation of use includes those with type I diabetes and those with an estimated glomerular filtration rate of <30 mL/min/1.73 m². Their popularity is partially due to their attractive efficacy profile in glycaemic control along with the added benefit of weight loss. However, in May 2015, the Food and Drug Association (FDA) issued an advisory stating that there had been 20 reported cases of ketoacidosis in patients treated with these drugs.^{1 2} A month later, the European Medicine Agency initiated a review and identified another 101 cases worldwide associated with their use in type II diabetes.³ Although diabetic ketoacidosis (DKA) is usually accompanied by hyperglycaemia (serum glucose >11.1 mmol/L), a few cases of euglycaemia (serum glucose 4–8 mmol/L) were observed.

SGLT2 inhibitors work by inhibiting SGLT receptors in the proximal collecting tubules of the kidney, thereby preventing reabsorption of glucose and facilitating its excretion in the urine. They work in a non-insulin-dependent manner and have a tendency to predispose patients towards a negative fluid balance and hyponatraemia.⁴ Nevertheless, the attractiveness of this drug has been its once a day formulation along with the

minimal risk of hypoglycaemia due to its glucose concentration-dependent mechanism of action.

Euglycaemic ketoacidosis (euKDA) is when a patient develops an anion gap metabolic acidosis characterised by increased ketone production and glucose concentration <11.1 mmol/L.⁵ It is hypothesised to be caused by factors such as partial treatment of DKA, food restriction and alcohol intake. As mentioned above, an association between euKDA and SGLT2 inhibitors has recently been reported, but the exact mechanism has not been fully elucidated. It is postulated that this rare, but potentially life-threatening, complication may occur due to the non-insulin-dependent mechanism of glucose clearance, hypergluconemia and volume depletion related to the use of SGLT2 inhibitors.⁶

CASE PRESENTATION

A previously well, 74-year-old man of Asian descent had been routinely seen in the hepatobiliary surgery clinic for surveillance of an asymptomatic cystic mass of the uncinate process of the pancreas. Over the course of 12 years, it grew in size from 4 mm to over 3 cm. In addition, pathology from a needle aspiration showed dysplastic or possible malignant cells. Given the concern of this being a mucinous cystic neoplasm with progression to cancer, a pancreaticoduodenectomy (Whipple) was recommended. His medical history included type II diabetes for 15 years, hypertension, benign prostatic hypertrophy and a previous diagnosis of tuberculosis more than 30 years ago. With respect to his diabetic regimen, he was previously on metformin and insulin glargine but was changed to canagliflozin 8 months prior to surgery due to a persistently elevated haemoglobin A1C (>7%). Additional history revealed that he had never had a previous episode of DKA, did not consume alcohol or use tobacco and has maintained a consistent low glycaemic diet without any specific dietary restrictions. Prior to surgery, this patient was reviewed in the preoperative clinic by the team consisting of an anaesthetist and pharmacist. The team felt that he was optimised for surgery and they had made recommendations to stop the canagliflozin the day before surgery, which was followed by the patient.

The patient underwent a pancreaticoduodenectomy without any intraoperative complications. He was transferred to the postanaesthesia care unit and subsequently to the surgical step-down unit. With respect to his glucose management, his canagliflozin was held and he was placed on an insulin sliding scale. His initial postoperative course was

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unremarkable and he remained euglycaemic requiring very minimal requirements of insulin via the sliding scale nomogram. On postoperative day 10, he was found to be mildly tachycardic with a heart rate up to 108 along with a critically low bicarbonate concentration of 9 mmol/L (reference 22–28 mmol/L), down from 14 mmol/L the day prior. The patient otherwise felt well, he denied any abdominal pain, nausea or vomiting, or fatigue. He was noted to have an increased urine output, with values >1600 mL/day.

INVESTIGATIONS

In regard to the remainder of his laboratory work, he was found to have an elevated serum creatinine of 123 µmol/L (reference 60–110 µmol/L), up from 71 µmol/L the day prior, and an elevated WCC of 15.3×10^9 /L (reference $5.5\text{--}10 \times 10^9$ /L). The performance of an arterial blood gas analysis gave results that were consistent with a metabolic acidosis: pH 7.24 (reference 7.35–7.45), pCO₂ of 23 mm Hg (reference 38–42 mm Hg) and a bicarbonate concentration of 9 mmol/L, with an anion gap of 23 mmol/L (reference 3–11 mmol/L). A full work up of the metabolic acidosis was completed, including a CT scan to ensure the absence of an anastomotic leak and intra-abdominal infectious/inflammatory source. The CT was within normal limits and additional laboratory values showed a lactate concentration of 0.9 mmol/L (reference <2 mmol/L), a negative ASA level, triglyceride concentration of 1.5 mmol/L (reference <1.7 mmol/L), serum ketone concentration of 8 mmol/L (reference <0.1 mmol/L) and his urinalysis showed a glucose concentration >55 mmol/L (reference 0–0.8 mmol/L), specific gravity >1.03 (reference 1.00–1.03) and a ketone concentration >15.6 mmol/L. It was noted that his capillary blood glucose concentrations over the past 48 hours ranged from 6.8 to 10.5 mmol/L.

