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CLINICAL CASE

Euglycemic ketosis in an adolescent with type 1 diabetes on insulin and dapaglifozin. Case report

Cetosis normoglicémica en adolescente con diabetes tipo 1 recibiendo insulina y dapaglifozina. Reporte de un caso

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Abstract

Introduction: Dapagliflozin, an insulin-independent sodium-glucose cotransporter 2 inhibitor (SGLT2-I) induces glycosuria and reduces hyperglycemia in adults with type 2 diabetes. Objective: To present an "euglycemic" diabetic ketosis in an adolescent with type 1 diabetes (T1D) receiving dapagliflozin, to alert about the risk of a drug not approved in children nor in T1D. Case report: A 17 years old adolescent with T1D during 9 years, was started on dapagliflozin 10 mg/day to reduce insulin dose and weight. During 11 months on treatment, capillary ketones were undetectable and she exhibited a reduction in body mass index 23.9 to 21.1 kg/m², basal insulin 40 to 17 U, glycated hemoglobin 8.3 to 7.5%, capillary glucose 175 to 161 mg/dl and glucose variability (standard deviation) 85 to 77. Suddenly nausea and vomits appeared. The patient was on an insulin pump and well calibrated continuous glucose monitoring, showing stable glucose levels under 200 mg/dl, and an insulin bolus was delivered. Vomiting without hyperglycemia persisted; three hours later, she was severely dehydrated and fainting, with ketones 4.6 nmol/l and glucose 224 mg/dl. She received IV saline fluids, ondansetron, carbohydrates and several insulin boluses. Hydration and general condition improved soon, however despite several insulin doses, ketosis continued for 24 hours. It is remarkable that the pump was working well and the cannula was not changed. After the ketosis was resolved, she continued using the same cannula with good metabolic control. Conclusion: Euglycemic ketosis is a life-threatening condition that must be suspected.

Keywords:

Ketosis; type 1 diabetes; dapagliflozin; SGLT2 inhibitor.

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Introduction

Type 1 Diabetes (T1D) is difficult to manage in adolescents¹. Sodium-glucose cotransporter type 2 inhibitors (SGLT2-I), is a group of drugs that increase glucose urinary excretion, inducing weight loss and improving metabolic control² (figure 1). In adults with Type 2 Diabetes (T2D), Dapagliflozin improves glycosylated hemoglobin (HbA1c) and fasting blood glucose both as monotherapy and in combination with other drugs³⁻⁶. Some studies have suggested that SGLT2-I could be useful as an adjuvant to insulin therapy in T1D to improve glycemic control and weight⁷⁻⁹. However, it has not been approved in children or in T1D.

It has been reported that SGLT2-I may increase the risk of diabetic ketoacidosis (DKA) with relatively low blood glucose levels in both T1D and T2D patients^{10,11}.

The mechanism by which SGLT2-I could induce or facilitate DKA is not known. Taylor et al.¹⁰ postulated that DKA by SGLT2-I could be induced by a low tissue glucose availability, secondary to increased glucosuria. Low or normal blood glucose induces a decrease in the supply of exogenous insulin, producing a relative

insulinopenia for the needs of the patient, triggering an increase of lipolysis and ketogenesis. In addition, SGLT2-I increase the tubular reabsorption of ketones, favoring their elevation in blood.

The risk of DKA in patients treated with SGLT2-I was reported by the Food and Drug Administration in the United States "FDA" in May 2015¹². Since then, a few other DKA cases have been published^{13,14}. However, large series of patients report a very low incidence of this association¹⁵⁻¹⁷.

DKA is a complication of T1D, defined by the triad: hyperglycemia (> 250 mg/dl), metabolic acidosis and ketones¹⁸. DKA without severe hyperglycemia is unexpected and has a very low incidence that might be due to the lack of recognition and under-registration. Near normal blood glucose levels, may hide DKA delaying timely intervention.

Objective

To present a "normoglycemic" diabetic ketosis in an adolescent with T1D who was receiving dapagliflozin as an adjuvant to insulin treatment. The aim is to warn about the risk of using a drug that looks promising but is not approved in children or in T1D.

