Case report

Dapagliflozin (SGLT2-i) induced euglycaemic diabetic ketoacidosis

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SUMMARY

Sodium glucose co-transporter-2 inhibitors (SGLT2-i) have become a popular therapeutic strategy in the management of hyperglycaemia in type 2 diabetes mellitus. The primary site of action of SGLT2-i is at the proximal renal convoluted tubule. They work by blocking SGLT2 receptors, sodium-dependent glucose co-transport molecules, which in turn prevents glucose reabsorption, facilitating glucosuria, improving glycaemic control as well as a moderate degree of weight loss. We report the case of a 51-year-old woman admitted to the acute medical unit with abdominal pain and vomiting, who was diagnosed with euglycaemic diabetic ketoacidosis secondary to recent initiation of an SGLT2-i medication (dapagliflozin). Clinicians should be aware of this rare side effect of SGLT2-i, to circumvent delays in patient management.

BACKGROUND

Diabetic ketoacidosis is an acute, potentially fatal, complication of diabetes mellitus. Ketoacidosis without the characteristic hyperglycaemia, euglycaemic diabetic ketoacidosis (euDKA), is equally serious but more challenging diagnostically owing to the absence of raised blood sugars. This often leads to delays in diagnosis and management. euDKA has rarely been reported in association with sodium glucose co-transporter-2 inhibitors (SGLT2-i), with the more common side effects of this class of drugs being: urinary tract infections (UTIs), genital infections, hypovolaemia and dehydration.

However, given the morbidity and mortality associated with diabetic ketoacidosis, the diagnosis of euDKA should be considered in all patients taking SGLT2-i medication.

Here we report the case of a 51-year-old woman who was admitted to the acute medical unit with abdominal pain and vomiting, who had been diagnosed with euDKA secondary to the initiation of dapagliflozin 3 days prior to presentation. Clinicians should be aware of this rare complication of SGLT2-i to allow for early recognition and treatment of euDKA.

CASE PRESENTATION

A 51-year-old Caucasian woman was admitted to the acute medical unit at our hospital in December 2018 with vomiting and abdominal discomfort. Initial consultation revealed a history of non-bilious vomiting for 3 days with no associated haematemesis. The patient also had mild lower abdominal pain,

well-formed brown stools with the absence of mucous and blood, no dysuria, but generalised malaise which she attributed to her fibromyalgia.

She had a background of fibromyalgia, type 2 diabetes mellitus (T2DM), irritable bowel syndrome, psoriasis, hypercholesterolaemia, osteoarthritis of the knees, non-alcoholic fatty liver disease, gastro-oesophageal reflux disease, stress urinary incontinence, depression and anxiety. She reported no drug allergies and to being prescribed the following medications: dapagliflozin 10 mg daily, metformin 1 g two times per day, liraglutide 1.2 mg daily, ezetimibe 10 mg daily, fultium d3 daily, solifenacin 10 mg daily, pravastatin 40 mg daily, pregabalin 150 mg two times per day, sertraline 100 mg daily, lansoprazole 30 mg daily and propranolol 40 mg daily.

She was a non-smoker, non-drinker and reported 'no' to taking illicit substances.

INVESTIGATIONS

On physical examination at admission she was alert, orientated and haemodynamically stable. Her oxygen saturation was 98% on room air, respiratory rate 17 coupled with vesicular breath sounds throughout all lung fields. Her blood pressure was 120/65 mm Hg with a regular pulse of 101 beats per minute, heart sounds were normal and jugular venous pressure was not raised. Glasgow Coma Scale was 15/15, temperature 36.1°C and capillary blood glucose 8.1 mmol/L. Her abdomen was soft with mild suprapubic tenderness, no guarding or rebound tenderness. No organomegaly was present and bowel sounds were normal. No rashes or lymphadenopathy were noted. Calves were soft non-tender. Her weight was 83 kg with a body mass index of 34.6.

In light of her presentation the following initial investigations were requested at accident and emergency: full blood count, bone profile, HbA1c, magnesium, liver function tests, urea and electrolytes, C reactive protein, thyroid function tests, plasma osmolality, glucose, lactate, venous blood gas (VBG), chest radiograph, ECG, urine dip.

RESULTS

- ▶ Full blood count—haemoglobin 137 g/L (normal), white cell count $8.6 \times 10^9/L$ (normal), platelets $294 \times 10^9/L$ (normal), mean corpuscular volume 81.3 fL (normal).
- ▶ Bone profile—albumin 47 g/L (normal), adjusted calcium 2.18 mmol/L (normal), alkaline phosphatase 94 u/L (normal).
- ▶ HbA1c—71 mmol/mol.

