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Case Report

Case Report: Prolonged Ketoacidosis in Sodium-Glucose Transport-2 Inhibitor (SGLT2i) User

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Abstract

Background: Sodium Glucose Transport-2 inhibitors (SGLT2i), initially approved for diabetes treatment, have demonstrated clinical benefits in heart failure and renal disease. Despite their increasing use, the potential for adverse drug events necessitates appropriate prescribing information. Notably, ketoacidosis is a significant complication associated with SGLT2i, leading to various complications, including renal, neurological, respiratory, and cardiac issues. Prolonged episodes of ketoacidosis are being increasingly common and this case report details a prolonged episode of diabetic ketoacidosis in a SGLT2i user.

Case Presentations: A 54-year-old male, admitted to the ICU for Diabetic Ketoacidosis (DKA), was using a SGLT2i at home. After three days of IV insulin treatment, his acidosis resolved. On day 4, transitioning to subcutaneous insulin led to a recurrence of acidosis. Monitoring continued, and by day 7, acidosis resolved again. The patient's beta-hydroxybutyric acid remained detectable for the first 9 days. Prolonged ketoacidosis was attributed to SGLT2i use in the context of poor renal function.

Conclusions: This case underscores the risk of prolonged ketoacidosis associated with SGLT2i use, especially in patients with compromised renal function. The report contributes to the growing literature on extended durations of acidosis secondary to SGLT2i use, emphasizing the need for heightened awareness, careful monitoring, and tailored interventions to mitigate adverse outcomes.

Keywords: SGLT2 Inhibitors; Euglycemic DKA; Hyperglycemic DKA; Diabetic ketoacidosis duration; Metabolic profiles

Introduction

Sodium-Glucose co-Transporter 2 inhibitors (SGLT2i) are an innovative class of oral antihyperglycemic drugs that function by inhibiting renal glucose reabsorption, thus promoting glucosuria and reducing blood glucose levels. SGLT2i's were initially approved for diabetes treatment, and have since demonstrated clinical benefits in heart failure and renal disease [1]. Despite their increasing use, the potential for adverse drug events necessitates appropriate prescribing education. DKA is a rare complication associated with SGLT2i use with reported incidence rates ranging from 0.6 to 2.2 events per 1,000 person-year in studies [2]. Several case reports have noted prolonged ketoacidosis related to SGLT2i use, with potential contributing factors including the slow dissociation rate from SGLT2 transporter, genetic polymorphisms, decreased renal function, and the lipophilicity of the drug [3]. Episodes of ketoacidosis are considered prolonged when the resolution extends beyond 24 hours [4]. This phenomenon is being increasingly common and may complicate a patient's clinical course. While case reports and case series have previously documented prolonged episodes of ketoacidosis resulting from SGLT2i use, the prevalence of this occurrence remains largely uncertain [3,8,15]. This case report provides a detailed account of a prolonged episode of DKA in a patient using a SGLT2i.

Case Presentation

A 54-year-old male presented to the Emergency Department (ED) with general weakness, rapid atrial fibrillation and DKA. He had a 4-day history of feeling weak with severe nausea and vomiting over the last 48 hours prior to ED visit. He had very little to eat in the last 48 hours. He denied any chest pain, syncope,

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Table 1: Laboratory values and metabolic panel.

Admission	HbA1C (%)	Blood glucose (mg/L)	pH	Bicarb (mmol/L)	Anion Gap (mmol/L)	BHOB (mmol/L)	Creatinine (mg/dL)	Treatment
Day (presentation)	13.7	800 (44.4 mmol/L)	7.0	7	27		2.32 (205 mmol/L)	IV Insulin Regular 2.4 units/kg/hr
Day 1		428 (23.8 mmol/L)	7.15	12.6	26	11.3	1.41 (125 mmol/L)	IV Insulin Regular 2.8 units/kg/hr
Day 3		228 (12.7 mmol/L)	7.32	16.8	13		1 (88 mmol/L)	IV Insulin Regular 1 unit/kg/hr
Day 4		210 (11.7 mmol/L)	7.28	17.9	17	5.35	1.09 (96 mmol/L)	Insulin Glargine 20 units SC daily
Day 5		367 (20.4 mmol/L)	7.24	15.3	21	3.23	0.94 (83 mmol/L)	Insulin Glargine 20 units SC daily
Day 7		207 (11.5 mmol/L)			10	1.90	0.83 (73 mmol/L)	Insulin Degludec 30 units SC daily
Day 8		267 (14.8 mmol/L)			13	2.64	0.8 (71 mmol/L)	Insulin Degludec 30 units SC daily
Day 9		193 (10.7 mmol/L)	7.41	32.3	11	1.89	0.79 (70 mmol/L)	Insulin Degludec 30 units SC daily

