Case Report

Euglycaemic DKA secondary to Canaglifozin, an easily missed diagnosis

RK Bhatnagar, I Kurera, R Perry & J Tringham

Abstract

Diabetic ketoacidosis (DKA) is a state of hyperglycaemia, ketosis and metabolic acidosis. This carries a significant morbidity and mortality particularly if left untreated or if the diagnosis is delayed.

We present a case of euglycaemic DKA in a 48 year old female with non-insulin treated T2DM who had good glycaemic control. Initial investigations revealed moderate metabolic acidosis, persistent ketonuria and blood glucose levels < 11mmol/l. There was a significant delay in diagnosing DKA following admission with multiple consultant reviews. Detailed history revealed the recent addition of Canagliflozin (SGLT2 inhibitor). This can rarely be a precipitant of euglycaemic DKA. With appropriate DKA treatment, rapid correction of acidaemia and ketosis occurred allowing her to be discharged home within 24 hours.

Keywords

DKA (diabetic ketoacidosis), Type 2 Diabetes Mellitus, SGLT-2 (sodium glucose co transporter 2) inhibitors.

Key Learning points

- Euglycaemic DKA is a recognised association of SGLT 2 inhibitors; it is an uncommon presentation on acute medical units which if unrecognised and untreated can increase morbidity and length of stay.
- With increasing use of SGLT 2 inhibitors in diabetes management, it is important for physicians to be aware of this condition to avoid delays in diagnosis and appropriate treatment.
- Careful review of the patients' drug history is required with consideration if medication may be the cause of the patients' presentation.

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Case report

A 48 year old female was admitted via the Emergency Department with a 4 day history of abdominal pain and cramps, and 2 days of vomiting. She was opening her bowels normally. She had type 2 diabetes and was treated with Metformin 2 mg, Gliclazide 120 mg, Sitagliptin 100 mg and Canaglifozin 300 mg per day. Initially on original diagnosis of her diabetes she was commenced on insulin. This was stopped after specialist review when the diagnosis was thought to be type 2 diabetes. Subsequently her diabetes remained very well controlled on oral agents with a HbA1c within target range of 48 -58 mmol/mol (6.5-7.5%) Canagliflozin had been added less than a month before this particular hospital admission, mainly for weight reduction. She had no other significant past medical history or family history. She worked as a retail assistant and was a non-smoker.

On examination she was clinically mildly dehydrated with a temperature of 37.6 ^{0}C, blood pressure 149/90 mmHg, heart rate 100 bpm, respiratory rate 19 bpm and oxygen saturations of 100% on air. The capillary blood glucose was 5.2 mmol/l. Systemic examination was unremarkable other than mild epigastric tenderness. Her body mass index was within normal range.

On Initial investigation the serum Sodium was 132 mmol/l, Potassium 4.9 mmol/l, Creatinine 58 µmol/l, Urea 4.4 mmol/l and eGFR >60 ml/min, which remained stable until discharge. The liver function tests and amylase were normal. Full blood count revealed raised white cell count of 15.2 x10^{3} and Hb 172 gm/L. The HbA1c was 56mmol/mol (7.3%). Chest and abdominal radiographs and an ECG were normal.

Bedside urine analysis revealed glucose 2+ and ketones 4+, but was negative for nitrites and leucocytes. The venous blood gas (VBG) analysis is shown in Table 1. The blood ketones were not measured as this service was not available. She was treated initially with intravenous fluids and an oral proton pump inhibitor, with a working diagnosis of gastritis. A CT scan of her abdomen and pelvis was unremarkable. Paracetamol and Salicylate levels were both normal. The diagnosis of DKA was considered, but initially dismissed by the medical team, based on the normal blood glucose. By the third day (51 hours after admission) she had had a urine dip checked 13 times and venous gas 6 times (see Table 1). There was a high anion gap metabolic acidosis, persistent 4+ ketones in urine and normal blood glucose levels. On-going monitoring and

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Table 1. Repeated VBGs prior to DKA diagnosis.