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- ▶ Magnesium—0.87 mmol/L (normal).
- ▶ Liver function tests—normal.
- ▶ Urea and electrolytes—sodium 136 mmol/L (normal), potassium 4.8 mmol/L (normal), urea 3.3 mmol/L (normal), creatinine 65 µmol/L (normal), estimated glomerular filtration rate (eGFR) 83 mL/min/1.73 m².
- ▶ C reactive protein—9 mg/L (normal).
- ▶ Thyroid-stimulating hormone—1.43 µU/L (normal).
- ▶ Plasma osmolality—289 mosm/kg (normal).
- ▶ Glucose—9.3 mmol/L (high).
- ▶ Lactate—1.83 mmol/L (normal).
- ▶ VBG (pH 7.249, partial pressure of carbon dioxide (pCO₂) 3.60, partial pressure of oxygen (pO₂) 9.21, bicarbonate concentration (CHCO₃⁻) 13.7)—metabolic acidosis with partial respiratory compensation.
- ▶ Chest radiograph—lung fields unremarkable, heart and mediastinal contours normal, no free air beneath diaphragm.
- ▶ ECG—sinus tachycardia, nil acute.
- ▶ Urine dip—protein (–), blood (–), glucose (++++), ketones (++)+, leucocytes (–), nitrites (+).

The patient was provisionally diagnosed with UTI and gastroenteritis with ketoacidosis by the attending medical registrar, admitted for observation overnight and treated with intravenous fluids, antiemetics, and antibiotics for UTI with a plan for repeat VBG in the morning.

Her repeat VBG (pH 7.271, pCO₂ 4.47, pO₂ 5.52, CHCO₃⁻ 16.6) showed improving metabolic acidosis, again with partial respiratory compensation. Blood glucose was now 5.1 mmol/L. The patient reported that her vomiting had settled to a degree, but that she had had one episode overnight. In light of her metabolic acidosis, the anion gap was calculated to be 19.8 mmol/L (high). With this in mind, and there currently being no clear precipitant for her high anion gap acidosis, further questioning revealed that the patient had only started dapagliflozin 3 days ago which coincided with her symptoms. In light of this, dapagliflozin was suspended as was metformin, paracetamol (5 mg/L normal) and salicylate levels (3 mg/L normal) were ordered, further intravenous fluids prescribed, and a diabetes review organised.

She was treated with intravenous fluids similar to DKA with monitoring of capillary blood glucose readings and urinary ketones. Insulin was not required in this case. Her metabolic acidosis improved, and she was discharged 36 hours after admission with a blood glucose of 5.9 mmol/L and bicarbonate of 23 (normal). See table 1 for inpatient blood gas results.

Interestingly, it transpired during the diabetes review that she had previously been on dapagliflozin for 3 months in 2016 as part of a clinical trial (ENERGIZE Study) which was stopped and re-started in the outpatient clinic 3 days prior to her current admission. With the exception of this addition to treatment her diabetic management had been the same since December 2016 (metformin 1 g two times per day, liraglutide 1.2 mg daily).

Table 1 Blood gas comparison table

	pH (7.36–7.42)	pCO ₂ (4.70–6.00)	pO ₂ (11.30–14.00)	CHCO ₃ ⁻ (22–26)	Lactate (0.50–2.22)
Initial VBG	7.249	3.60	9.21	13.7	1.83
Second VBG	7.271	4.47	5.52	16.6	1.63
Third VBG	7.289	4.87	7.51	17.5	0.79
Final ABG	7.366	4.20	11.30	19.0	1.13

ABG, arterial blood gas; VBG, venous blood gas.

DIFFERENTIAL DIAGNOSIS

- ▶ Dapagliflozin-related euDKA.
- ▶ New-onset type 1 diabetes mellitus.
- ▶ Alternative causes of high anion gap metabolic acidosis.

TREATMENT

The patient was managed with intravenous fluids and monitoring of glucose and ketones. Intravenous insulin was not used as metabolic acidosis improved with hydration alone. It was decided to discontinue dapagliflozin permanently. Liraglutide was to be continued to control blood sugars in the community, with review of diabetic medications and HbA1c planned at the diabetic clinic review in 2 weeks' time.

OUTCOME AND FOLLOW-UP

The patient was followed up in the diabetes clinic at 2 weeks following a diagnosis of euDKA. The reasons for her initial presentation with metabolic acidosis were unclear. The patient had a 3-day history of vomiting prior to admission which coincided with starting dapagliflozin. This medication can rarely cause euDKA but it is very rare with such few doses.

It was noted that the patient's blood sugar levels had started to rise in the community, so the general practitioner re-started metformin. Renal function was stable and HbA1c was 71 mmol/mol (0–41). In view of this, and her recent presentation, it was advised best to avoid SGLT2-i (dapagliflozin and family), but should she continue with suboptimal glycaemic control then consideration should be given to the introduction of pioglitazone or a sulfonylurea. If significant deterioration in glucose control was noted, then basal insulin would be considered. She was planned for further follow-up with diabetes and endocrinology in 6 months' time.