DKA: Diabetic Ketoacidosis
HbA1C: Hemoglobin A1C%
BHOB: Beta-hydroxybutyric acid
Bicarb: Bicarbonate

palpitations or dyspnea. He also did not have any cough, fever, expectorant, diarrhea, no signs and symptoms of bleeding. The patient had a history of type II diabetes, hypertension and dyslipidemia. His medical conditions were being managed with Empagliflozin 10 mg daily, Glyburide 5 mg twice daily, Metformin 1000 mg twice daily, Atorvastatin 20 mg daily, Ramipril 10 mg daily and Aspirin 81 mg daily. Regarding his diabetes history, the patient received a diagnosis of type 2 diabetes approximately five years prior his admission. Initially, he was prescribed Metformin, and over the first two years, the dosage was gradually increased to 2000 mg per day. In his third-year post-diagnosis, Glyburide was added to his treatment regimen as his hemoglobin A1C% (HbA1C%) remained above target at 7.4%. Despite these medications, over the next two years, his HbA1C level continuously increased to 11.2% two months before admission, prompting his family physician to introduce a third agent, the SGLT2i Empagliflozin. Upon admission, the patient was taking a combination of Metformin, Glyburide, and Empagliflozin. However, due to feeling unwell, experiencing nausea and vomiting in the 48 hours leading up to his admission, he had not taken any of his diabetes medications.

Additionally, the patient stated to be a non-smoker and reported no consumption of alcohol or illicit substances. However, the patient did report a slight increase in weight over the last year, and admitted to a poor baseline glucose control with levels ranging from 215 to 320 mg/dL (12 to 17 mmol/L). Of note, his kidney function was normal prior to admission with a creatinine of 1.04 mg/dL (92 umol/L).

In the emergency department, the patient had a temperature of 35.8°C, blood pressure of 112/53 mmHg, heart rate of 166 bpm, a respiratory rate of 22 bpm and a SpO2 of 100%. He received 15 mg of Diltiazem intravenously for suspected atrial fibrillation as patient presented with tachycardia with premature atrial complexes on his initial electrocardiogram. Importantly, his initial laboratory values showed a glucose of 800 mg/dL (44.4 mmol/L). His initial blood gas analysis revealed a pH of 7.00, bicarbonate level of 7 mmol/L, and an anion gap of 27 mmol/L. Additionally, his ketone (beta-hydroxybutyric acid) concentration was measured at 11.30 mmol/L. Based on these findings, he was diagnosed with DKA, characterized by a pH below 7.30, an elevated Anion Gap (AG) metabolic acidosis (AG >12 mmol/L and bicarbonate [HCO3] <24 mmol/L), and elevated ketone levels. To address his hyperglycemic presentation, 10 units of rapid insulin was administered subcutaneously. Following hospital protocol, intravenous fluids were initiated to manage the suspected DKA and the severe dehydration reported over the last few days. With an estimated fluid loss of 6 to 9 liters in typical DKA presentations, 50% of the total volume loss was administered upon admission. The patient was initially given 2 liters of normal saline, followed by Ringer's Lactate at a rate of 100 mL/hour for an additional 2 liters.

A septic work-up was completed and his laboratory values demonstrated an elevated white blood cell count of 19.8 x10^9/L, a creatinine of 2.32 mg/dL (205 mmol/L), an eGFR of 35 mL/min, and a corrected sodium of 147 mmol/L.

