Guidance on the risk of diabetic ketoacidosis with the use of Sodium-Glucose Cotransporter-2 inhibitors (SGLT-2i) in the management of Type-2 diabetes

Recommendation [2, 5, 15]

Ipswich Hospital NHS Trust diabetes team and Ipswich and East Suffolk Clinical Commissioning Group make the following recommendations related to the use of SGLT-2i in the management of Type-2 diabetes:

- **AVOID or STOP** SGLT-2i at least 24 hours prior to a major elective surgery or any planned invasive procedures. This will include any procedure where patients need fasting including endoscopic procedures.

- **STOP** prior to emergency surgery or in patients who present with trauma.

- **INTERRUPT** treatment with the SGLT-2i in patients who are hospitalised for major surgery or acute serious illnesses (medical or surgical).

- In the above situations once the patient has recovered and is eating normally the SGLT-2i can be **RESTARTED**. Discuss with diabetes team if required.

- **REMEMBER** patients on SGLT-2i may present with euglycaemic DKA (i.e. with normal plasma glucose); all unwell patients on SGLT-2i must have blood ketones measured since their plasma glucose and urinary ketones might remain normal.

- **AVOID or STOP** SGLT-2i at least 24 hours prior to anticipated severe stressful physical activities such as running a marathon.

- **ADVISE** patients not to consume excess alcohol intake and very low calorie diets when taking SGLT-2i.

- **SGLT-2i are NOT LICENSED** in Type-1 diabetes. Such patients are usually in clinical trials and insulin should not be stopped in response to reduction in blood glucose levels without careful consideration of the risk of ketoacidosis and monitoring of ketones.
Rationale

Sodium glucose co-transporter 2 inhibitors (SGLT2i) are licensed for use in adults with type 2 diabetes to improve glycaemic control. As of now they are unlicensed in any other form of diabetes including type 1 diabetes and gestational diabetes.

SGLT2 i - medicines in this class
The following brand names are marketed in the UK:

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Active drug</th>
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<tbody>
<tr>
<td>Jardiance®</td>
<td>Empagliflozin tablets (10 mg and 25 mg)</td>
</tr>
<tr>
<td>Synjardy®</td>
<td>Empagliflozin/metformin tablets (5 mg/850 mg, 12.5 mg/850 mg, 5 mg/1000 mg, 12.5 mg/1000 mg)</td>
</tr>
<tr>
<td>Forxiga®</td>
<td>Dapagliflozin tablets (5 mg and 10 mg)</td>
</tr>
<tr>
<td>Xigduo®</td>
<td>Dapagliflozin/metformin tablets (5 mg/850 mg and 5 mg/1000 mg)</td>
</tr>
<tr>
<td>Invokana®</td>
<td>Canagliflozin tablets (100 mg and 300 mg)</td>
</tr>
<tr>
<td>Vokanamet®</td>
<td>Canagliflozin/metformin tablets (50 mg/850 mg, 50 mg/1000 mg, 150mg/850mg, 150mg/1000mg)</td>
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Reports of diabetes ketoacidosis (DKA)

Serious and life-threatening cases of DKA have been reported in patients taking SGLT2i. In several cases, blood glucose levels were only moderately elevated (e.g. <14 mmol/L), which is atypical for DKA. [1, 2] This atypical presentation could delay diagnosis and treatment. A recent meta-analysis of 10 eligible RCTs involving 13,134 patients and 14 DKA events found the overall event rate of 0.1% in the SGLT-2 inhibitor group versus 0.06% in the control group.[3] The majority of cases of SGLT2 inhibitor associated DKA have occurred in people with type 1 diabetes in the clinical trial setting. In the EMPA-REG study involving the use of Empagliflozin in type 2 diabetes, 5 DKA cases were reported over 3 years; 0.5 per 1000 patient-years with 10 mg dosage and 0.2 per 1000 patient-years with both 25 mg dosage and with placebo. [4]

Precipitating factors

Usually, in the cases of diabetic ketoacidosis reported in association with SGLT-2i, there is a precipitating factor both in patients with type 1 and type 2 diabetes i.e. surgery, exercise, MI, stroke, severe infection, prolonged fasting, excessive alcohol consumption, severe injury, hypovolaemia, pancreatitis, marathon running, stroke, very low calorie diets and stressful physical or mental condition. This may be related to the stress induced shift of metabolism from carbohydrate to fat dependence. Half of the cases occurred during the first 2 months of treatment. Some cases occurred shortly after stopping the SGLT2i. [5, 6]
Pathophysiology

