Canagliflozin-associated Diabetic Ketoacidosis with Lower-than-anticipated Glucose Levels

Sonali Vadi, Manjusha Agarwal

Departments of Critical Care Medicine and Internal Medicine, Gleneagles Global Hospitals, Mumbai, Maharashtra, India

Abstract

The Food and Drug Administration has approved the use of sodium-glucose co-transporter 2 (SGLT-2) inhibitors for use in Type II diabetics. These are a relatively new addition to the armamentaria of diabetes management. Postmarketing surveillance is a witness to several side effects, a morbid one being ketoacidosis. Herein is discussed a scenario of a Type II diabetic who presented with substantial ketoacidosis without significant hyperglycemia. The absence of the customary precipitating factors and the presence of a recent introduction of canagliflozin, a SGLT-2 inhibitor to the diabetes prescription, hinted at the causal relationship. Of note, she had never experienced diabetic ketoacidosis in the past prior to commencement of SGLT-2 inhibitor therapy. As clinicians, we need to be aware of the treatment-emergent adverse effect of this relatively new class of diabetic treatment.

Keywords: Canagliflozin, diabetic ketoacidosis with lower-than-anticipated glucose levels, euglycemic diabetic ketoacidosis, sodium-glucose co-transporter 2 inhibitors

Introduction

As clinicians, we need to be aware that medications used for disease management can paradoxically induce effects, causing an already sick patient to become worse. Sodium-glucose co-transporter 2 (SGLT-2) inhibitors, a fairly recent addition to the pool of diabetes medications, are associated with a variety of side effects, the fatal one being ketoacidosis. This adverse effect reported in the postmarketing surveillance significantly adds to the morbidity of illness. Herein is discussed this treatment-emergent adverse effect that clinicians need to be aware of.

Case Report

A middle aged lady presented to the emergency room with nausea and emesis for 4 days, fever for 2 days, and malaise. Her medical comorbidities included Type II diabetes, hypertension, and hypothyroidism. Her body mass index was 22.3 kg/m². Hospitalized a month ago for community-acquired pneumonia, she was discharged on a combination of glimepiride-metformin, teneligliptin, human actrapid insulin, and canagliflozin as an add-on. Her serum glycosylated hemoglobin levels were at 11.1% then. At a follow-up 15 days later following an improvement in her glucose control, insulin was discontinued. Initially admitted to the floors with the said complaints, she was later transferred to the Intensive Care Unit following severe metabolic acidosis with serum bicarbonate levels at 3.3 mmol/L and pH at 6.89 on her arterial blood gas. She complained of dryness of mouth and was very thirsty. Clinically dehydrated, she was administered intravenous fluids. Other medications included intravenous sodium bicarbonate, human actrapid insulin infusion titrated as per the glucose levels, and symptomatic treatment for her gastrointestinal symptoms. Severe metabolic acidosis without very high serum glucose levels and the contemporaneous existence of canagliflozin raised the suspicion of diabetic ketoacidosis (DKA) with lower-than-anticipated glucose levels. Table 1 shows the acid–base results while Table 2 depicts the fingerstick glucose levels on the day of presentation. Meanwhile, other laboratory results returned as normal complete blood count, blood urea nitrogen at 12 mg/dl (normal: 9.8–20.1 mg/dl), serum creatinine at 1.4 mg/dl (normal: 0.57–1.11 mg/dl), serum D3-Hydroxybutyrate

Canagliflozin-associated Diabetic Ketoacidosis with Lower-than-anticipated Glucose Levels

Sonali Vadi, Manjusha Agarwal

Departments of Critical Care Medicine and Internal Medicine, Gleneagles Global Hospitals, Mumbai, Maharashtra, India

Access this article online

Quick Response Code:
Website: www.ijccm.org
DOI: 10.4103/ijccm.IJCCM_328_17

Address for correspondence: Dr. Sonali Vadi, Gleneagles Global Hospital, 35 E. Borges Road, Parel, Mumbai - 400 012, Maharashtra, India. E-mail: sonalivadi@hotmail.com

How to cite this article: Vadi S, Agarwal M. Canagliflozin-associated diabetic ketoacidosis with lower-than-anticipated glucose levels. Indian J Crit Care Med 2017;21:793-5.
Table 1: Arterial blood gas results on the day of presentation

<table>
<thead>
<tr>
<th>Time</th>
<th>Location</th>
<th>pH</th>
<th>PaCO₂ (mmHg)</th>
<th>PaO₂ (mmHg)</th>
<th>HCO₃⁻ (mmol/L)</th>
<th>Lactate (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0044</td>
<td>Floors</td>
<td>6.89</td>
<td>17.2</td>
<td>56.3</td>
<td>3.3</td>
<td>1.35</td>
</tr>
<tr>
<td>0236</td>
<td>ICU</td>
<td>7.08</td>
<td>18.3</td>
<td>160.1</td>
<td>5.5</td>
<td>1.08</td>
</tr>
<tr>
<td>0908</td>
<td>ICU</td>
<td>7.17</td>
<td>13.1</td>
<td>150.3</td>
<td>4.8</td>
<td>0.59</td>
</tr>
<tr>
<td>1612</td>
<td>ICU</td>
<td>7.37</td>
<td>25.8</td>
<td>112</td>
<td>14.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

