Diabetic ketoacidosis precipitated by therapy with antidiabetic agents SGLT2 inhibitors: two cases

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a new class of oral antidiabetic agents for the management of type 1 and type 2 diabetes mellitus.[1] Clinical trials of these agents for type 2 diabetes have shown improved glucose tolerance and reduced glycosylated haemoglobin concentrations. Examples of these agents include dapagliflozin, empagliflozin and canagliflozin.[2] These agents are used as monotherapy, or dual therapy with metformin, and have recently been approved for use in Australia. The predominant mechanism of action in these inhibitors is that they cause glycosuria, which results in improved blood glucose control.

Reports in the medical literature suggest that SGLT2 inhibitors increase the risk of diabetic ketoacidosis (DKA) in patients with both type 1 and type 2 diabetes.[3] This has prompted the United States Food and Drug Administration (FDA) to issue a safety alert.[4] These agents have been approved by the Australian Therapeutic Goods Administration and have recently been introduced into clinical practice in Australia.

The purpose of our report is to inform the intensive care community of this potential complication of SGLT2 inhibitors as they are being used with increasing frequency in the management of diabetes. Our identification of SGLT2-induced DKA in two patients in rapid succession prompted us to prepare our report.

Clinical records

Patient 1

A 63-year-old man was admitted to the intensive care unit on 9 July 2015 after an uneventful elective coronary artery bypass grafting procedure. His medical history included type 2 diabetes for which he had been started on metformin, empagliflozin and alogliptin by his general practitioner. He had continued taking these medications up to the night before the surgery. The patient's preoperative (8 July) and immediate postoperative (9 July) biochemical profiles did not reveal any abnormality (Table 1). On the morning after the surgery (10 July), his biochemical profile revealed a raised anion gap with a normal serum lactate. Testing for ketones in the urine revealed strongly positive ketonuria with euglycaemia. This was managed with insulin and glucose infusions. His oral antidiabetic agents were ceased temporarily. The patient's history, the clinical setting and the course of the patient's progress did not warrant a search for other causes of the raised anion gap. The patient made an uneventful recovery from his ketosis and he recommenced metformin without the SGLT2 inhibitors and was discharged home on Day 6.

Patient 2

A 42-year-old woman, known to have type 1 diabetes, was admitted to the ICU on 19 July 2015 with an episode of ketoacidosis (Table 2). She had been on regular insulin therapy and, 1 month before her admission, her glycated haemoglobin (HbA_{1c}) level was 58 mmol/mol (7.5%). Her treatment had recently been changed by her GP from insulin to dapagliflozin. The episode of ketoacidosis was managed with intravenous fluids and insulin. Despite a significant level of ketoacidosis, her hyperglycaemia was mild and the patient made an uneventful recovery from ketosis and was recommenced on insulin.

Discussion

These cases illustrate the development of ketoacidosis in patients who have been on SGLT2 inhibitors for the management of diabetes. One patient was diagnosed with DKA in the ICU after elective surgery, and the other patient presented as an emergency with ketoacidosis after changing treatment from insulin to an SGLT2 inhibitor. Both patients had an elevated anion gap with normal albumin levels, ketonuria, normal serum lactate and an absence of any other cause of a raised anion gap acidosis. Both patients were characterised by the following: current use of SGLT2 therapy; euglycaemia or mild hyperglycaemic ketoacidosis; minimal dehydration (shown by minimal perturbation of urea levels); and rapid recovery. These characteristics are consistent with previous reports in the literature on SGLT2-induced ketoacidosis. Other causes of euglycaemic ketoacidosis (such as starvation and alcoholic ketosis) were considered, but were excluded on the basis of the patients' histories and clinical presentations.

SGLT2 inhibitors are known to increase the risk of ketoacidosis in patients with both type 1 and type 2 diabetes. Multiple mechanisms have been suggested to explain how these drugs might trigger an episode of ketoacidosis.[3] Because of the glucose-lowering effect of these drugs, a patient's dose of exogenous insulin is often

Table 1. Biochemical profile of Patient 1

Biochemical variable	8 July 2015 (preop.)	9 July 2015* (immediately postop.)	10 July 2015	11 July 2015	Reference range
Sodium (mmol/L)	138	142	143	136	137–147
Potassium (mmol/L)	3.8	3.2	4.2	3.9	3.5–5.0
Chloride (mmol/L)	100	109	105	104	96–109
Bicarbonate (mmol/L)	25	21	17	23	25–33
Anion gap (mmol/L)	17	15	25**	13	4–17
Glucose (mmol/L)	12.9	8.2	7.7	9.7	3.0–7.7
Albumin (g/L)	46	na*	45	34**	35–50
Lactate (mmol/L)	Not checked	1.0	0.9	1.1	< 2.5
Urea (mmol/L)	7.1		5.4	6.8	3.0–8.5
Urine ketones	Not checked	Not checked	+++	Not checked	–

na = not available. * All measurements were made using a laboratory analyser except the 9 July measurement, which was made using using a blood gas analyser (as formal blood testing in the laboratory is not part of immediate postoperative management); hence, albumin measurements were not available on 9 July. ** Abnormal value.

reduced. This, in turn, would result in increased lipolysis and ketogenesis. It has also been postulated that these drugs might increase acetoacetate reabsorption in the renal tubules. These drugs have also been reported to increase glucagon release by the alpha cells of the pancreas, which can lead to hepatic ketogenesis.

These cases highlight several learning points for the intensivist. The presentation of DKA from exogenous insulin deficiency may differ from that of SGLT2-associated ketoacidosis. Ketoacidosis associated with SGLT2 may be accompanied by euglycaemia[5] or not accompanied by significant hyperglycaemia. Home monitoring of glucose may not alert the patient to the evolving metabolic crisis and may result in delayed presentation to the hospital. For the same reason, initial assessment of the patient's biochemical profile in the hospital may prompt the clinician to undertake additional investigations for the causes of a raised anion gap, but may not trigger testing for ketones as blood sugar levels may be normal or only mildly elevated. Also, despite identification of a ketotic process, the presence of normal or mildly elevated blood sugar levels might lead the clinician to search for alternative causes of ketosis, such as alcohol or starvation. Finally, it is important to note that although DKA is traditionally thought to be associated with type 1 diabetes, there are now several reports of this metabolic emergency occurring in patients with type 2 diabetes.[6,7] The introduction of SGLT2 inhibitors for the management of type 2 and, to a lesser extent, type 1 diabetes certainly increases the likelihood of this presentation in this cohort.

There have now been several cases reported worldwide of SGLT2-therapy-induced ketoacidosis. This has prompted

Table 2. Biochemical profile of Patient 2

Biochemical variable	19 July 2015	20 July 2015	21 July 2015	22 July 2015	Reference range
Sodium (mmol/L)	134	137	136	139	137–147
Potassium (mmol/L)	5.0	4.0	3.3	3.1	3.5–5.0
Chloride (mmol/L)	107	114	108	99	96–109
Bicarbonate (mmol/L)	10*	8*	18*	28	25–33
Anion gap (mmol/L)	22*	19*	13	15	4–17
Glucose (mmol/L)	12.1*	–	17.2	16.1	3.0–7.7
Albumin (g/L)	49	42	35	35	35–50
Lactate (mmol/L)	1.1	–	–	–	< 2.5
Urea	3.2	1.9	1.1	2.0	3.0–8.5
Urine ketones	+++	–	–	–	–

* Abnormal value.

the FDA to issue an alert. Given that it is a recent addition to the armamentarium in the management of diabetes in Australia, it is important that clinicians are aware of this complication.

Competing interests

None declared.

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