Venous blood gas	Day 1 , 11:33	Day 1, 20:56	Day 2, 03:08	Day 2, 09:05	Day 2, 16:41	Day 3, 11:30
pH	7.23	7.26	7.24	7.35	7.34	7.34
pCO2 kPa	4.17	3.22	2.67	3.03	3.59	3.11
Base excess mmol/L	-13.1	-15.1	-17.6	-12	-10.2	-12
HCO3 mmol/L	12.9	10.6	8.4	12.5	14.3	12.5
Anion gap mmol/L	13.6	15.4	13.9	13.3	12.6	13.9
Glucose mmol/L	9.7	7.5	5.2	8.3	6	6.6
Lactate mmol/L	2.4	1.4	0.8	1.0	0.7	0.7

efforts to establish a diagnosis were evident from the medical notes.

The pH had improved with intravenous hydration but she remained unwell with nausea and retching. On a subsequent ward round, 3 days after her admission, the patient was correctly diagnosed with euglycaemic DKA secondary to the SGLT2 inhibitor Canaglifozin. DKA treatment was started with fixed rate intravenous insulin in line with hospital guidelines. She was commenced on a lower dose of fixed rate insulin infusion than protocol (3 units per hour) so as to avoid hypoglycaemia given her baseline normoglycaemic status. She responded well to this treatment and the DKA and abdominal symptoms fully resolved within 24 hours. (Table 2) No infection or any other obvious precipitant cause for DKA was found. Canaglifozin was stopped and she was discharged home on a combination of insulin and metformin.

Discussion

Euglycaemic DKA has been associated with the use of SGLT-2 inhibitors both in clinical trials and real life scenarios. The increasingly frequent use of these drugs makes it important for acute physicians, who diagnose and treat most cases of DKA, to be aware of.

SGLT-2 inhibitors are a relatively new class of oral hypoglycemic agents. The first agent Dapagliflozin was approved to be used in Europe in 2012. These agents reduce HbA1c by 5.5–11 mmol/mol (0.5%–1.0%) without significant risk of hypoglycemia. Additional potential advantages include weight loss, small reductions in blood pressure (2–4 mmHg systolic/1–2 mmHg diastolic)[1] and some renal benefits.[2] Revised NICE guidelines in July 2016 recommended the use of SGLT2 inhibitors in patients with T2DM either as monotherapy or combination therapy including with insulin.[3] A large multinational multicenter study carried out on Empagliflozin (the EMPA-REG Outcome study) showed a significant reduction in cardiovascular mortality. There was a reduction in hospitalization for heart failure of 35%, reduced cardiovascular death by 38% and reduced all-cause mortality of 32%.[4] There has been a significant increase in prescribing these agents following this study and the NICE guidance.

The history of how SGLT2 inhibitors came into the diabetes world dates back to 1835 when French chemists isolated phlorizin from the bark of apple trees.[5] This was bitter in flavor and was referred to as the "glycoside from the bark of apple trees." It was used to treat fevers, infectious disease and malaria. Later it was discovered that high doses of phlorizin caused glycosuria. During the late 1980's it was realized this could have potential benefits in the management of diabetes.[5] The SGLT2 receptors are blocked by SGLT 2 inhibitors leading to the prevention of reabsorption of glucose in the proximal renal tubule. This leads to glycosuria with subsequent weight loss and improvement in glycaemic control.

Table 2. VBGs and urine ketones during course of treatment

Time	Before insulin commenced	4h after insulin commenced	8h after insulin commenced	12h after insulin commenced	26h after insulin commenced
pH	7.34	7.38	7.38	7.42	7.42
HCo3	12.5	17.7	22.6	22.1	23.3
Base excess	-12	-6.4	-1.7	-1.6	-1.4
Lactate	0.7	1.1	1.2	0.7	1.2
Glucose	6.6	8.6	13.1	5.7	10.8
Urine ketones	4+	4+	2+	trace	Negative

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Table 3. Factors that may precipitate DKA whilst taking SGLT2 inhibitors.

A low beta cell function reserve (e.g. patients with type 2 diabetes who have low C-peptide levels or those with latent autoimmune diabetes in adults)
Restricted food intake (e.g. low calorie diet, prolonged fasting)
Severe dehydration
A sudden reduction in insulin being taken or increase in insulin requirements.
Extreme exercise (e.g. marathon running)
Alcohol abuse
Serious illness: Myocardial infarction, stroke, severe infection, serious injury, pancreatitis or surgery.