ICU: Intensive Care Unit

Table 2: Fingerstick glucose trends

<table>
<thead>
<tr>
<th>Time</th>
<th>0200</th>
<th>0400</th>
<th>0500</th>
<th>0600</th>
<th>0700</th>
<th>0800</th>
<th>1000</th>
<th>1200</th>
<th>1400</th>
<th>1600</th>
<th>1800</th>
<th>2000</th>
<th>2200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingerstick glucose levels (mg/dl)</td>
<td>215</td>
<td>240</td>
<td>295</td>
<td>205</td>
<td>109</td>
<td>150</td>
<td>161</td>
<td>174</td>
<td>140</td>
<td>146</td>
<td>152</td>
<td>169</td>
<td>199</td>
</tr>
</tbody>
</table>

at 11.79 mmol/L (normal: 0.02–0.27 mmol/L), serum potassium at 6.0 mEq/L (without simultaneous electrocardiogram changes), anion gap: 24, measured serum osmolality: 330 mOsm/kg (normal: 275–300 mOsm/kg), and serum glycosylated hemoglobin levels at 11.1%. Calculated serum osmolality was 306 with osmolar gap of 24 mOsm/kg. Ultrasound of her abdomen was nonreveleatory.

Clinical recovery was evident within the following 24 h with an improvement of acidosis and stabilization of serum glucose levels. Seventy-two hours later, she was transferred back to the floors and later discharged on oral hypoglycemic agents without canagliflozin. At 6-month follow-up, her serum glucose levels have remained well under control without any further episodes of euglycemic DKA.

**Discussion**

Approved by the Food and Drug Administration (FDA) and released for use in 2013, SGLT-2 inhibitor canagliflozin acts by blocking glucose reabsorption in the proximal renal tubules with a resultant glycosuria.\(^1\) Pancreas decreases its insulin secretion following a reduction in blood glucose. Ensuing increased glucagon-to-insulin ratio\(^2\) leads to gluconeogenesis, ketogenesis,\(^3\) and a consequent ketoacidosis.\(^4,5\) In the same vein, these effects are pronounced following a reduction in insulin intake.\(^6\) On the other hand, given the inhibition of glucose reabsorption at the renal tubular level, an advantage of this group of medication is that the occurrence of hyperglycemia is moderated without consequent hypoglycemia.\(^7\) This combination of ketoacidosis without significantly elevated serum glucose levels is euglycemic DKA with lower-than-anticipated glucose levels.\(^8\) Postmarketing surveillance has seen the occurrence of DKA following the use of canagliflozin. The FDA issued a warning in May 2015 about SGLT-2 inhibitors leading to ketoacidosis\(^9\) that was updated in December 2015. Reported triggers for occurrence of ketoacidosis in patients on SGLT-2 inhibitors include acute illness, sepsis, recent surgery, starvation, decrease in carbohydrate intake, decrease in insulin intake, and significant changes in the level of physical activity, or pregnancy.\(^8,10\)

Given her symptomatic presentation with nausea, emesis, and feeling thirsty with a background of uncontrolled blood glucose levels, a diagnosis of DKA was entertained. However, severe acidosis with high serum D3-Hydroxybutyrate levels and modestly elevated serum glucose levels in the presence of a SGLT-2 inhibitor prescription led to the diagnosis of DKA with lower-than-anticipated glucose levels. Given a satisfactory glycemic control about 2 weeks later and to prevent the occurrence of hypoglycemia, insulin was discontinued. This stoppage of insulin was the likely trigger factor for DKA with lower-than-anticipated glucose levels in the scenario. She was managed on the lines of a standard DKA protocol.\(^9\) Of note, she had never been hospitalized in the past for DKA prior to commencing SGLT-2 inhibitor.

Thus, ketoacidosis in the absence of marked hyperglycemia should alert an astute physician about DKA with lower-than-anticipated glucose levels in a diabetic on a SGLT-2 inhibitor prescription. Additionally, it would be prudent to add SGLT-2 inhibitors to the existent list of etiologies for DKA with lower-than-anticipated glucose levels.

**Conclusion**

On the spectrum of DKA lies DKA with lower-than-anticipated glucose levels that is characterized by ketoacidosis without significant hyperglycemia. The discussed scenario highlights the significance of the existence of an ominous off-shoot of SGLT-2 inhibitors, DKA with lower-than-anticipated glucose levels, the occurrence of which can be possibly predicted by urine or serum ketone testing in symptomatic individuals despite the absence of significant hyperglycemia. As clinicians, we need to be aware about this life-threatening treatment-emergent adverse effect of SGLT-2 inhibitors which have recently been added to the armamentarium of diabetes management.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

7. Chao EC. SGLT-2 inhibitors: A new mechanism for Glycemic control.