Investigations

Chest X ray on admission and day 2 of visit demonstrated cardio-mediastinal contours within normal limits and clear lungs. Both urine and blood cultures were negative on admission. Subsequent electrocardiograms on admission demonstrated atrial fibrillation. An echocardiogram on admission day 4 demonstrated a mildly dilated left ventricular size and a ventricular ejection fraction of 41%.

Treatment

In the emergency department, he was promptly initiated on Ceftriaxone for possible infection of which the source was unknown. In regards to his home medications, Empagliflozin, Glyburide, Metformin and Ramipril were not continued on admission given his dehydrated status. For his DKA, the patient was administered Insulin regular IV infusion at 10 units/hour and titrated as per glycemia based on institutional protocol. He was also administered dextrose 10% IV along with potassium-containing IV maintenance fluids and transferred to the Intensive Care Unit (ICU). The above regimen was administered for 24 hours and the following day (post-admission day 1) his blood gas was reevaluated; pH of 7.15, bicarbonate of 12.6 mmol/L and an anion gap of 26 mmol/L. His beta-hydroxybutyric acid was 11.3 mmol/L and his hemoglobin A1C result on admission was 13.7%. Given the small improvements in his metabolic profile, the decision was made to continue the DKA protocol with insulin regular IV infusion.

On admission day 4, the patient's blood gas demonstrated

a pH of 7.28, bicarbonate of 17.9 mmol/L and an anion gap of 17 mmol/L. The patient's beta-hydroxybutyric acid was also reducing now at 5.35 mmol/L. Given the improvements in the patient's clinical status and bloodwork, the decision was made to transition the patient to long-acting insulin Glargine along with sliding scale rapid acting insulin aspart. The following day, on admission day 5, the patient become more acidotic with a pH decreased to 7.24, bicarbonate decreased to 15.3 mmol/L and his anion gap increased to 21 mmol/L. Given the patient was otherwise clinically stable, he was maintained on the same insulin regimen. Furthermore, it is crucial to emphasize that no new medications initiated, and no additional electrolyte or metabolic abnormalities identified to account for the exacerbation of acidosis. On admission day 7, his anion gap was normalizing again at 10 mmol/L and his beta-hydroxybutyric acid was 1.90 mmol/L. His glucose levels remained persistently elevated and the decision was made to initiate ultra-long acting insulin Degludec instead of Glargine for a more stable and prolonged blood glucose lowering effect. On admission day 8, the patient's anion gap increased slightly to 13 mmol/L with a rise in his beta-hydroxybutyric acid. Again, the patient was clinically stable and so no immediate changes were made to his insulin regimen. As of admission day 9, the patient still had detectable ketones in his blood with a beta-hydroxybutyric acid of 1.89 mmol/L (Table 1).

Given the patient's elevated HbA1C% of 13.7% upon admission, the treatment plan involved maintaining the patient on a basal-bolus insulin regimen. This regimen consisted of insulin Aspart, administered subcutaneously at meal times (5 to 10 units as per sliding scale), and insulin Degludec, administered subcutaneously at bedtime. Concurrently, the medications Metformin, Glyburide, and Empagliflozin were discontinued. Follow-up care was arranged at the outpatient diabetes clinic in two weeks. Prior to discharge, the patient received comprehensive diabetes education covering various aspects such as lifestyle modifications (including dietary adjustments to avoid high glycemic foods, exercise, and stress management), insulin administration and dosage adjustment, as well as the risks associated with hypo- and hyperglycemia, including guidelines for seeking medical assistance when necessary.