DKA is a diabetic emergency that has a high morbidity. Overall DKA frequency in the background of the whole diabetic population has been reported to be between 0.32 and 7.1 per 1000 patient-years.[6] 23-32% of these DKA cases are thought to occur in patients with type 2 diabetes.[6] A much higher incidence has been reported in patients with type 1 diabetes.[6]

The majority of cases of SGLT-2 inhibitor associated DKA have occurred in people with type 1 diabetes. Some cases have occurred in patients with a prolonged history of type 2 diabetes due to likely reduced beta cell reserves. In the canagliflozin clinical trials, 6 of the 12 patients that developed ketoacidosis had low C-peptide levels (<0.51 ng/mL) and were positive for GAD65 autoantibodies suggesting underlying type 1 diabetes.[7-9] In a review of reported cases, we found the MHRA had received 118 Yellow Card reports of DKA associated with the use of this class up to February 2016.[10] A substantial proportion of the cases concerned off-label use in patients with type 1 diabetes. There have been warnings from both the ADA and the EMA regarding the risk of euglycaemic DKA with SGLT-2 inhibitors.[11-12] A search by the EMA in the Eudravigilance database in 2015 highlighted 102 cases (in patients on canagliflozin, dapagliflozin and empagliflozin) where the association appeared causal.[11] In many of these cases, as in our case, the presentation was atypical with normal or only moderately raised glucose levels and there are also many cases involving diagnostic delay. A case published in 2016 by Clement and Senior presented a similar case to ours with that of a 42 year old woman with type 2 diabetes, recently started on canagliflozin presenting with euglycaemic DKA.[13] The presentation was atypical and the patient was found to have a very low c-peptide level indicating low endogenous insulin levels.

The mechanism by which SGLT2 inhibitors might lead to DKA has not been clearly established.

Table 4. Diagnosis of DKA in patients taking SGLT-2 inhibitors.[15]

Arterial pH	Less than 7.3
Blood ketones	Above 3mmol/L
Anion gap	Above 10
Bicarbonate	Less than 15 mmol/L
Clinical	Deteriorating level of consciousness in severe cases.

However, many reported cases simply represent a shift of metabolism from a glucose-dependent one to a fat-dependent resulting in ketosis. SGLT-2 inhibitors can produce this shift in people with or without diabetes.[14]

Risk factors for development of DKA whilst taking SGLT2 inhibitors are listed in Table 3. These are well described in the Association of British Clinical Diabetologists (ABCD) position statement published in November 2016.[15]

These factors may result in a shift of metabolism from carbohydrate to fat. It is important to discuss these risk factors with patients at the point of initiation of SGLT-2 inhibitors and educate them to identify symptoms of DKA. However, care should be taken not to put patients off taking these medications due to the many previously mentioned beneficial cardiovascular, glycaemic and blood pressure lowering effects and the relative rarity of this complication. Once DKA is confirmed, SGLT-2 inhibitors should be stopped and ketoacidosis treated following local trust or national guidelines. The focus of treatment is to correct pH, bicarbonate and the anion gap. A variable rate intravenous insulin infusion (VRIII) with dextrose and potassium rather than a fixed rate insulin infusion is recommended to avoid hypoglycaemia and hypokalaemia.

The diagnosis of DKA should be considered when patients with diabetes on SGLT-2 inhibitors present with acidosis and ketonuria even if glucose levels are normal. The appropriate investigations are listed by the ABCD panel in their position statement on patients taking SGLT2 inhibitors.[15] (Table 4)

In our patient's case at her original diagnosis of diabetes it was unclear whether she had type 1 or type 2 diabetes. She was started on insulin which was stopped shortly after, following a specialist review. She had a borderline low c-peptide level (reflecting low beta cell reserve) and she was also on a calorie controlled diet.

Abdominal symptoms are a common manifestation of DKA, which may lead to inappropriate radiological and endoscopic investigations. In our case, the abdominal CT could be justified in view of her severe acidosis and diagnostic uncertainty, although it proved to be normal.

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Diagnosis was delayed, in part, due to lack of awareness of the phenomenon of euglycaemic DKA amongst the admitting clinicians; following initiation of intravenous insulin treatment and discontinuation of the precipitating medication her condition rapidly improved with complete resolution of her abdominal symptoms.

Declaration of competing interests

Nothing to declare

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