Safety of use of sodium-glucose co-transporter-2 inhibitors in patients with COVID-19

Nasser Mikhail1 and Soma Wali

1Division of Endocrinology, Department of Medicine, Olive-view-UCLA Medical Center, David-Geffen-UCLA Medical School, CA, USA

*Corresponding Author: Nasser Mikhail, Division of Endocrinology, Department of Medicine, Olive-view-UCLA Medical Center, David-Geffen-UCLA Medical School, CA, USA

Received date: March 08, 2021; Accepted date: March 24, 2021; Published date: March 27, 2021

Citation: Mikhail N. and Wali S. (2021) Safety of use of sodium-glucose co-transporter-2 inhibitors in patients with COVID-19, International J. of Biomed Research 1(2); DOI: 10.31579/IJBR-2021/007

Copyright: © 2021 Nasser Mikhail, This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background: Theoretical benefits exist regarding the use of sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients hospitalized with coronavirus disease 2019 (COVID-19). However, the safety of these agents is not established in this setting.

Objective: To present an update on the safety of the use of SGLT2 inhibitors in patients with COVID-19.

Methods: Pubmed search up to March 8, 2021. Search terms included SGLT2 inhibitors, diabetes, diabetic ketoacidosis, safety, mortality, empagliflozin, dapagliflozin, canagliflozin, ertugliflozin. Randomized trials, retrospective studies, case reports, pertinent reviews, and guidelines of professional societies are reviewed.

Results: In non-COVID-19 subjects with type 2 diabetes, the risk of euglycemic DKA may be significantly elevated during hospitalization. Risk factors of development of euglycemic DKA with SGLT2 inhibitors include infection, fasting, and surgery, i.e. factors commonly encountered in the hospital setting. Available evidence from retrospective studies suggest that outpatient use of SGLT2 inhibitors does not affect susceptibility to develop COVID-19. Twelve cases of euglycemic diabetic ketoacidosis (DKA) were described among hospitalized COVID-19 patients who were using SGLT2 inhibitors, 11 cases with type 2 diabetes and a single patient with type 1 diabetes. Besides, 5 other patients were reported as part of case series, making the total number 17 cases. Current guidelines recommend that the use of SGLT2 inhibitors should be avoided in the hospital setting. A randomized well-designed trial is underway to evaluate the benefits and safety of dapagliflozin in hospitalized COVID-19 patients with and without type 2 diabetes.

Conclusions: The risk of euglycemic DKA due to SGLT2 inhibitors is markedly increased in hospitalized patients. SGLT2 inhibitors should be discontinued after hospital admission in all patients including those with COVID-19 until their safety and efficacy become established by randomized trials.

Keywords: SGLT2 inhibitors, COVID-19, euglycemic diabetic ketoacidosis, safety, mortality

Introduction

In the last few years, strong evidence emerging from well-designed randomized trials showed a significant reduction in cardiovascular and renal events, and overall mortality with the use of various SGLT2 inhibitors [1-4]. These benefits were equally demonstrated among patients with and without type 2 diabetes [2, 4]. The rationale of using SGLT2 inhibitors in patients with COVID-19 is based on 2 main theories. First, SGLT2 inhibitors may exert anti-inflammatory actions and therefore may virtually suppress excess cytokine release i.e. cytokine storm, the main reason for respiratory failure in severe COVID-19 [5]. Second, since certain cases of COVID-19 may be complicated by cardiac and kidney failure [6, 7], it is hoped that SGLT2 inhibitors might provide cardiorenal protection in patients with COVID-19 similar to non-COVID-19 subjects. However, there are several concerns about the previous 2 theories. Firstly, the pathophysiology of chronic cardiac and renal disease due to type 2 diabetes and other pre-existing disorders may be distinct from that of cardiac and renal complications that occur acutely in COVID-19. Secondly, there is very limited data regarding the use of SGLT2 inhibitors in the hospital setting. In a pilot randomized study from Netherlands conducted before the COVID-19 pandemics, Damman et al [8] evaluated the efficacy and safety of empagliflozin (10 mg/d) versus placebo for 30 days in 80 hospitalized patients with acute heart failure. Empagliflozin did not have significant effects on any components of the primary outcome that included: dyspnea score, diuretic response, change in N-terminal pro brain natriuretic peptide (NT-proBNP), and length of hospital stay [8]. While no excess adverse effects were noted with empagliflozin compared with placebo, this trial was too small and patients with severe co-morbidities were excluded [8]. Further studies are needed to better evaluate the safety and efficacy of SGLT2 inhibitors in hospitalized patients with COVID-19.
Safety of SGLT2 inhibitors in patients with type 2 diabetes without COVID-19

