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Mini Review



# Ketoacidosis During Treatment with SGLT2 Inhibitor A Complication Not to be Ignored

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## Sumarry

SGLT2 inhibitors are particularly useful in type 2 diabetic patients due to their associated effects on cardiovascular and renal protection. Like all effective medications, SGLT2 inhibitors can cause side effects, some of which are potentially serious. Ketoacidosis falls into this category and although rare, it should be well known because its euglycemic character can be confusing. In addition to the importance of insulinogenic, the factors favoring its determinism are similar for some of those of lactic acidosis during the intake of metformin, which facilitates the memorization of the precautions for use in the event of an intercurrent event. However, this drug class is particularly useful in type 2 diabetic patients due to its effect on cardiovascular and renal protection.

**Keywords:** Diabetes, SGLT2 Inhibitor, Adverse effect, Euglycemic ketoacidosis

## Introduction

The availability of SGLT2 inhibitors (SGLT2i or gliflozins) represents considerable progress in the management of type 2 diabetic patients thanks to the cardiovascular and renal protection afforded by this drug class. Among the long series of side effects associated with these drugs, some are frequent and generally mild, such as urinary infection and genital mycoses, which are more common in women. Others are rare but potentially very serious, such as cases of euglycemic ketoacidosis, especially as their clinical presentation is misleading.

## Frequency of Cases of Ketoacidosis During Treatment with SGLT2i

A few cases of euglycemic ketoacidosis have been reported in studies evaluating the efficacy and safety of use of the various molecules of this drug class, particularly in type 1 diabetes. A meta-analysis of 60,580 type 2 diabetic patients treated with SGLT2i in 39 controlled trials reported 85 cases of ketoacidosis with a risk multiplied by a factor of 2.13 in the event of treatment with SGLT2i [1]. An even more recent meta-analysis of 7 randomized trials including 42,375 participants and 5 cohort studies involving 318,636 participants showed that the incidence of ketoacidosis in patients randomized to receive SGLT2i ranged from 0.6 to 2.2 events per 1,000 person-years with an increased risk of a factor of 2.5 compared to an antidiabetic treatment that does not include this drug class. In the 5 observational studies, the frequency of these accidents varied from 0.6 to 4.9 per 1,000 person-years with a rate 1.7 times higher compared to other drugs [2]. Finally, in a "real life" study conducted in France with dapagliflozin in 941 patients, a single case of ketoacidosis was reported [3]. These cases are therefore rare in absolute value but approximately twice as frequent under SGLT2i. These accidents are the result of a class effect and occur regardless of the molecules.

## Mechanisms

The pathophysiology of these ketoacidosis events is a bit confusing since it is not associated with a rise in blood sugar as is usual in diabetes. The explanation lies in the ketogenic action of gliflozins, a phenomenon that could explain their protective effect on the heart by providing the myocardium with a very good energy substrate. The decrease in glycaemia induced by glycosuria leads to

a decrease in the secretion of insulin and an increasing secretion of glucagon. This phenomenon promotes lipolysis and the production of free fatty acids, the metabolism of which leads to the production of ketone bodies, while their urinary excretion is reduced by SGLT2i [4]. This mechanism explains why these accidents occur preferentially in cases of insulinogenic, fasting state and why this drug class is not recommended in type 1 diabetes and type 2 diabetes with insulinogenic.

## Symptomatology

Symptoms revealing ketoacidosis related to SGLT2i intake can be confusing, especially since blood sugar levels are low, usually less than 2.5 g/l. The most frequent signs are represented by nausea, vomiting or abdominal pain associated with asthenia. In the event of severe acidosis, deep polypnea with fruity breath, then changes in the state of consciousness such as confusion, agitation or behavioral disorders may set in. Confirmation of the diagnosis is ensured by the demonstration of an increase in blood ketone usually greater than 3 mmol/L associated with a fall in serum bicarbonates below 20 mmol/L and blood pH below 7.20 measured by arterial blood gas.

## Contributing Factors and Prevention

The circumstances of appearance of this severe complication are multiple and can be summarized as the occurrence of a destabilizing event in the state of health of the diabetic patient, if there is insulinogenic, particularly in type 1 diabetes.

A risky situation is represented by the postoperative period or by acute cases of medical pathology. Emergency physicians and intensive care medical doctors must be well informed of this fact so as not to overlook incipient ketoacidosis when blood sugar level remains normal or low. Alcohol consumption and reduction of insulin therapy are also situations favoring the occurrence of ketoacidosis [5]. Naturally, if the diagnosis is suspected, treatment with SGLT2i should be discontinued immediately and definitively. The precautions to be taken are similar for some of those for the use of metformin. The intake of SGLT2i must be interrupted in the event of an acute medical or surgical accident and reintroduced when the patient has regained a satisfactory diet and clinical state. Thus, taking gliflozins should be stopped 3 to 4 days before surgery under general anesthesia [6].

## Treatment

Depending on the severity of the case, hospitalization in intensive care may be necessary. The treatment is based on the immediate cessation of SGLT2i intake and on intravenous insulin therapy associated with rehydration with glucose serum enriched with salt and potassium according to the blood results. Although debated, the administration of bicarbonate through the blood may be indicated in cases of severe acidosis [7]. The control of blood glucose and ketone levels then directs insulin and infusion rates. Once the acute episode has passed, the previous treatment can be resumed but, apart from the case where an obvious error was at the origin of the accident, it seems preferable to avoid the resumption of this drug class.

## Conclusion

The availability of SGLT2i, which was eagerly awaited, undoubtedly improves the treatment of type 2 diabetic patients by providing them with cardiovascular and renal protection. This drug class is accompanied by many adverse effects that must be well known to inform the patient and thus avoid their occurrence. Euglycemic ketoacidosis is rare but potentially very serious. Its clinical presentation can be confusing, and the diagnosis can be misunderstood, especially in emergency and surgical units, which implies the need to be aware of this risk. However, despite these cases of ketoacidosis, the risk-benefit ratio remains largely in favor of SGLT2i.

## Disclosures

The authors declare that they have carried out specific interventions at the request of the following pharmaceutical companies: AstraZeneca, Boehringer, Eli Lilly, Jansen, Merck Sharp & Dohme, Novo Nordisk, Pfizer and Sanofi.

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