Euglycaemic Ketoacidosis Secondary to Canagliflozin (SGLT2 Inhibitor) – A Peri-operative Concern

Duncan Tong,1 Yvonne Chow,2 Thuy Bui1,3

1. Pharmacy Department, Alfred Health, Melbourne, Victoria 2. Endocrinology & Diabetes Department, Alfred Health, Melbourne, Victoria, 3. Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Victoria

Background

Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated for treatment of type 2 diabetes mellitus (T2DM), first approved by the Therapeutic Goods Administration in 2014. As with all new medications, there are unexpected adverse effects that become apparent as use becomes more widespread.

We present a case of euglycaemic ketoacidosis (euDKA) secondary to canagliflozin use in an individual with T2DM undergoing surgery.

Case Report

A 48-year-old female was admitted to The Alfred Hospital for elective left craniothyroid and clipping of left middle cerebral artery aneurysm. Medical history included T2DM diagnosed following gestational diabetes in the context of obesity and past bariatric surgery. Her most recent HbA1c was 7.0%; glutamic acid decarboxylase (GAD) and insulinoma antigen-2 (IA2) antibodies were undetected. On admission medications included metformin, canagliflozin, and insulin glargine and aspart (Table 1). The patient’s total daily insulin dose was 52 units.

Table 1. T2DM medications on admission and discharge

<table>
<thead>
<tr>
<th>On Admission</th>
<th>On Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin XR 1000mg BD</td>
<td>Ceased</td>
</tr>
<tr>
<td>Canagliflozin 300mg mane</td>
<td>Ceased</td>
</tr>
<tr>
<td>Insulin Glargine (Lantus®) 28 units mane</td>
<td>Insulin Glargine (Lantus®) 20-30 units mane</td>
</tr>
<tr>
<td>Insulin Aspart (NovoRapid®) 8 units TDS with meals</td>
<td>Insulin Aspart (NovoRapid®) 6-14 units TDS with meals</td>
</tr>
</tbody>
</table>

The patient’s progress in hospital is described in the figure below.

Day 1 post-operative

- Oral hypoglycaemics withheld
- Intravenous fluid (IVF) infused
- Alkaline shift noted
- Baseline ketones present
- Metformin ceased
- Increase TDS insulin doses
- Insulin withheld during surgery
- Post-operative ketones negligible
- Low baseline ketones detected
- Canagliflozin withheld
- Lansoprazole administered
- Fasting blood glucose (FBG) and ketones lowered

Day 2 post-operative

- Baseline ketones undetectable
- FBG normalised
- Canagliflozin restarted on post-operative day 1
- Medical ordered
- Ketones persist
- Canagliflozin withheld
- Metformin reinitiated
- Ketones undetectable
- FBG normalised

Discussion

DKA is a serious complication of diabetes mellitus. It is defined by hyperglycaemia (BSL>13.9mmol/L), anion gap acidosis and increased plasma ketones.1

Ketoacidosis can also occur in the setting of mildly elevated or, rarely, normal serum glucose levels. This phenomenon is termed euDKA.

The potential mechanism of euDKA induced by SGLT2 inhibitors is likely multifactorial, see below figure, incorporating the following:

- Reduced plasma glucose due to increased urinary glucose excretion, leading to reduction in insulin secretion.
- Elevated glucagon levels due to inhibition of SGLT2 receptors at the pancreatic α-cells, or secondary effects mediated by decreased insulin levels.2
- Hypoammonaemia secondary to diuresis, leading to increased levels of glucagon, cortisol and adrenaline.

These proposed mechanisms lead to lipolysis, free fatty acid (FFA) production, eventuating in ketone production.

Triggers for euDKA include: acute illness, infection, trauma, prolonged starvation, reduced caloric and/or fluid intake, alcohol use, and reduced insulin dose.1,3

Patients treated with SGLT2 inhibitors undergoing surgery are at an increased risk of euDKA, due to fasted states before surgery. Post-operative nausea and vomiting may lead to further reduction in oral intake. Delayed recognition can occur as the clinical signs may be attributed to surgery, and plasma glucose may be within acceptable ranges due to persistent glycosuria induced by SGLT2 inhibitors.4

The half-life of SGLT2 inhibitors is approximately 12 hours; however pharmacodynamic effects may persist longer. Therefore, withholding SGLT2 inhibitors 24-48 hours before surgery may have little benefit.4

Potential recommendations for perioperative management of patients prescribed SGLT2 inhibitors include routine ketone body testing in the post-operative setting, especially in individuals who are unwell. SGLT2 inhibitors should only be restarted if the patient is tolerating a full diet.

Conclusion

SGLT2 inhibitors are increasingly used for the management of diabetes mellitus. Clinicians, especially those caring for surgical patients, need to be aware of and monitor for euDKA secondary to SGLT2 inhibitors. Further research is required to inform appropriate perioperative management.

Table 2: Arterial blood gas results on day 3 post-operative

<table>
<thead>
<tr>
<th>Arterial Blood Gas</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.44</td>
<td>7.38-7.43</td>
</tr>
<tr>
<td>pCO2</td>
<td>18mmHg</td>
<td>35-45 mmHg</td>
</tr>
<tr>
<td>pO2</td>
<td>108mmHg</td>
<td>78-99 mmHg</td>
</tr>
<tr>
<td>Base Excess</td>
<td>-21</td>
<td>-3 to 3</td>
</tr>
<tr>
<td>Calculate Bicarbonate</td>
<td>6mmol/L</td>
<td>20-30mmol/L</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.1mmol/L</td>
<td>0.8-1.8mmol/L</td>
</tr>
<tr>
<td>Anion Gap</td>
<td>15mmol/L</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Capillary blood glucose and ketones on day 3 post-operative

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary blood ketones</td>
<td>≥3.0 mmol/L</td>
<td>≤0.6 mmol/L</td>
</tr>
<tr>
<td>Capillary blood glucose</td>
<td>4.2-10.1mmol/L</td>
<td>4.0-8.0 mmol/L</td>
</tr>
</tbody>
</table>

Based on the limited literature available, canagliflozin was considered the causative agent. The patient was commenced on insulin infusion and transferred to the intensive care unit for further management over 6 days. Upon discharge it was recommended that the patient’s oral hypoglycaemic agents not be restarted, and that she continue on insulin glargine and aspart only.

References


Figure 1: Mechanisms of euglycaemic ketoacidosis (euDKA) secondary to SGLT2 inhibitors.