Diabetic ketoacidosis (DKA) is uncommon, but serious adverse effect of all SGLT2 inhibitors. It is commonly described as “euglycemic” DKA because plasma glucose levels are commonly below 250 mg/dl [9-11]. In a large retrospective study from the state of Victoria in Australia, Hamblin et al [12] estimated that the incidence of DKA was 1.02 per 1000 (95% CI 0.74-1.41) in users of SGLT2 inhibitors versus 0.69 per 1000 (95% CI 0.58-0.82) in non-users; odds ratio (OR) 1.48 (95% CI 1.02-2.15; P=0.037). Mechanisms of euglycemic DKA associated with the use of SGLT2 inhibitors include: fasting (leading to decrease insulin release), stress of infection (leading to release of anti-insulin hormones), and surgery (frequently associated with fasting, stress, and holding insulin) [9-11]. Since hospitalization may involve all these risk factors, it is not surprising that the incidence of DKA markedly rises among hospitalized patients who were treated with SGLT2 inhibitors. In fact, the study of Hamblin et al [12] showed that during hospitalization, DKA developed in 38% of patients with type 2 diabetes using SGLT2 inhibitors compared with 2% among patients with type 2 diabetes using other diabetes medications, OR 37.4 (95% CI 8.0-175.9; P<0.001).

SGLT2 inhibitors and susceptibility to COVID-19

In a retrospective study from UK, Sainsbury et al [13] compared the risk of having COVID-19 (confirmed or clinically suspected) between patients prescribed SGLT2 inhibitors and another group of patients prescribed di-peptidyl peptidase-4 (DPP-4) inhibitors after propensity score matching (n=7,676 subjects in each group). No significant difference in development of COVID-19 was found between the 2 groups, with incidence rates of 19.7/1000 person-years and 24.7/1000 person-years in the SGLT2 inhibitors and DPP-4 inhibitors, respectively (adjusted hazard ratio 0.92 (95% CI: 0.66-1.29) [13].

Safety of outpatient use of SGLT2 inhibitors in COVID-19

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient’s age and gender, type of diabetes</th>
<th>Type and dose of SGLT2 inhibitor</th>
<th>Plasma glucose levels on diagnosis of DKA (mg/dl)</th>
<th>Outcomes/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitale et al [15]</td>
<td>79-year-old man with type 2 diabetes</td>
<td>Empagliflozin mg/d</td>
<td>286</td>
<td>Discharged on HD 47 days</td>
</tr>
<tr>
<td>Vitale et al [15]</td>
<td>52-year-old man with type 2 diabetes</td>
<td>Empagliflozin mg/d</td>
<td>146</td>
<td>Death at HD 18 from ARDS</td>
</tr>
<tr>
<td>Vitale et al [15]</td>
<td>69-year-old man with type 2 diabetes</td>
<td>Empagliflozin mg/d</td>
<td>166</td>
<td>Discharged on HD 33</td>
</tr>
<tr>
<td>Vitale et al [15]</td>
<td>53-year-old woman with type 2 diabetes</td>
<td>Empagliflozin mg/d</td>
<td>151</td>
<td>Discharged on HD 11</td>
</tr>
<tr>
<td>Vitale et al [15]</td>
<td>70-year-old woman with type 2 diabetes</td>
<td>Canagliflozin mg/d</td>
<td>190</td>
<td>Discharge on HD 28</td>
</tr>
<tr>
<td>Dass et al [16]</td>
<td>59-year-old woman with type 2 diabetes</td>
<td>Empagliflozin (dose not reported)</td>
<td>154</td>
<td>Discharge (HD not reported)</td>
</tr>
<tr>
<td>Gorthi et al [17]</td>
<td>65-year-old male with type 2 diabetes</td>
<td>Empagliflozin (dose not reported)</td>
<td>158</td>
<td>Discharge on HD 15</td>
</tr>
<tr>
<td>Palermo et al [18]</td>
<td>53-year-old woman with type 2 diabetes</td>
<td>Empagliflozin mg/d</td>
<td>192</td>
<td>HD not reported</td>
</tr>
<tr>
<td>Oriot and Hermans [19]</td>
<td>60-year-old with type 1 diabetes</td>
<td>Empagliflozin mg/d</td>
<td>232</td>
<td>Discharge from intensive care after 6 weeks</td>
</tr>
<tr>
<td>Batista et al [20]</td>
<td>56-year-old man with type 2 diabetes</td>
<td>Empagliflozin mg/d</td>
<td>118</td>
<td>Discharge on HD 20</td>
</tr>
<tr>
<td>Morrison et al [21]</td>
<td>Man in “his 40s”</td>
<td>Empagliflozin mg/d</td>
<td>177</td>
<td>Discharge on HD 4</td>
</tr>
</tbody>
</table>

Israel et al [14] retrieved data from nationwide registries in Denmark to compare outcomes of COVID-19 between patients using SGLT2 inhibitors (n=342), glucagon-like peptide 1 receptor agonists (GLP-1 RA) (n=370) and DPP-4 inhibitors (n=284). Of note, most patients had COVID-19 of mild severity because less than 30% of them were hospitalized [14]. The adjusted relative risk (RR) for 30 day-mortality, the primary outcome, of GLP-1 RA vs SGLT-2 inhibitors was not significant being 0.89 (95% CI 0.34-2.33). The corresponding RR of DPP-4 inhibitors vs SGLT2 inhibitors was 2.42 (0.99-5.89), which was close to statistical significance [14]. Risks of hospital admission, intensive care unit admission, and mechanical ventilation were overall similar between the 3 drug classes [14]. This study provides reassurance about the safety of SGLT2 inhibitors in patients with COVID-19 before hospitalization. However, it was not known from this study, whether patients continued or stopped SGLT2 inhibitors after admission.