Although an exhaustive explanation related to the pathophysiological basis of DKA with the use of SGLT-2i is beyond the scope of this document, the cardinal mechanisms involve a relative insulin deficiency along with glucagon excess promoting a shift of metabolism towards fat, increased glycogenolysis and gluconeogenesis relative insulin resistance increased by lipolysis which coupled with an increase in counter regulatory hormones leads to reduced glucose utilisation by tissues. [7]

SGLT-2 inhibition in pancreatic alpha cells may result in increased glucagon production because of reduced paracrine inhibition by insulin and SGLT mediated glucose transfer into alpha cells. [7-9]

Lower than expected hyperglycaemia in SGLT-2i associated DKA may be a result of a combination of factors, i.e. partial treatment of DKA, fasting, carbohydrate avoidance, dehydration, alcohol consumption and glycosuria. [10, 11]

Presentation

In most cases, DKA would present in such patients with classical symptoms and high glucose levels. However, it is important to note that some cases might present with lower than expected hyperglycaemia. This type of euglycaemic or lower than expected hyperglycaemic ketoacidosis has been described extensively in literature.[10-12]. In the cases described to date blood glucose levels have not been consistently reported. The lowest reported level was 5 mmol/L and 13 cases have been reported with levels <10 mmol/L. The majority, however, had glucose levels above 13.8 mmol/L [2]. There does not appear to be a fixed level of glucose below which DKA can be excluded with certainty.

Immediate management of DKA

Diabetic ketoacidosis, which may be euglycaemic (euDKA), should be considered in all patients taking SGLT-2i who present with typical symptoms of diabetic ketoacidosis i.e. abdominal pain, nausea, vomiting, fatigue, and dyspnoea and an appropriate workup should be carried out as per local Trust guidelines which are based on the JBDS guidelines.[13]

The diagnosis should NOT depend only upon the presence of ketones in the urine (which may be false negative or may not be associated with ketosis or ketoacidosis) or even blood glucose but should be based on low bicarbonate (<15), low pH (<7.3) or quantitative excess of blood ketones over the limit that is considered diagnostic of DKA i.e. 3 mmol/L. Where available, test capillary blood for ketones using appropriate test strips in the capillary blood PXP meter or send blood to the lab for β-hydroxybutyrate measurement. Glucose levels are usually higher than11 mmol/l but can be lower and therefore in a person known to have diabetes the diagnosis of diabetic ketoacidosis should always be entertained irrespective of blood glucose.[14]
Diagnosis of DKA in patients taking SGLT-2 inhibitors [2,13]

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<tr>
<td>Arterial pH</td>
<td>&lt; 7.3</td>
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<tr>
<td>Blood ketones</td>
<td>&gt; 3 mmol/L</td>
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<tr>
<td>Anion gap</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>&lt;15</td>
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<tr>
<td>Clinical</td>
<td>Deteriorating level of consciousness in severe cases</td>
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</table>

Further management of DKA
Once DKA is confirmed, stop the SGLT-2i immediately. Treat DKA as per local Trust guidelines; it is important to note that in such patients monitoring of pH, bicarbonate and anion gap is more important than blood glucose. Fixed rate insulin is required until the blood ketones fall to < 0.6 mmol/L and acidosis resolves. If the glucose concentration is < 14 mmol/L, give 10% glucose via a 2nd IV line to maintain the blood glucose to enable the use of fixed rate insulin until the ketones have cleared and the acidosis has resolved. Remember that in spite of stopping the drug, an SGLT-2 inhibitor mediated increase in urinary glucose loss and therefore fat dependent metabolism may persist for several days.

Recommendations
Please see boxed recommendations in the beginning of this document.

Conclusions
The overall incidence of DKA in type 2 diabetes subjects is infrequent and based on current evidence; the risk-benefit ratio will overwhelmingly favour continuing the current practice of using SGLT-2 inhibitors with no change in current recommendations as long as they are used for their licensed indications.

The diagnosis of DKA should be considered when patients from high risk groups and with high risk conditions present with acidosis or symptoms compatible with acidosis.

SGLT-2 inhibitors should be discontinued in patients that have developed DKA and should not be restarted unless a clear alternative cause of DKA is identified.

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References


