

Sodium Glucose Co-transporter 2 Inhibitor associated perioperative Diabetic Ketoacidosis

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Abstract

Introduction

Sodium glucose co-transporter 2 (SGLT2) inhibitors were originally developed for the treatment of diabetes mellitus, however their approved use has expanded over recent years to include the treatment of heart failure and chronic kidney disease. This case series illustrates a spectrum of perioperative SGLT2 inhibitor related diabetic ketoacidosis (DKA), both euglycaemic and hyperglycaemic. We hope to highlight the challenges of both diagnosis and management of this condition.

Cases

Case 1: Euglycaemic DKA in a 54-year-old post-emergency laparotomy, which recurred following resumption of her SGLT2 inhibitor.

Case 2: Euglycaemic DKA in an 82-year-old post-emergency laparotomy.

Case 3: Hyperglycaemic DKA in a 52-year-old patient who underwent arthroscopic shoulder surgery as a day case.

Case 4: Euglycaemic DKA in a 78-year-old post-emergency lower limb revascularisation.

Results

These cases highlight that the use of SGLT2 inhibitors carries the risk of perioperative DKA which can be difficult to diagnose and requires prompt management.

Discussion

As the indications for the use of these medications expand, we must maintain a high clinical suspicion for DKA with their perioperative use.

Introduction

Sodium glucose co-transporter 2 (SGLT2) inhibitors were developed for the treatment of diabetes mellitus. Blood glucose levels are reduced via inhibition of glucose reabsorption from the proximal convoluted tubules and induction of glycosuria. While initially introduced to improve glycaemic control, their approved use has expanded significantly over recent years. SGLT2 inhibitors have been shown to reduce hospitalisation and the risk of cardiovascular death in patients with heart failure^{1,2}. They are now an integral component of heart failure treatment^{3,4}. SGLT2 inhibitors have also been shown to slow the progression of chronic kidney disease (CKD) and to reduce the incidence of death from cardiovascular causes in patients with CKD⁵. They are now recommended in patients with CKD, both with and without co-existing diabetes⁶. More recently there is emerging evidence that SGLT2 inhibitors may reduce the incidence of COPD exacerbations and hospital admissions⁷. The expanding indications for SGLT2 inhibitors have resulted in an increase in the number of patients prescribed these medications presenting for surgery.

SGLT2 inhibitor use during the perioperative period is particularly associated with the development of euglycemic diabetic ketoacidosis (euDKA)⁸. Guidelines informing the perioperative management of SGLT2 inhibitors are in constant evolution reflecting our growing experience with these medications perioperatively. This case series will illustrate a spectrum of perioperative SGLT2 inhibitor related DKA cases, both euglycaemic and hyperglycaemic. From elective ambulatory surgery in otherwise healthy patients to elderly patients undergoing emergency surgery, we describe the development of euDKA (intra-op, post-op and recurrent) and post-operative hyperglycaemic DKA (hDKA) in patients taking SGLT2 inhibitors. This study will highlight the challenges of both diagnosis and management of this condition.

Case 1

A 54-year-old female presented with a four-day history of abdominal pain and constipation. Her past medical history included schizophrenia, epilepsy, type two diabetes (T2DM) and a previous appendicectomy. A CT abdomen revealed a small bowel obstruction secondary to adhesions. The patient was brought to theatre and underwent an exploratory laparotomy and adhesiolysis. On arrival to recovery, following an approximately two-hour surgery, the patient was noted to be obtunded. Naloxone was initially administered with minimal improvement. A blood gas showed a mixed acidosis with normoglycaemia. Considering her chronic SGLT2 inhibitor use capillary ketones were measured and found to be 5.1mmol/L. A diagnosis of euDKA was made and the patient commenced on a fixed rate insulin and dextrose infusion. She was admitted to the High Dependency Unit (HDU) where her blood gas normalised and

insulin treatment discontinued. She was de-escalated to ward level care after 24 hours. The patient resumed diet and was recommenced on her usual diabetic medications. On post-op day three, a clinical deterioration was observed with increased drowsiness. Ketones were again found to be elevated at 5.6mmol/L with hypoglycaemia (3.3mmol/L). Treatment was begun for recurrent euDKA and the patient was readmitted to the HDU and responded well to treatment. Following resolution of the euDKA, the patient was discharged to the ward to continue her recovery. On the advice of the endocrinology service, she was commenced on an alternative diabetic medication prior to discharge.

