Annals of Case Reports
Lombard X, et al. Ann Case Rep: 9: 101777
www.doi.org/10.29011/2574-7754.101777
www.gavinpublishers.com

OPEN ACCESS

Case Report

GAVIN PUBLISHERS

Empagliflozin-Associated Acidoketosis: A Sneaky Friend

Xavier Lombard[1], Hafid Khelifa[2], Ayoub Jaafari[3*], Rachid Attou[3]

[1]Emergency department, Bois de l'Abbaye Hospital Centre, Liège, Belgium

[2]Intensive care unit, Bois de l'Abbaye Hospital Centre, Liège, Belgium

[3]Intensive care unit, C.H.U Brugmann, 1000 Bruxelles, Belgium

[*]**Corresponding author:** Ayoub Jaafari, Intensive care unit, C.H.U Brugmann, 1000 Bruxelles, Belgium.

Citation: Lombard X, Khelifa H, Jaafari A, Attou R (2024) Empagliflozin-Associated Acidoketosis: A Sneaky Friend. Ann Case Report 9: 1777. DOI: 10.29011/2574-7754.101777

Received: 20 April 2024; **Accepted:** 24 April 2024; **Published:** 24 April 2024

Abstract

High anion gap (HAG) metabolic acidosis is nowadays one of the most common acid-base disorders in the critical care unit (ICU). Early investigation of possible aetiologies is crucial to treatment in order to avoid potentially fatal outcomes. Among these, diabetic ketoacidosis (DKA) is unlikely to be missed in the context of a clear history of diabetes and/or pathognomonic laboratory values (elevated blood glucose, hyperlactatemia, ketonuria). Nevertheless, in rare cases, patients may present with HAG metabolic acidosis with normal or slightly above-normal blood glucose levels, as in those taking sodium-glucose cotransporter 2 (SGLT2) medications, making it easy to overlook by physicians, and potentially life-threatening. In this report, we present an infrequent case of severe metabolic acidosis associated with empagliflozin and the significant role of early and appropriate management with a view of the literature.

Keywords: Euglycemic Diabetic Ketoacidosis; High Anion Gap Metabolic Acidosis; Sodium-Glucose Cotransporter-2 Inhibitor Diabetic Ketoacidosis; SGLT2 Inhibitor DKA; SGLT2 Inhibitor Euglycemic DKA; Intensive Care Unit

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a group of drugs used in type 1 and type 2 diabetes mellitus (DM) that have enjoyed great success in recent years due to their beneficial effects on diabetes, cardiovascular, and kidney disease [1]. Although they are generally well tolerated, like all medicines they can have side effects. One of these potential side effects is diabetic euglycemic ketoacidosis (DKA), typified by metabolic acidosis with normal or moderately elevated blood glucose levels. The exact mechanism is not fully comprehended but is assumed to be related to its effects on renal function and glucose metabolism [2]. Furthermore, there is no consensus/criteria regarding the management of SGLT2 inhibitor-induced DKA, leading to it being easily overlooked and potentially life-threatening. Here we report a rare case of severe metabolic acidosis associated with empagliflozin and its management in ICU/clinical practice according to the literature.

Case Report

A 44-year-old Belgian female patient was brought to the emergency department by her family because of decreased consciousness and decreased oral intake for 48 hours. Given the clinical history, which limited the patient's confusional state, a hetero-anamnesis was carried out with her mother. The mother explained that her daughter had been found near her bed, on the floor, exhausted. She explained that she had stumbled while trying to go to the bathroom because of her heavy, painful periods. In addition, the patient had not been hydrated or fed for 48 hours. Worried, her mother decided to call an ambulance and take her to the emergency. She reported that her daughter had no chest pain, had some nausea and vomiting (2 times), no fever, no cough, no alcohol or drug use, and no other complaints. Her medical and surgical history included type 2 DM treated with Metformin 850mg, Jardiance 25mg, hypercholesterolemia treated with Artechol 1x/day, and anxiety-depression treated with Venlafaxine 75mg. The parameters on arrival were as follows: blood pressure of

170/100mm Hg, heart rate of 127 beats/min, O_2 saturation of 95% on room air, breath rate of 29/min, and temperature within normal limits. She was moderately dehydrated, with dry oral mucosa and poor skin turgor. On clinical examination, cardiopulmonary auscultation was unremarkable, the abdomen was supple, and the neurological examination was reassuring with a Glasgow score of 11/15 (E4V2M5). Bearing in mind the patient's condition at the time of consultation, complementary exams were realized. Arterial blood gas showed a pH of 6.98, $pC0_2$ of 14.9mm Hg, PaO_2 of 119mm Hg, HCO_3- of 3mmol/L, the excess base of -28mmol/L, normal lactate of 0.9mmol/L, and glucose of 237mg/dL. A urine dip shows the presence of sugar (+3) and plenty of acetone (+4), but no nitrite. Laboratory showed results as follows: normal blood form numbering; normal coagulation; urea normal; creatinine of 0.58 mg/dl; uric acid of 8.7 mg/dl; MDRD > 60 ml/min/1.73m; sodium of 136 mmol/L; potassium of 4.7 mmol/L; chloride of 108 mmol/L; serum glucose of 237 mg/dl; albumin 47.8 gr/L; liver and pancreatic function tests are within normal limits; blood ethanol levels were normal; and B-HCG < 5 U/L. The anionic gap was measured at 29mmol/L. Other causes of increased anion gap metabolic acidosis (Salicylates, methanol, ethylene glycol) were excluded. Within a few hours, the patient rapidly developed a worsening of her acute confusional state, necessitating precautionary intubation to protect her airway. She was then admitted to intensive care with a diagnosis of diabetic ketoacidosis secondary to empagliflozin, although no other factors precipitating her acute confusional state could be identified (Negative viral, bacterial, and fungal infections panels). The patient was successfully treated with intravenous insulin infusion and intensive intravenous rehydration therapy. The patient was de-extubated very early, with clinical and biological improvement.

