Sodium–glucose co-transporter-2 inhibitors and the risk of perioperative euglycaemic diabetic ketoacidosis

Sodium–glucose co-transporter-2 inhibitors are increasingly prescribed for patients with type 2 diabetes. Their use has been associated with life-threatening diabetic ketoacidosis. The risk is increased during times of fasting and intercurrent medical illness, which are common in the perioperative period. Diagnosis can be difficult, so perioperative clinicians must be familiar with preventing and recognising such complications.

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Introduction

Patients with diabetes make up 10–15% of the surgical population. This group has a higher incidence of surgical complications and length of stay than patients who do not have diabetes (Centre for Perioperative Care, 2021). With almost 10% of the population expected to have diabetes by 2035 (Public Health England, 2016), it is vital that robust measures are in place to minimise poor outcomes in these patients in the perioperative period.

Diabetic ketoacidosis

Diabetic ketoacidosis is a serious, life-threatening complication of type 1 and sometimes type 2 diabetes mellitus, characterised by a triad of hyperglycaemia (capillary blood glucose >11.0 mmol/litre), acidosis (pH <7.3 or bicarbonate <15.0 mmol/litre) and ketosis (ketones >3.0 mmol/litre or urine ketones >2+) (Joint British Diabetes Society Inpatient Care Group, 2021). Insulin deficiency and elevated levels of catecholamines cause unrestrained lipolysis and supply of free fatty acids, leading to ketosis (Thiruvenkatarajan et al, 2019).

Euglycaemic diabetic ketoacidosis

A less well-known complication of diabetes, euglycaemic diabetic ketoacidosis, is characterised by normal, or near-normal, capillary blood glucose levels (<14 mmol/litre), which can result in delayed diagnosis and treatment. Risk factors for euglycaemic diabetic ketoacidosis include acute medical illness, cirrhosis, insulin cessation, pancreatitis, pregnancy, starvation and surgery.

Sodium–glucose co-transporter-2 inhibitors

Sodium–glucose co-transporter-2 inhibitors, such as empagliflozin, are novel drugs used to treat type 2 diabetes and heart failure. They can increase the risk of developing euglycaemic diabetic ketoacidosis, particularly during times of intercurrent illness, starvation or surgery (Thiruvenkatarajan et al, 2019). Indeed, patients undergoing emergency surgery are likely to undergo prolonged periods of starvation. It is estimated that patients taking sodium–glucose co-transporter-2 inhibitors have a sevenfold increased risk of developing euglycaemic diabetic ketoacidosis than those taking dipeptidyl peptidase-4 inhibitors (Blau et al, 2017).

Sodium–glucose co-transporter-2 inhibitors act on the sodium-glucose co-transporter-2 receptor, preventing glucose reabsorption in the proximal tubule of the kidney (Barski et al, 2019). Increasing urinary glucose excretion reduces insulin secretion by pancreatic beta cells, thereby lowering the anti-lipolytic actions of insulin, resulting in increased production of free fatty acid (and subsequently ketone).

With the introduction of novel sodium–glucose co-transporter-2 inhibitors, euglycaemic diabetic ketoacidosis has become more clinically relevant in the perioperative period.

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Diagnosing euglycaemic diabetic ketoacidosis

Euglycaemic diabetic ketoacidosis is a diagnostic challenge. Symptoms can be non-specific but may include vomiting, abdominal pain and shortness of breath. As capillary blood glucose readings are often near normal, the index of suspicion of diabetes-related metabolic complications is likely reduced. Sodium–glucose co-transporter-2 inhibitors also facilitate reabsorption of ketone bodies in the kidney, rendering the measurement of urine ketone levels unreliable as they may be undetectable on dipstick testing (Thiruvenkatarajan et al, 2019). This has important implications for easy diagnosis of euglycaemic diabetic ketoacidosis, as blood ketone meters are not available in all departments.

Management of euglycaemic diabetic ketoacidosis

The Centre for Perioperative Care (2021) published guidance on the management of patients taking sodium-glucose co-transporter-2 inhibitors, stating that emergency surgical patients who are nil-by-mouth and take insulin should receive 80% of their usual insulin dose in addition to a variable rate insulin infusion. Patients taking sodium-glucose co-transporter-2 inhibitors should have them paused at the point of admission and blood ketone levels checked daily.

The treatment of euglycaemic diabetic ketoacidosis is similar to that of diabetic ketoacidosis, using a fixed rate insulin infusion (0.1 IU/kg/hr) to suppress ketosis, tight capillary blood glucose control with 10% dextrose and potassium replacement. Fluid resuscitation is important, but smaller volumes of fluid are likely to be needed than those used for patients with diabetic ketoacidosis. It is important to remember that intravenous fluid alone will not correct the acidosis. Insulin therapy is vital and, in the presence of normal or near-normal capillary blood glucose readings, a simultaneous dextrose infusion should be administered to maintain capillary blood glucose levels in the target range.

Conclusions

The number of surgical patients with type 2 diabetes and heart failure taking sodium–glucose co-transporter-2 inhibitors continues to rise. Owing to the diagnostic challenges and significant metabolic consequences, a high index of suspicion for euglycaemic diabetic ketoacidosis is required for prompt diagnosis and management.

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