Safety of SGLT2 inhibitors in hospitalized patients with COVID-19

A review of the literature up to March 8, 2021 revealed a total of 12 cases of euglycemic DKA attributed to the use of SGLT2 inhibitors in patients with COVID-19 admitted to the hospital (summarized in table 1) [15-22]. The vast majority of patients had type 2 diabetes, with only one case reported with type 1 diabetes [18]. In 10 cases, empagliflozin was the implicated SGLT2 inhibitor, and in 1 case canagliflozin was the culprit (Table 1). In addition, 5 more cases of DKA associated with SGLT2 inhibitors were reported in patients with COVID-19 but mentioned as part of case series among other cases of DKA unrelated to SGLT2 inhibitors [23-25]. Thus, at least 17 cases of euglycemic DKA were described in relation with SGLT2 inhibitors in hospitalized COVID-19 patients with diabetes. However, this number is likely an underestimation as medication history may not be completely obtained from acutely ill patients with severe COVID-19. Interestingly, in 10 of the 12 patients depicted in table 1, plasma or blood glucose levels were below 200 mg/dl at the time of diagnosis consistent with euglycemic DKA. This observation implies high index of alertness by providers to avoid delay in diagnosis.
Abbreviations
DKA: diabetic ketoacidosis, HD: hospital day, ARDS: acute respiratory distress syndrome.

<table>
<thead>
<tr>
<th>Fang et al [22]</th>
<th>52-year-old man</th>
<th>Empagliflozin (dose not reported)</th>
<th>113</th>
<th>Patient stopped all medications 2 days before admission.</th>
</tr>
</thead>
</table>

Table 1. Cases of euglycemic diabetic ketoacidosis in patients with diabetes and COVID-19 taking SGLT2 inhibitors

Current status of in-hospital use of SGLT-2 inhibitors

In view of the increasing number of DKA episodes recorded in hospitalized patients in general receiving SGLT2 inhibitors, the latest guidelines released by the American Diabetes Association (ADA) stated that SGLT2 inhibitors are not recommended for routine in-hospital use and should be avoided in all cases of severe illness [26]. Moreover, the Federal Drug Administration (FDA) has warned that SGLT2 inhibitors should be stopped 3 days before scheduled surgery (4 days in case of ertugliflozin) [26].

Initiation of SGLT2 inhibitors in hospitalized patients with COVID-19

Very limited data exist regarding the initiation of SGLT2 inhibitors in patients with COVID-19 but without diabetes after hospital admission. In a brief report from Italy, Bossi et al [27] started off-label empagliflozin 10 mg/d in 3 non-diabetic patients (aged 50-60-year-old) immediately after their hospitalization with COVID-19 pneumonia. Treatment with empagliflozin lasted for 5-7 days without any improvement in their clinical condition [27-28].

The DARE-19 trial

That SGLT2 inhibitors might reduce cardiorenal events and mortality in hospitalized patients with COVID-19 clearly requires conduct of well-designed clinical trials to test this hypothesis. From April 15, 2020, a randomized double-blind international trial called the “Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19) started [29]. DARE-19 will randomize 900 hospitalized COVID-19 patients in 1:1 ratio to either dapagliflozin 10 mg/d or placebo [29]. In addition to COVID-19 respiratory involvement, inclusion criteria include any one of the following: type 2 diabetes, hypertension, chronic kidney disease stage 3-4 (eGFR between 25-60 ml/min/1.73 m^2) [29]. Key exclusion criteria include type 1 diabetes, history of DKA, and expected need for mechanical ventilation [29]. The primary endpoint will be the time to the first occurrence of all-cause mortality or new/worsened organ dysfunction through 30 days of follow-up [29]. The safety of dapagliflozin is one of the main objectives of DARE-19 trial. Thus, careful monitoring of acid-base balance and serum bicarbonate is mandated.

Conclusions and current needs

Strong evidence derived from large randomized trials has shown beneficial effects of SGLT2 inhibitors with for reduction of cardio-renal events and mortality in outpatients with and without type 2 diabetes. No major safety concerns emerged in these trials [1-4]. (Delete) Meanwhile, the safety and efficacy of SGLT2 inhibitors were not adequately evaluated in hospitalized patients. This issue is crucial because hospitalized patients are particularly vulnerable to develop euglycemic DKA as an adverse effect of SGLT2 inhibitors. Therefore, the use of SGLT2 inhibitors should be avoided in the hospital setting in general. Patients hospitalized with COVID-19 may be even more prone to develop euglycemic DKA as result of multiple co-morbidities, infection, critical illness, and fasting. Results of the ongoing trial DARE-19 will be helpful to determine the safety and efficacy of dapagliflozin in hospitalized patients with COVID-19 [29].

Conflict of interest

The authors do not have any conflict of interest to declare.

References