Discussion

High anion gap (HAG) metabolic acidosis is one of the most common metabolic derangements seen in critical care patients. The symptoms of metabolic acidosis with a high anion gap are generally non-specific, dyspnoea being common owing to stimulation of the central respiratory center, but other symptoms may also occur, such as confusion that may even lead to coma, Kussmaul respirations (i.e., deep, slow breathing instead of rapid, shallow breathing), dryness of the mucous membranes, and ketotic odour in diabetic ketoacidosis, etc [3].The detailed mechanism of diabetic ketoacidosis (DKA) is not fully elucidated, but in our view, we speculate that SGLT2 inhibitors promote glucosuria, which leads to a decrease in plasma glucose levels in the blood. They also enhance glucagon production and reduce insulin release, leading to diabetic ketoacidosis and hypoglycaemia. Triggering factors such as surgery, acute illness, starvation or insulin deficiency can trigger highly complex metabolic and renal processes that can lead to life-threatening metabolic acidosis [4]. Additionally, prolonged hypoglycemia leads to ketosis, which may be worsened by the increased resorption of ketone bodies by SGLT2 inhibitors [4]. According, to the literature, the efficacy and safety of SGLT2 inhibitors in intensive care patients have never been randomly assessed. A pilot, observational study conducted by Mårtensson et al. showed that Empagliflozin did not show a significant association with acid-base status and ketoacidosis in subjects with type 2 diabetes mellitus admitted to ICU [5]. Nonetheless, several biases are present in this study and results cannot be generalized to all patients. More randomized studies are needed. In our view, there is no consensus/criteria regarding the management of SGLT2 inhibitors-induced DKA, leading to it being easily overlooked and potentially life-threatening. Additionally, several cases have been reported in the literature concerning this euglycemic DKA and the conundrum it causes for emergency and intensive care physicians, insofar as there is an obvious delay in diagnosis and patient management [6-8]. It is therefore clear that we need to find standardized solutions that could be useful to everyone, to guarantee rapid medical management and potentially reduce hospital stays in the ICU. One idea (that might be investigated in further studies) would be to be able to screen patients at risk of developing this condition, and possibly measuring this drug so that it can be included in the calculation of our anion gap.

Conclusion

Despite their beneficial impact on diabetes, cardiovascular, and renal disease, SGLT-2 inhibitors are not devoid of side effects. Euglycemic DKA represents a significant challenge for all physicians, particularly in the acute phase, and should be considered in the differential diagnosis of patients with a history of diabetes mellitus especially those taking SLGT-2 inhibitors, or high anion gap metabolic acidosis with normal or slightly above-normal blood glucose levels.

Acknowledgment: No Acknowledgments

Disclosure and Conflict of Interest: The authors declare no conflict of interest.

Informed Consent Statement: Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Data Availability Statement: The data used and analyzed in this study are available from the corresponding author on reasonable request.

References

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, et al. (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 373:2117-28.

2. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, et al. (2021) Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. Circulation 143:326-36.

3. Brubaker RH (2023) High anion gap metabolic acidosis. U.S. National Library of Medicine.

4. Diaz-Ramos A, Eilbert W, Marquez D, (2019) Euglycemic diabetic ketoacidosis associated with sodium-glucose cotransporter-2 inhibitor use: a case report and review of the literature, Int. J. Emerg. Med. 12 (1): 1-4.

5. Mårtensson J, Cutuli SL, Osawa EA, Yanase F, Toh L, et al. (2023) Sodium-glucose CO-TRANSPORTER-2 inhibitors in intensive care unit patients with type 2 diabetes: A pilot case-control study - critical care. BioMed Central. Crit Care. 27(1):189

6. Kang CY, Khamooshi P, Reyes Pinzon V (2022) An Unsuspected Case of Euglycemic Diabetic Ketoacidosis With Twists. Cureus 14(4):e24016.

7. Soni P, Kumar V, Saradna A, Kupfer Y (2018) Empagliflozin-Associated Euglycemic Diabtetic Ketoacidosis. Am J Ther.

8. Hernandez-Quiles C, Ramirez-Duque N, Acosta-Delgado D (2019) Ketoacidosis Due to Empagliflozin, a Paradigm Shift: Case Report and Review of Literature. Curr Diabetes Rev 15(4):259-262.