Case 2

An 82-year-old female presented with abdominal pain and nausea. Background history included a right hemicolectomy for colorectal carcinoma, idiopathic pulmonary fibrosis, T2DM, and atrial fibrillation. A CT abdomen pelvis was performed which revealed a closed loop bowel obstruction with associated signs of ischaemia. She underwent an emergency exploratory laparotomy with a small bowel resection. She was admitted to HDU post-operatively. On day two post-op, the patient developed an evolving metabolic acidosis with a normal blood glucose. Her ketones were found to be 6mmol/L and a diagnosis of euDKA was made. Treatment was initiated as per the local DKA protocol with a fixed dose insulin and dextrose infusion. Despite improvement in her DKA parameters, the patient continued to deteriorate clinically requiring increasing organ support. She ultimately passed away following withdrawal of life sustaining treatment.

Case 3

A 52-year-old female presented for elective arthroscopic capsular release. Her past medical history was significant for hypertension and T2DM for which she took a biguanide, a sulfonylurea, an SGLT2 inhibitor and insulin. The patient withheld her SGLT2 inhibitor for 48 hours pre-operatively as advised. The procedure was a planned day case and aside from transient nausea and vomiting in recovery, was uneventful. The patient was discharged home that evening with a plan to resume her usual diabetic medication. On post-op day one, there was further sustained nausea with anorexia. She ultimately presented acutely unwell to the emergency department of another institution two days post-procedure. She was found to have developed hyperglycaemic DKA with a pH of 6.89, ketones of 4.7mmol/L and a blood glucose of 18.8mmol/L. She was admitted to critical care and responded well to the DKA protocol. The endocrinology service was consulted and her SGLT2 inhibitor was discontinued. They also subsequently revised her underlying diagnosis to probable latent autoimmune diabetes in adults (LADA).

Case 4

A 78-year-old male was admitted with critical lower limb ischemia with a background history of peripheral vascular disease, CKD, T2DM, hypertension, and previous coronary artery bypass grafting. He underwent an emergency lower limb angioplasty and popliteal to dorsalis pedis bypass restoring circulation. He was admitted to HDU as the anaesthetic team had identified him as being at risk of euDKA as his SGLT2 inhibitor had not been held. On post-op day two, the patient developed a metabolic acidosis with ketones of 4mmol/L and normal blood glucose levels. He was commenced on a fixed dose insulin and dextrose infusion according to the local DKA protocol. He subsequently developed ischaemic bowel requiring a return to theatre for an exploratory laparotomy, extensive bowel resection and stoma formation. He remained on treatment for his DKA as guided by the endocrinology service. Dysglycaemia due to impaired absorption and high stoma output stabilised when the patient became established on parenteral nutrition. The patient was transitioned to a variable rate insulin infusion prior to ultimately resuming subcutaneous insulin.

Discussion

Classic hyperglycaemic DKA is defined by plasma glucose >11 mmol/L, ketonemia (capillary or blood ketones >3 mmol/L, or significant ketonuria on urine dipstick) and acidosis (pH < 7.3 and or bicarbonate <15 mmol/L)⁹. In contrast, euDKA is defined by ketonemia, acidosis with normal or slightly elevated blood glucose levels.

DKA severity is classified based on acidosis and bicarbonate levels¹⁰.