Discussion

SGLT2i lead to ketoacidosis through mechanisms initiated by glycosuria—the increased urinary excretion of glucose resulting from these drugs preventing glucose reabsorption in the kidneys [5]. This leads to a reduction in blood glucose levels, thereby reducing the need for insulin, which is essential for glucose uptake by cells for energy. The diminished insulin availability impairs glucose entry into cells, pushing the body to switch to alternative energy sources like burning fats (lipid oxidation) and producing glucose from non-carbohydrate sources (gluconeogenesis). This metabolic shift not only leads to the production of ketone bodies as a by-product of fat metabolism but is also amplified by an increase in glucagon release. Glucagon, which counters insulin, promotes glucose and ketone production in the liver, especially under low insulin conditions. The combined effect of lipid oxidation and gluconeogenesis, fueled by the imbalance between glucagon and insulin due to SGLT2i, culminates in an increased production of ketones, setting the stage for ketoacidosis [5]. Furthermore, beyond the previously discussed processes, it has been proposed that SGLT2i could decrease the kidney's ability to clear ketone bodies, potentially by increasing the reabsorption of ketones in the kidney tubules that have been filtered from the blood. This occurs due to the inhibition of sodium reabsorption mediated by SGLT2i, which leads to an increase in sodium concentrations in the renal tubular fluid. As a result, the elevated sodium levels enhance the electrochemical gradient responsible for the carrier-mediated reabsorption of negatively charged ketone bodies [6].

Together, these mechanisms—increased glycosuria leading to reduced glycemia and insulin release, a shift in energy metabolism towards lipid oxidation, elevated glucagon levels and ketogenesis along with and tubular reabsorption of ketones—converge to create an environment conducive to the production and accumulation of ketone bodies, setting the stage for ketoacidosis in individuals taking SGLT2i.

To determine the probability of the SGLT2i being responsible for this adverse event in this case, the Naranjo Adverse Reaction Probability scale was utilized, yielding a total score of +5. This score suggests that the prolonged ketoacidosis episode was likely induced by the SGLT2i. It is noteworthy that due to the absence of drug re-introduction, varying dosages, and serum concentration monitoring, precise interpretation of the Naranjo Probability scale is challenging. In light of the numerous emerging cases documented and our evolving comprehension of the mechanism of action of SGLT2i concerning ketone production and reabsorption, coupled with the absence of any other plausible explanation for this metabolic phenomenon, we have concluded that the SGLT2i is implicated in this adverse event [7,8].

In our analysis of the patient's prolonged episode of DKA, the primary hypothesis centers around the accumulation of the SGLT2i due to decreased renal clearance. This scenario is particularly plausible given that the patient was admitted with an acute kidney injury, a condition that significantly impairs the body's ability to eliminate drugs, especially those, like SGLT2i, that are primarily excreted by the kidneys. This impaired elimination likely led to prolonged drug effects, including sustained ketone reabsorption, which was observable up to the ninth day of the hospital stay, even after the cessation of the medication upon admission.

However, the occurrence of prolonged DKA in cases where patients presented with normal renal function upon admission suggests the existence of other contributing mechanisms beyond simple drug accumulation due to impaired renal clearance [3]. In this context, genetic factors come into play. All three agents, Dapaglifozin, Empagliflozin and Canagliflozin undergo hepatic metabolism by glucuronidation and are excreted by the kidneys [9]. It is still unclear if genetic polymorphisms of the SLC5A2 gene, which is responsible for encoding SGLT2 transporter expression, play a role in inter-individual differences that would cause a more pronounced mechanism of action [10]. Similarly, genetic variability can be seen in drug metabolizing enzymes involved in the glucuronidation pathway which could potentially affect how SGLT2i are metabolized to their metabolites [11]. However, no clinical studies have investigated metabolic or transporter polymorphisms on pharmacokinetics of SGLT2i and patient outcomes.

Furthermore, the inherent pharmacokinetic properties of SGLT2i, such as their slow dissociation rate or "slow off-rate," allow these medications to maintain their pharmacodynamic effects even when plasma concentrations are low. This could also explain the persistent and prolonged effects of ketone reabsorption of these agents despite drug discontinuation [12]. Additionally, within the drug class, Canagliflozin is the most lipophilic of the SGLT2i and therefore, may have an effect on the

pharmacokinetics of the drug. In patients with increased adiposity, the drug has a larger volume of distribution and may increase the elimination half-life [13]. Empagliflozon has the highest selectivity of SGLT2 over SGLT1 which would place a larger emphasis for this agent to exert its effects on urinary glucose excretion [14].

