SGLT2 inhibitors and the risk of diabetic ketoacidosis

Abstract
This case report highlights the potentially potent glucose lowering effect of adding an SGLT2 inhibitor to insulin therapy in patients with insulin-treated diabetes. For our patient this had serious, unintended consequences. We describe a 58-year-old lady who had a presumed diagnosis of type 2 diabetes treated with metformin and a twice-daily biphasic insulin regimen. She was commenced on dapagliflozin by her general practitioner and her blood glucose levels fell significantly over a period of several weeks, leading, on occasions, to hypoglycaemia. Consequently, steady insulin dose reductions were made over this period leading eventually to the complete withdrawal of insulin treatment. Within 36 hours of the cessation of insulin treatment the patient was admitted to hospital as an emergency with severe diabetic ketoacidosis (DKA), requiring management on an intensive care unit.

This case highlights that DKA can develop in patients with diabetes treated with insulin and SGLT2 inhibitors. Whether type 1 or type 2 diabetes, the SGLT2 inhibitor can reduce insulin requirements significantly. While the glucose may be falling even into normal ranges, the patient is likely becoming insulinopenic leading to muscle and fat metabolism and ketosis. The importance of this being a recognised consequence of SGLT2 inhibitor therapy was recently highlighted in a US Food and Drug Administration alert. Copyright © 2015 John Wiley & Sons.

Key words
dapagliflozin; SGLT2; diabetes; ketoacidosis

Introduction
Dapagliflozin is an SGLT2 inhibitor which is currently licensed for use as an oral glucose lowering agent in patients with type 2 diabetes. There is also growing interest and a clinical trials programme to explore the use of this drug class alongside insulin therapy for patients with type 1 diabetes.

Dapagliflozin inhibits subtype 2 of the sodium-glucose transport proteins (SGLT2) which are responsible for at least 90% of the glucose reabsorption in the kidney. Blocking this transporter mechanism causes blood glucose to be eliminated through the urine. In clinical trials, dapagliflozin lowered HbA1c by 0.84 percentage points when added to metformin,1 and 0.96 percentage points when added to insulin in patients with inadequately controlled type 2 diabetes.2

Due to its mechanism of action it seems logical that it may be an effective adjunct to insulin in the treatment of type 1 diabetes, with the added benefit of weight loss in obese patients.

Case
This case relates to a 58-year-old woman who had been diagnosed with presumed type 2 diabetes by her GP in January 2013. She had a past medical history of autoimmune hypothyroidism, chronic fatigue syndrome and past gynaecological surgery. She had no family history of diabetes.

preceding her diagnosis she had gained 2–3kg in weight, weighing 85kg at the time of diagnosis, with mild osmotic symptoms. Her HbA1c at diagnosis was 54mmol/mol, with no documented evidence of ketosis around this time. She initially underwent a short trial of diet and exercise, before metformin was added in June 2013 when her HbA1c was 80mmol/mol. She continued on metformin alone, but started home blood glucose monitoring. By March 2014 her blood sugars were consistently above 10mmol/L, reflected in a rise in her HbA1c to 112mmol/mol. There was no evidence of ketosis at that stage. Subsequently, she was started on insulin in May 2014. Initially, she was treated with Insulatard 10–15 units twice daily, but by July 2014 she was switched to a mixed insulin, Insman Comb 25 and titrated to a dose of 30 units twice daily.

In January 2015 her HbA1c had settled to 79mmol/mol but remained above target, with the patient weighing 67kg at this point (an 18kg reduction from diagnosis). At that stage, her GP elected to commence her on dapagliflozin 10mg once daily. The rapid fall in her blood sugars in response to this therapy and
associate a rapid recovery and was discharged from hospital revealing positive GAD antibodies >2000u/ml and low urinary C-peptide ratio 0.73nmol/mmol.

Discussion
We felt that this case highlighted an important pitfall in the use of SGLT2 inhibitors in combination with insulin in patients with diabetes. This coincides with a recent FDA warning regarding the risk of DKA developing in patients treated with this class of drug. A seemingly highly effective therapeutic response in this case led to excessive lowering of blood glucose which in turn led to a flawed clinical decision to withdraw insulin therapy completely. SGLT2 inhibitors are clearly powerful glucose lowering agents in certain circumstances and there may be a danger that they could lead to harmful management of those with insulin-dependent diabetes.

The recent FDA alert was based on a search of the FDA Adverse Event Reporting System (FAERS) database. It identified 20 cases of acidosis reported as diabetic ketoacidosis (DKA), ketoacidosis, or ketosis in patients treated with SGLT2 inhibitors from March 2013 to 6 June 2014. The FAERS cases were not typical for DKA because most of the patients had type 2 diabetes and their blood sugar levels, when reported, were only slightly increased compared to typical cases of DKA. Factors identified in some reports as having potentially triggered the ketoacidosis included major illness, reduced food and fluid intake, and reduced insulin dose.3

The biochemical bases for these metabolic changes have been explored by various research groups. Animal studies reveal a shift to ketone body production in mice treated with SGLT2 inhibitors.4 The authors highlighted the potential metabolic benefits in terms of weight loss, reduced hepatic steatosis and improved insulin resistance. They don’t, however, comment on the risk of ketosis in an insulin deficient state. Within a number of small studies involving the use of SGLT2 inhibitors in type 1 diabetes the cases of patients presenting with DKA have been closely reviewed. Although no direct causal relationship was observed, there was concern regarding the modification of presentation in those admitted in DKA. It was clear that blood glucose levels had been lower than expected for this supports the possibility of euglycaemic DKA occurring.5

Declaration of interests
There are no conflicts of interest declared.

References
References are available at www.practicaldiabetes.com.

Key points
- SGLT2 inhibitors are potentially powerful glucose lowering drugs
- SGLT2 inhibitors added to insulin therapy can lead to ketosis even in light of a normal glucose
- There is clear concern that the use of SGLT2 inhibitors in type 1 diabetes may lead to euglycaemic DKA
- There is also concern in patients with insulin deficient type 2 diabetes that the effectiveness of the SGLT2 inhibitors may lead to insulin withdrawal and potentially DKA
- We would suggest careful consideration when withdrawing insulin in patients with type 2 diabetes

Table 1. The patient’s home capillary blood glucose readings over a 2-month period of dapagliflozin therapy, with concurrent insulin dosing

<table>
<thead>
<tr>
<th>Date</th>
<th>Inuman Comb 25 dose (IU)</th>
<th>Fasting blood sugar (mmol/L)</th>
<th>Pre-lunch blood sugar (mmol/L)</th>
<th>Pre-dinner blood sugar (mmol/L)</th>
<th>Bedtime blood sugar (mmol/L)</th>
</tr>
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<td>12.3</td>
<td>14.5</td>
<td>15.5</td>
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<td>8.7</td>
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<td>17/17</td>
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<td>8.7</td>
<td>7.2</td>
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<td>6.5</td>
<td>9.7</td>
</tr>
<tr>
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<td>2/2</td>
<td>6.4</td>
<td>–</td>
<td>–</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Box 1. Admission bloods and subsequent antibody and C-peptide results:
- pH: 6.84
- Blood sugar: 30.8mmol/L
- Ketones: 5.1mmol/L
- Bicarbonate: 5.6mmol/L
- eGFR: 31ml/min
- CRP: 37mg/L
- GAD: >2000u/ml
- TPO antibodies: negative
- C-peptide/creatinine ratio: 0.73nmol/mmol
References


3. FDA safety alert, 15 May 2015. 'FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood.'