Severity	Arterial pH	Serum Bicarbonate (mmol/L)	Anion Gap	Mental Status
Mild	7.25–7.30	15–18	>10	Alert
Moderate	7.00–7.24	10–15	>12	Alert/drowsy
Severe	<7.00	<10	>12	Stupor/coma possible

Table 1: DKA severity criteria

DKA management involves fluid resuscitation and a fixed-rate insulin infusion to correct the ketoacidosis, alongside intravenous dextrose as required to maintain normoglycaemia. Insulin should be continued until the ketoacidosis resolves. Premature insulin withdrawal or early

reintroduction of the SGLT2 inhibitor can lead to relapse. While euDKA is most commonly seen with SGLT2 inhibitor use, hDKA may also be observed (42% of cases)¹⁰.

The perioperative use of SGLT2 inhibitors carries a small but real risk of euDKA occurring in approximately 0.17% of elective surgery and 1.1% of emergent surgery¹¹. Risk factors for the development of euDKA include fasting, emergency surgery, infection, and malignancy¹². Patients with diabetes taking insulin have a 2.8-fold increased risk¹³. In addition, misclassification of autoimmune diabetes may further contribute to vulnerability, with one study showing 25% of patients with SGLT2 inhibitor associated DKA who underwent pancreatic autoantibody testing being reclassified as having LADA rather than type 2 diabetes¹⁴. Although significantly less common, there are case reports describing the development of euDKA in non-diabetic patients receiving SGLT2 inhibitors¹⁵.

EuDKA is a potentially fatal complication that can be challenging to recognise, given other confounding factors, particularly in the unwell comorbid patient undergoing emergency surgery. The perioperative period can be marked by significant physiological change. This is due to the impact of surgical trauma, perioperative fasting, anaesthesia and other potential factors including malignancy and infection. Surgical stress results in an increase in circulating catecholamines stimulating gluconeogenesis, lipolysis, and ketone production all of which can cause metabolic derangements similar to those seen in euDKA¹⁶. General anaesthesia also masks many of the classic signs and symptoms of DKA such as excessive thirst, lethargy, confusion, and GI upset. A high index of suspicion should be maintained for the development of euDKA in patients taking SGLT2 inhibitors. Prompt recognition and treatment with insulin and dextrose are necessary to prevent a metabolic crisis.

A consensus statement from multiple UK anaesthesia and diabetes organisations published earlier this year has highlighted the lack of evidence in this area and aimed to support shared decision making¹⁷. They recommend patients taking these medications should not take them on the day prior, or the day of surgery in the elective setting. They also acknowledge the multitude of factors which can contribute to the development of glycaemic dysregulation and a ketotic state in such patients. The United States Food and Drug Administration recommend discontinuing SGLT2 inhibitors at least three–four days before all scheduled surgery. This has been endorsed by other American organisations including the American Diabetes Association and the American College of Cardiology¹⁸. How and when these medications should be resumed post-operatively is also a necessary consideration as case three attests. The Centre for Perioperative Care recommends daily ketone measurement until both ketones and blood sugars are within normal ranges, at which point SGLT2 inhibitors can be recommenced¹⁹. However, the multidisciplinary consensus statement mentioned previously, while recommending frequent checking of blood glucose and ketones, does not specify this frequency due to the lack of evidence and institutional capacity.

It is important to recognise that the cessation of SGLT2 inhibitors is not without risk. Discontinuing these medications, particularly in patients with heart failure, can lead to adverse outcomes. The EMPEROR trial demonstrated that the rate of cardiovascular death or hospitalisation for heart failure in the first 30 days increased alongside an increase in heart failure symptoms²⁰. The risk of DKA must be weighed against the risk of heart failure decompensation, or other cardiac events related to abrupt cessation of therapy.

The clinical indications and the use of SGLT2 inhibitors are expanding. As evidence emerges, we anticipate further guidelines and protocols surrounding the perioperative use of SGLT2 inhibitors. Until that time we advise a cautious and individualised approach to SGLT2 inhibitor management in the perioperative setting. Heightened clinical suspicion for DKA should be maintained, especially in the post-operative period, and any decision to withhold or resume therapy should involve careful consideration of both metabolic and cardiovascular risks.

Declarations of Conflicts of Interest:

None declared.

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