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Diabetic ketoacidosis with sodium–glucose cotransporter type 2 inhibitors: a case series

TO THE EDITOR: Sodium–glucose cotransporter type 2 (SGLT2) inhibitors — dapagliflozin, empagliflozin and now ertugliflozin — have become established second line options for type 2 diabetes, with favourable potential for weight loss and cardiovascular protection.¹ However, it soon became clear post-marketing that they had potential for several pronounced side effects, including euglycaemic ketoacidosis — an unusual form of diabetic ketoacidosis where blood sugar levels remained relatively normal.²

The Therapeutic Goods Administration (TGA) first sent an alert about euglycaemic ketoacidosis in relation to SGLT2 inhibitors in 2015; subsequent alerts in 2018 from the TGA and the Australian Diabetes Society warned specifically about perioperative risks.^{3,4}

Austin Health has a well developed culture of adverse drug reaction reporting. A multidisciplinary committee includes representation from pharmacy, clinical pharmacology, dermatology and infectious diseases. During 2018, our adverse drug reaction committee forwarded 302 reports to the TGA, estimated to be around 15% of all reports received from Australian hospitals.

Since 2016, our adverse drug reaction committee has received 12 reports of patients with diabetic ketoacidosis related to SGLT2 inhibitors, including eight in 2018. The growth in incidence locally in such a short period is alarming. Most patients (75%) had a blood sugar level of 11 mmol/L or lower at presentation. Our committee reviewed the cases in the Box to evaluate severity and causality. SGLT2 inhibitors were considered a probable cause in ten cases; the reaction was considered severe in nine cases, with one death during admission. We report our cases with the aim of increasing awareness around contributing factors, particularly concurrent illness resulting in poor oral intake. Only two of the 12 cases related to a perioperative setting, and in neither situation was the SGLT2 inhibitor withheld prior to surgery.

We remind clinicians that the precipitants for diabetic ketoacidosis extend beyond the perioperative period. We advise caution when patients are experiencing other contributing factors illustrated by our case series, including acute illness, reducing insulin doses, poor oral intake, severe dehydration and low carbohydrate diet. Patients should be counselled about the signs of ketoacidosis and advised to seek medical help if they occur. SGLT2 inhibitors should be withheld if a patient is acutely unwell or undergoing surgery, and should only be restarted when the patient is eating and drinking normally.⁵

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Cases of ketoacidosis related to sodium–glucose cotransporter type 2 inhibitors

Case	Year	Medication	Dose	Severity	Causality	Potential contributing factors
1	2016	Empagliflozin	10 mg daily	Moderate	Probable	Low dietary intake in perioperative setting
2	2016	Dapagliflozin	5 mg twice a day	Severe	Probable	Perioperative setting
3	2017	Dapagliflozin	10 mg daily	Severe	Probable	Unwell for 3 days prior to presentation — patient had type 1 diabetes
4	2017	Empagliflozin	10 mg daily	Severe	Possible	Concurrent influenza
5	2018	Empagliflozin	10 mg daily	Severe	Probable	Narcosis leading to poor oral intake
6	2018	Empagliflozin	12.5 mg twice a day	Severe	Probable	Weight loss since commencing — worse in the months prior to admission
7	2018	Empagliflozin	25 mg daily	Moderate	Probable	Concurrent pneumonia
8	2018	Dapagliflozin	10 mg daily	Moderate	Possible	Low carbohydrate diet
9	2018	Empagliflozin	10 mg daily	Severe	Probable	Patient unwell with some vomiting for several days before admission
10	2018	Dapagliflozin	5 mg twice a day	Severe	Probable	5–7 days of loss of appetite
11	2018	Dapagliflozin	10 mg daily	Severe (died during admission)	Probable	Illness for 10 days before admission Pancreatitis
12	2018	Empagliflozin	25 mg daily	Severe	Probable	5 days of gastroenteritis before admission