Sodium–glucose co-transporter 2 inhibitors

Think twice about diabetic ketoacidosis

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CASE

A Caucasian woman aged 54 years presented, acutely unwell, to a regional hospital emergency department. She had a progressive three-week history of increasing nausea, abdominal pain, lethargy and shortness of breath. On presentation she was noted to have mottled skin and Kussmaul breathing. Her vital signs on presentation are shown in Table 1. She had a past medical history of latent autoimmune diabetes in adults (LADA) diagnosed at age 42 years on the basis of a positive test for glutamic acid decarboxylase (GAD) antibodies (GAD titre 63 U/mL) and C-peptide <0.05 nmol/L. Three weeks prior to presentation the patient had been switched from her basal-bolus insulin regimen to oral hypoglycaemic therapy consisting of dapagliflozin and metformin, with a reduced nocte long-acting insulin dose. In the days prior to presentation, the patient had limited oral intake and reported her blood glucose levels (BGLs) had been stable at 7–10 mmoL.

The results of her arterial blood gas and urinalysis on presentation to the emergency department are shown in Tables 2 and 3. Notably, she was acidotic, with a blood pH of 6.98, and had blood ketones of 6.3 mmol/L and a mildly elevated BGL of 14.4 mmol/L. She had no signs of acute coronary syndrome or infective illness. The patient had a body mass index of 21.6 kg/m^2, exercised regularly and had not consumed alcohol in the days prior to presentation. She had a family history of type 1 diabetes mellitus (T1DM). Before switching from insulin to oral therapy, the patient had had no prior episodes of diabetic ketoacidosis (DKA), but had requested the switch to oral therapy because of frequent nocturnal hypoglycaemic episodes.

Question 1

What is the diagnosis?

Answer 1

The diagnosis is euglycaemic DKA (euDKA). This is a reported complication of sodium-glucose co-transporter 2 (SGLT2) inhibitors in the treatment of type 2 diabetes mellitus (T2DM), but there are limited cases reported in the setting of T1DM and no cases previously reported with dapagliflozin use in T1DM. LADA is a subtype of T1DM, characterised by progressive autoimmune β-cell failure causing insulin deficiency and subsequent insulin dependence. It is most often diagnosed in adulthood, although cases are reported in childhood.[1] Cases of euDKA are characterised by presentations of DKA with blood glucose levels that are normal or only slightly increased, compared with typical cases of DKA.[2]

Understanding of the pathophysiology of euDKA with SGLT2 inhibitors is evolving. SGLT2 inhibitors lower plasma glucose levels by inducing glycosuria. In this setting, plasma glucagon concentrations increase significantly, leading to a low level of insulin relative to the level of glucagon, thus stimulating lipolysis and in turn, ketogenesis. With profound insulin deficiency in T1DM, this process is augmented.[3] In this case the dramatic reduction in insulin therapy could have precipitated DKA alone, but whether the dapagliflozin augmented the DKA process or simply prevented the hyperglycaemia is unclear.

CASE CONTINUED

The patient was admitted to the intensive care unit and commenced on the DKA protocol. She responded well to rehydration, insulin, dextrose and electrolyte replacement. Her ketonaemia resolved in the days following admission. Once stable, she was recommenced on her previous basal-bolus insulin regimen and the dapagliflozin and metformin were ceased.

Question 2

Should an SGLT2 inhibitor have been prescribed for this patient ?

Question 3

How can this complication be avoided in the community?

Answer 2

SGLT2 inhibitors are only approved for use in T2DM. SGLT2 inhibitors are not approved for use in patients with T1DM as the safety and efficacy of these medications in this patient group has not been established. Despite this, there is increasing off-label use of SGLT2 inhibitors in T1DM because of the favourable weight loss and improved glycaemic control when used as adjunct therapy to insulin.[4] In this case, the SGLT2 inhibitor was used in combination with metformin as a replacement for insulin, rather than as an adjunct therapy as is proposed in the literature. This

switch to oral hypoglycaemic medication was inappropriate as the patient was insulin dependent.

Answer 3

Greater clinician and patient awareness is needed regarding the risk of euDKA with the use of SGLT2 inhibitors. Patients should be educated about the signs and symptoms of DKA and, when concerned, counselled to test for blood ketones, if possible on their glucose meter, or seek medical attention. In addition, dramatic reductions in insulin therapy should be avoided and special counselling given around times of fasting, such as in preparation for surgery or concomitant illness, in which case the SGLT2 Inhibitor should be reviewed and cessation considered until full oral intake resumes.[5,6] SGLT2 inhibitors alter the classic presentation of DKA, so diagnosis is frequently delayed because of the misleading presence of normoglycaemia. In this case, there was a three-week history of gradual deterioration. It is likely that the patient was in DKA for a protracted amount of time, becoming increasingly acidotic until euDKA was diagnosed.[7] The diagnosis of euDKA could have been made earlier had blood ketones been checked.

Key points

- SGLT2 inhibitors are only approved for use in T2DM.
- Patients treated with SGLT2 inhibitors should be monitored for blood ketones when clinically unwell, as DKA may not present classically with hyperglycaemia.
- Patients treated with SGLT2 inhibitors must be educated regarding the risk of euDKA and be given an action plan to identify and manage this condition.
- Once diagnosed, euDKA responds readily to treatment with DKA protocols.
- LADA is a subtype of T1DM that quickly progresses to insulin dependence. Given its late onset, it can be confused for T2DM by patients and clinicians alike, resulting in inappropriate therapy.

Table 1. Vital signs on presentation

Vital sign	Result
Respiratory rate	26 breaths per minute
Oxygen saturation	100% on room air
Blood pressure	140/80 mmHg
Peripheral pulse rate	120 beats per minute
Peripheral pulse regularity	Regular
Temperature, axilla	37.0°C

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Table 2. Arterial blood gas on presentation

Result summary	Result
Inspired oxygen	21%
Blood pH	6.98
Blood pO_2	169 mmHg
Blood pCO_2	8 mmHg
Blood O_2 saturation	99%
Blood HCO_3	2 mmol/L
Blood oxyhaemoglobin	96.5%
Blood potassium	4.3 mmol/L
Blood chloride	111 mmol/L
Blood creatinine	56 µmol/L
Blood glucose level	14.4 mmol/L
Blood lactate	1.7 mmol/L
Blood calcium ionised	1.33 mmol/L
Blood carboxyhaemoglobin	0.8%
Blood deoxyhaemoglobin	1.5%
Blood ketones	6.3 mmol/L

Table 3. Urinalysis on presentation

Result summary	Abnormalities detected
Specific gravity	1.020
pH	5.0
Leukocytes	0 (Neg)
Blood	5–10 erythrocytes/µL
Nitrite	Negative
Ketones	80 mg/dL
Bilirubin	Negative
Urobilinogen	Normal
Protein	30 mg/dL (+)
Glucose	1000 mg/dL (++++)
Urine colour	Straw

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