SGLT2i have been linked to cases of prolonged episodes of ketoacidosis in multiple studies. In one case report, a 81-year-old woman with type 2 diabetes who became delirious due to dehydration and constipation. Even after stopping canagliflozin metformin, and perindopril, she developed euglycemic DKA two days after admission. Insulin therapy normalized her blood pH within a day, but she experienced persistent ketonemia after insulin was stopped. This required prolonged insulin treatment for 16 days to achieve resolution [3]. A separate study underscored two instances of euglycemic DKA induced with SGLT2i use, wherein both patients with type 2 diabetes continued their SGLT2i before surgery despite inadequate glycemic control and existing symptoms, likely contributing to their prolonged DKA duration, lasting 92 hours for resolution [8]. In another case report, a 57-year-old woman with type 2 diabetes who presented with breast abscess-related sepsis and was subsequently diagnosed with euglycemic Diabetic Ketoacidosis (DKA) despite having glucose levels consistently below 150 mg/dL (8.3 mmol/L). Notably, the patient had been taking empagliflozin for three weeks prior to admission. Despite discontinuation of empagliflozin upon admission and appropriate management with intravenous insulin, the patient experienced persistent ketonuria for at least 14 days after the last dose of empagliflozin [15]. Most recently, the FDA reviewed post-marketing data, identifying 29 adults with type 2 diabetes taking SGLT2i who experienced prolonged episodes of ketoacidosis persisting between 3 to 20 days. Notably, seven of these cases experienced prolonged episodes of ketoacidosis after reducing insulin doses or switching to injectable subcutaneous insulin [16].

In considering the complexities surrounding our patient's prolonged episode of ketoacidosis in the context of SGLT2i use, it is imperative to acknowledge the potential influence of additional contributing factors beyond drug therapy alone. While our case report provides a discussion on the mechanisms by which SGLT2i can precipitate ketoacidosis, including renal impairment, genetic polymorphisms, and drug pharmacokinetics, it is essential to recognize that patient care is often multifaceted. Concurrent medications, comorbidities, and lifestyle factors can all significantly impact metabolic homeostasis and contribute to the observed clinical outcomes. The concomitant use of medications such as diuretics, corticosteroids, and antipsychotics, which were not documented in this study, have the potential to exacerbate conditions such as dehydration, electrolyte imbalances, or insulin resistance, thereby heightening the risk of ketoacidosis. However, the precise interaction between these medications and SGLT2i in precipitating ketoacidosis and prolonging its episodes remains largely unexplored. Comorbidities such as chronic kidney disease or liver dysfunction can further complicate metabolic pathways, altering drug metabolism, renal clearance, or hormonal regulation. Lifestyle factors including dietary habits and physical activity levels may affect glycemic control and insulin sensitivity, potentially modulating the risk and severity of ketoacidosis. Moreover, psychosocial determinants like socioeconomic status, access to healthcare, and cultural beliefs influence treatment adherence, dietary choices, and overall health behaviors, thereby indirectly affecting metabolic outcomes in patients admitted with poorly controlled diabetes. Thoroughly assessing these interconnected factors underscores the importance of integrating a comprehensive discussion on alternative explanations for the prolonged episodes of ketoacidosis observed, beyond solely attributing it to SGLT2i use.

As mentioned before, although DKA is a rare complication linked with SGLT2i use, it is important to assess the overall risk-benefit balance of these medications. For the majority of patients, the advantages of using a SGLT2i typically outweigh the potential risk metabolic complications. Nevertheless, healthcare providers need to stay vigilant, especially in specific patient groups where the risk might be higher. Known risk factors for an increased likelihood of DKA when using SGLT2i include underlying health conditions, recent surgeries, reduced carbohydrate intake, dehydration, and excessive alcohol consumption. While the risk factors linked to prolonged episodes of DKA from SGLT2i use continue to be studied, promptly discontinuing the SGLT2i upon DKA presentation is a critical initial measure to prevent exacerbation of acidosis and the potential for prolonged ketoacidosis episodes. By carefully considering these factors and monitoring patients accordingly, healthcare providers can effectively minimize the risk of DKA while maximizing the therapeutic benefits of this drug class.