TREATMENT

He was subsequently transferred to the surgical step-down unit for closer monitoring along with the initiation of a bicarbonate infusion. The endocrinology team was consulted and his treatment pathway for his anion gap metabolic acidosis mimicked that of DKA, despite being euglycaemic. Over the course of the next 48 hours, he continued on a bicarbonate and insulin infusion. His anion gap closed and his bicarbonate concentration improved to 18 mmol/L. He remained completely asymptomatic from an osmotic standpoint, including no change in level of concentration, no hyperpnoea, abdominal pain, or nausea and vomiting.

OUTCOME AND FOLLOW-UP

From this patient's history, the consensus as to the aetiology of the presumed euglycaemic DKA (euDKA) was secondary to his prior use of an SGLT2 inhibitor in the context of background acute kidney injury (AKI). It is also suspected that the increase in physiological stress secondary to his recent operation likely exacerbated the effect of the SGLT2 inhibitor. Furthermore, it is postulated that his AKI was secondary to hypoperfusion secondary to an osmotic diuresis. As such, canagliflozin's role in this patient's euDKA likely contributed to the AKI. He was eventually transitioned to a combination of metformin, linagliptine and lantus prior to discharge with excellent glycaemic control. Arrangements were made for him to follow-up with his endocrinologist in the community.

DISCUSSION

As demonstrated in the case, the recognition of euDKA is of importance in the surgical patient. In the immediate postoperative period, there is a decrease in insulin levels and an increase in glucagon and cortisol levels in response to the physiological stress of surgery. Given that SGLT2 inhibition induces a rapid increase in urinary glucose, unlike in DKA, glucose levels fall along with insulin levels. Glucagon levels begin to rise and gluconeogenesis occurs along with ketoacidosis in the same sequence of events as in DKA.^{1 6} Furthermore, given that renal clearance of glucose with SGLT2 is high, euDKA develops. One could imagine that this pathway would be even more pronounced in larger surgeries, such as a Whipple procedure, where there is greater stress on the body. Moreover, postoperative hypovolaemia and SIADH causing hyponatraemia are fairly common in the immediate days following surgery. Hypovolaemia further drives a catabolic response, which further increases insulin resistance, lipolysis and ketogenesis. One could therefore postulate that SGLT2 inhibitors would have an additive effect in the postoperative period.

The first case series describing euDKA associated with the use of SGLT2i was published in September 2015 in which 13 episodes of euDKA or ketosis were documented in 9 patients.⁶ Seven of these cases had type I diabetes and two had type II diabetes. The major inciting events were believed to be related to an active infection and alcohol intake. There were also two postoperative cases included in this series—an elective sigmoid resection and elective bilateral cervical foraminalotomy. The authors found that when these reported patients presented for acute medical care, their providers often failed to recognise that they were in DKA because of the lack of hyperglycaemia. Other small case reports and series describing episodes of euDKA in SGLT2i-treated patients have also begun to appear in the literature.^{7–9}

Type II diabetes has become a major global public health concern. Our case exemplifies the need for recognition of DKA in the postoperative diabetic patient who is on SGLT2 inhibitors for glycaemic control. It is conceivable that during the immediate postoperative phase, this new class of medications can exacerbate hypovolaemia and glucogenolysis without affecting glucose levels, thereby making the diagnosis of DKA challenging. Although this case highlights a correlation, future studies would be of great benefit in establishing a true association between SGLT2i and euDKA. We believe that this case highlights two important points in the surgical patient.

1. Perioperative planning: Perioperative glucose control is important and often times overlooked. When deciding on appropriate glucose management, individual patient factors, including the proposed surgery, expected postoperative course and preoperative glycaemic control, should be taken into account. The half-life of SGLT2 inhibitors is ~12 hours and perhaps these drugs should be stopped in the preoperative phase.¹⁰ A multidisciplinary approach, including the patient's surgeon, anaesthetist and endocrinologist, may be of great benefit.
2. Recognition of signs and symptoms of euglycaemic DKA: Key clinical features of DKA may include a change in level of consciousness, nausea/vomiting, polyuria and abdominal pain. Any patient with these features who also show biochemical signs of anion gap metabolic acidosis should go on to have urine ketones. The emphasis of this case report is the importance of early recognition, which can lead to a quick resolution of an otherwise potentially life-threatening condition.

Learning points

- ▶ SGLT2 inhibitors are a new and increasingly popular oral antihyperglycemic drug that can be associated with euglycaemic diabetic ketoacidosis (euDKA).
- ▶ In the setting of a postoperative patient, the use of these drugs may exacerbate the normal physiological stresses of the body and increase the risk of developing euDKA.
- ▶ A multidisciplinary approach should be used regarding optimal perioperative use of SGLT2 inhibitors.
- ▶ euDKA can be a 'predictable, detectable, and preventable safety concern'.¹

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