Canagliflozin associated diabetic ketoacidosis in a patient with Type 2 Diabetes Mellitus

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Introduction

In August 2015 the Therapeutic Goods Administration (TGA) released a warning statement highlighting the association between Sodium Glucose Co-Transporter 2 (SGLT-2) inhibitors and episodes of serious diabetic ketoacidosis (DKA)1. These episodes often occurred in relation to acute illness, prolonged fasting and surgery.

Case presentation

A 56-year-old Australian female was admitted on 2nd March 2015 for the surgical management of a perineal abscess. Her past medical history included Type 2 Diabetes Mellitus (T2DM) and hypertension, both managed on oral therapy (Table 1).

Table 1. Medications on admission

<table>
<thead>
<tr>
<th>Medication</th>
<th>Formulation</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>IR Tablet</td>
<td>1g</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>IR Tablet</td>
<td>300mg</td>
<td>Daily: Mornings</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>IR Tablet</td>
<td>1g</td>
<td>Four times daily</td>
</tr>
<tr>
<td>Amiodipine/Valsalvan</td>
<td>IR Tablet</td>
<td>10mg/300mg</td>
<td>Daily: Mornings</td>
</tr>
</tbody>
</table>

The following morning:

The patient was flagged for discharge.

The pharmacist noticed a significant drop in the patient's bicarbonate, from 22mmol/L to 6mmol/L (Figure 1).

The pharmacist contacted the surgical team, discouraged discharge and requested an immediate medical review.

Nursing staff documented increasing drowsiness, pain, tachypnea and tachycardia.

The medical team ordered urgent bloods (Table 2).

The patient lost consciousness and was transferred to the intensive care unit (ICU).

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Table 2. Laboratory results 4th March 2015

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCC</td>
<td>31.29</td>
<td>3.0-11x10⁹/L</td>
</tr>
<tr>
<td>CRP</td>
<td>290</td>
<td>&lt;5mg/L</td>
</tr>
<tr>
<td>Serum ketones</td>
<td>++++</td>
<td>&lt;0.1mmol/L (negative)</td>
</tr>
<tr>
<td>VBG - pH</td>
<td>6.69</td>
<td>7.28 - 7.43</td>
</tr>
<tr>
<td>VBG - bicarbonate</td>
<td>5</td>
<td>22-30mmol/L</td>
</tr>
<tr>
<td>VBG - Anion gap</td>
<td>26</td>
<td>&gt;14mmol/L</td>
</tr>
</tbody>
</table>

Management and outcomes:

The patient was diagnosed with severe DKA complicated by sepsis.

An insulin/dextrose infusion was commenced.

Wound management included surgical debridement, broad-spectrum antibiotics and hyperbaric therapy.

After stabilisation and ward transfer, the patient was:

- Commenced basal-bolus insulin
- Restarted metformin
- Ceased canagliflozin

HbA1c during admission was 13.3%.

The patient was discharged on the 14th March 2015 after a 13 day inpatient admission.

Discussion

SGLT-2 inhibitors (Figure 2) represent a novel class of oral medications to improve glycaemic control independent of insulin2.

The inhibition of SGLT-2 transporters in the proximal renal tubules prevents the reabsorption of filtered glucose, leading to increased urinary excretion of glucose and ultimately the lowering of blood glucose levels6.

SGLT-2 inhibitors carry a low risk of precipitating hyperglycaemia, however the glaucosemura may precipitate troublesome genital and urinary infections2.

Figure 2. Sodium Glucose Co-Transporter 2 (SGLT-2) inhibitors currently registered in Australia.

Since the introduction of SGLT-2 inhibitors there have been various cases of DKA reported in the literature7,8,9,10,11. The TGA highlighted common risk factors to include:

- Acute illness
- Trauma and surgery
- Reduced oral intake and fasting
- Reduced insulin dosing and omitted insulin
- SGLT-2 inhibitor associated DKA may present as atypical, with BGLs only mildly elevated (<14mmol/L)1. It’s hypothesised that atypical BGLs may be related to urinal blood glucose excersation.

The American Association of Clinical Endocrinologists and the American College of Endocrinology produced a position statement in June 2016 on the association of SGLT-2 inhibitors and DKA7. They concluded:

- It is unclear if the incidence of DKA has increased since the introduction of SGLT-2 inhibitors, however they recognise that diagnosis and treatment may be delayed due to low BGLs.
- They recommend cessation of SGLT-2 inhibitors 24 hours prior to elective surgery11.

If DKA is suspected, SGLT-2 inhibitors should be ceased immediately and the patient should be commenced on an insulin/dextrose infusion according to hospital protocol11.

Conclusion

SGLT-2 inhibitors may pre-dispose patients at risk to serious episodes of diabetic ketoacidosis. Pharmacists provide an important role in monitoring patient parameters, recognising adverse drug reactions and advocating appropriate medication management for patients.