The clinical implications of this case report, particularly within critical care settings, underscore the importance of recognizing the potential risks associated with SGLT2i in ICU patients. Prolonged ketoacidosis in SGLT2i users holds significant clinical importance for intensivists, profoundly influencing the immediate care provided to these individuals. Firstly, it is crucial to consider withholding SGLT2i in patients admitted to the ICU with specific underlying health conditions, such as recent surgeries, severe infections, reduced carbohydrate intake, dehydration, and excessive alcohol consumption. Secondly, continuous monitoring of patients' acid-base status over an extended period is advisable due to the inherent risk of prolonged ketoacidosis and the potential for reopening the anion gap. This comprehensive approach may necessitate more frequent laboratory assessments, prolonged continuous intravenous insulin infusion, and meticulous acid-base status monitoring to expedite acidosis resolution and potentially reduce ICU stays. Finally, transitioning patients to long-acting insulin in the ICU may involve promptly discontinuing the SGLT2i, educating patients about the associated risks of ketoacidosis, and scheduling appropriate follow-up with a specialist to mitigate further complications related to metabolic abnormalities associated with SGLT2i use

In assessing the risk of prolonged episodes of ketoacidosis in SGLT2i users admitted with DKA, understanding the generalizability of this potential risk should include an understanding of the multifaceted dynamics of patient demographics and regional prescribing practices is paramount. Patient characteristics, including age, race, income level, and healthcare access, significantly impact medication adherence, disease management, and metabolic complication risk. Concurrently, regional variations in prescribing practices driven by healthcare policies, formulary restrictions, and physician preferences shape SGLT2i utilization and associated adverse events. Lack of physician awareness regarding the risk of prolonged ketoacidosis from SGLT2i among inpatients can result in a lack of frequent laboratory assessments, extended intravenous insulin infusion, and poor monitoring of acid-base status necessary for metabolic resolution. Moreover, insufficient patient education, limited monitoring resources, and socioeconomic barriers can exacerbate this risk

in vulnerable populations. Thus, a comprehensive understanding of these factors offers valuable insights into the contextual determinants of prolonged ketoacidosis in SGLT2i users, aiding clinicians in devising tailored interventions to meet the specific needs of patients in their region and similar settings.

In summary, while decreased renal clearance leading to drug accumulation is the most likely explanation for our patient's prolonged episode of ketoacidosis following SGLT2i discontinuation, we cannot overlook the potential influence of genetic and other pharmacokinetic factors. These elements may significantly contribute to the drug's extended activity and the observed prolonged effects on ketone reabsorption, underscoring the complexity of managing DKA in patients treated with SGLT2i.

There are limitations to this case report, most notably, the retrospective nature of the study may have affected adequate identification, reporting and documentation in the patient's medical chart. Additional factors that may limit the certainty of association include the reporting timing of for measurements for creatinine, glucose and other metabolic measurements (eg. bicarbonate, anion gap, etc) which were used to report on the duration of the acidosis. In addition, it remains unclear if the prolonged duration of action of the SGLT2i is what caused ongoing ketoacidosis or reduced ketone clearance in the context of kidney dysfunction.

Conclusion

In summary, this case report highlights the prolonged episode of ketoacidosis in a 54-year-old patient admitted with DKA while using a SGLT2i. Despite discontinuation of the SGLT2i upon admission, the patient exhibited persistent ketonemia for nine days, implicating potential factors such as acute kidney injury and pharmacokinetic properties of the drug in prolonging the metabolic derangement. This case report contributes to the expanding body of literature and highlights the need for comprehensive patient education regarding the appropriate management of SGLT2i therapy to mitigate the risk of severe metabolic complications. Moreover, critical care providers should remain vigilant for the potential for prolonged ketoacidosis in SGLT2i users, necessitating enhanced monitoring and tailored care strategies.

Author Statements

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of Supporting Data

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Author's Contributions

All authors contributed to the conception and design of the article, drafted the manuscript, revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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