DISCUSSION

SGLT2-i have become popular second-line and third-line agents in the management of T2DM since being adopted by The National Institute for Health and Care Excellence (NICE) in November 2012.¹ Their success can be attributed to the emerging clinical benefits of SGLT2-i compared with alternative agents; including lower risks of hypoglycaemia, improvements in cardiovascular mortality and reductions in both weight and hypertension.^{2–4} Pending further safety data from randomised control trials SGLT2-i are not currently approved for use in patients with type 1 diabetes mellitus, as short-term clinical trials had observed euDKA.⁵

The primary site of action of the SGLT2-i drugs is at the proximal renal convoluted tubule. They work by blocking SGLT2 receptors, sodium-dependent glucose co-transport molecules, which in turn prevents glucose reabsorption, facilitating glucosuria and improving glycaemic control.^{6,7} This mechanism functions independently from that of insulin, allowing for the

Box 1 Diagnostic features of euglycaemic diabetic ketoacidosis

Plasma pH <7.3

▶ Metabolic acidosis—base excess <–5 mmol/L

▶ Plasma bicarbonate <15 mmol/L

Raised anion gap: anion gap >12 mmol/L

Normal or mildly increased plasma glucose: glucose <14 mmol/L

Increased plasma ketones

Urinary ketones—normal or increased

Box 2 Predisposing factors for diabetic ketoacidosis in patients on sodium glucose co-transporter-2 inhibitors

- ▶ Reduction in insulin doses.
- ▶ Withdrawal of insulin in type 2 diabetes mellitus.
- ▶ Postoperative stress.
- ▶ Intercurrent illness.
- ▶ Alcohol consumption.
- ▶ Low carbohydrate diet.

avoidance of hypoglycaemia and scope for combination with additional antihyperglycaemic medications.⁶⁷

Case reports of euDKA as a side effect of the SGLT2-i drugs are beginning to surface in the literature, yet cases occurring specifically with dapagliflozin are few.^{8–10} A recent meta-analysis published by Burke *et al*, identified 34 cases of DKA associated with SGLT2-i use.¹¹ Twenty-four (70%) of these cases were in patients with T2DM.¹¹ The average blood glucose on presentation was 14.7 ± 7.8 mmol/L (265.6 ± 140.7 mg/dL) with presenting symptoms similar to the case we describe—nausea, vomiting and abdominal pain.¹¹ Analysis of most cases highlighted a precipitating factor for SGLT2-i euDKA such as infection, recent surgery or medication non-compliance.^{8–11}

The diagnostic features of euDKA are equivalent to those of DKA—without the apparent hyperglycaemia (box 1). With blood glucose being the most readily triaged clinical parameter in patients with diabetes, significant risk of delay in diagnosis or inappropriate treatment exists within this patient cohort.

The precise mechanism underpinning euDKA is uncertain. Leading hypotheses propose that SGLT2-i cause a reduction in insulin secretion from pancreatic β -cells as a response to increased glycosuria and reduced circulating blood glucose levels.^{9 12 13} Reductions in available insulin has a resulting impact: (1) Depletion of insulin stimulates an increase in lipolysis within the adipose tissues and the production of free fatty acids. (2) Less insulin results in the uninhibited transport of fatty acids into the hepatic mitochondria—forming ketone bodies through β -oxidation.^{9 12} This occurs due to the influence insulin usually has on the inhibition of carnitine palmitoyltransferase-I (CPT-I), a mitochondrial enzyme responsible for increasing the rate of β -oxidation.¹² Glucagon is also likely to play a role with an association

demonstrated between SGLT2-i use and increased glucagon secretion.¹² Glucagon is known to increase CPT-I activity and therefore will further increase the production of ketone bodies, causing subsequent metabolic acidosis.^{12 14}

More recent proposals for the pathophysiology of SGLT2-i-associated euDKA suggests certain susceptible individuals must have a more nuanced phenotype when compared with others.¹³ Finucane outlines that this may be a variant of SGLT2 which has a greater affinity for the *gliflozins*, resulting in disrupted glucose transporter 2 (GLUT2) mediated glucose sensing and causing a transient reduction in β cell insulin secretion.¹⁴ Predisposing factors for euDKA in those taking SGLT2-I can be seen in box 2.

Developments in novel theories may become particularly relevant to the case we describe in future as there was no obvious precipitating factor contributing to the euDKA. This would therefore support a hypothesis which describes a genetic sensitivity in particular patients exposed to SGLT2-i. Moreover, the FDA published data reporting 73 cases of ketoacidosis associated with initiation or increase in the dose of an SGLT2-i, with time of onset ranging from 1 day to 1 year (median 43 days).¹⁵ This breadth of time would further endorse a more variable, hitherto unrecognised action of the SGLT family which is individual specific.

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Learning points

- ▶ Euglycaemic diabetic ketoacidosis (euDKA) is a rare, but serious complication of sodium glucose co- transporter-2 inhibitors (SGLT2-i) use and physicians should be made more widely aware of the condition in order to avoid delays in diagnosis and treatment.
- ▶ While most cases of euDKA associated with SGLT2-i have an additional precipitating factor, introduction of, or increase in SGLT2-i use alone can be the sole precipitant.
- ▶ euDKA can occur within days of starting an SGLT2-i. Therefore, patients should be counselled on the signs and symptoms of euDKA when introducing the treatment.
- ▶ SGLT2-i should be stopped at times of dehydration and also in the perioperative period due to their propensity to worsen the hypovolaemic state.¹⁶
- ▶ Patients who develop ketoacidosis on SGLT2-i should not be re-challenged immediately due to increased risk of recurrence of ketoacidosis.¹⁶

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