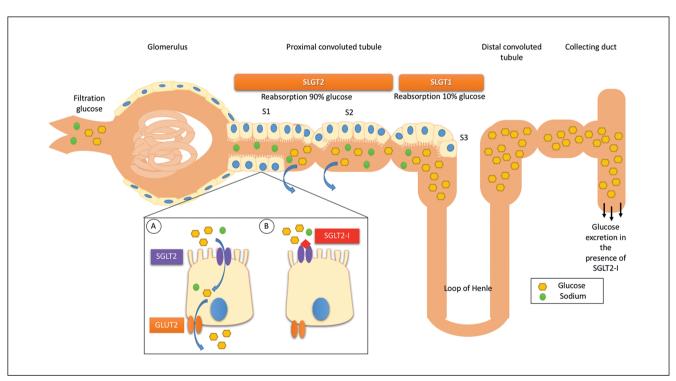


Figure 1. Mechanism of Action of Sodium Glucose Cotransporter-2 Inhibitors (SGLT2-I). The nephron is shown with its parts (glomerulus, proximal convoluted tubule, distal convoluted tubule and collecting duct), filtration of glucose and sodium. The proximal tubules in the kidney are divided in three segments (S1, S2 and S3) anatomically. Normally, glucose is reabsorbed in segments S1 and S2 through SGLT2 channels (90%) and S3 for the SGLT1 channel (10%) whereby glucose excretion is zero. **A)** It is shown how glucose and sodium are reabsorbed in the epithelium of the proximal convoluted tubule through the SGLT2 channel and later the glucose is transported to the vessel through the glucose transport 2 (GLUT2), preventing its excretion by the collecting duct. **B)** The mechanism of SGLT2-I is to block the sodium-glucose cotransporter by inhibiting glucose reabsorption and causing its excretion through the collecting duct.

Clinical case

We present a 17-year-old female adolescent whose T1D onset was at age 8 years. She was on aspart insulin as continuous subcutaneous insulin infusion (medtronic 640G pump) and continuous glucose monitoring (MCG). The patient had had menarche at age13 years, never presented ketosis, severe hypoglycemia, or hospital admissions during 9 years with T1D. She had good adherence to her treatment; however, she could not reach the goal HbA1c \leq 7.5% and could not lose weight with diet and exercise.

For this reason, Dapagliflozin (10 mg/day) was started as an adjuvant to insulin therapy with informed consent about this off label indication. Table 1 shows the patient characteristics and her metabolic control before and 11 months after she was started on Dapagliflozin.

Treatment with SGLT2-I was successful during 11 months before the onset of ketosis, improving metabolic control and glucose variability. During this period, weekly controls of beta hydroxybutyrate (ketones) in capillary blood (with Free Style Neo glucometer) were undetectable most of the time (range 0.0 to 0.5 nmol/l).

One uneventful day, she had blood glucose 118 mg/dl on awakening and 176 mg/dl before lunch; at 5:00 PM the patient perceived symptoms that she usually had associated with high blood sugar (metallic taste in the mouth, thick saliva and mild malaise), however, her suspicion of hyperglycemia was ruled out by a capillary blood glucose 181mg/dl (figure 2) and by the sensor readings (figure 3). She delivered a correction insulin bolus and increased water intake. At 6:30 PM, he felt nauseous, had arches and vomited scant saliva.

Table 1. Characteristics of the patient and their control before and after 11 months with Dapaliflozin

Variables	Before treatment	After treatment (11 month)
Heigth (cm)	174.4	174.4
Weight (kg)	72.8	64.5
BMI (kg/m²)	23.9	21.1
Age (years)	17.0	17.9
HbA1c (%)	8.3	7.5
Glycemias per day (No.)	3.6	3.6
Carbohydrates consumption per day (g)	120	210
Dose of insulin per day (unit)	51.1	46.4
Mean blood glucose (mg/dl)	175	161
SD glucose varibility (mg/dl)	85	77

BMI: Body mass index; HbA1c: glycated haemoglobin; No.: number; SD: standard deviation.

Subsequently, the patient presented 3 vomits, felt decay and weakness. It is important to highlight that the continuous glucose sensor showed interstitial glucose in a reasonable range below 200 mg / dl at all times (shown in figure 2).

At 10:11 PM with blood glucose of 223 mg/dl, the patient had capillary blood ketones of 4.9 nmol/l, confirming the presence of ketosis with a subtle glucose elevation. The insulin pump was maintained; however, considering the possibility of a technical failure in the infusion set, an additional aspart insulin bolus (4U) was administered S.C. with syringe. She persisted with profuse vomiting and oral rehydration failed.

At 00:15 AM the patient was fainting and she was admitted in the emergency room presenting general weakness, severe dehydration, decay and drowsiness with ketones 4.6 nmol/l and blood glucose 224 mg / dl. She received a second S.C. aspart insulin bolus (7U) with syringe, I.V. saline solution (1700ml) and Ondansetron 4mg I.V; in addition the insulin pump basal infusion rate was increased to 130%, since there were no signs of dysfunction of the infusion system.

At 1:30 AM the patient stopped vomiting, her blood sugar was 183 mg/dl and sugar juice (25g of carbohydrates) oral intake was started to prevent hypoglycemia since she had quite active insulin on board. From that moment her general condition showed a fast improvement, she maintained adequate hydration, tolerated oral feeding and did not vomit again. Figures 2 and 3 show capillary blood glucose and ketones evolution during this episode.

Discussion

Our patient received Dapaglifozin during 11 months, improving her metabolic control and reducing glycemic variability. Suddenly, she developed a "normoglicemic" ketosis without a triggering factor. This is the first case in our pediatric unit and we did not find any similar case published in our country.

A limitation in this case is the lack of venous blood gases to confirm the presence of metabolic acidosis, because the patient was evaluated in an emergency room where her metabolic disturbance was underestimated. Thus, the case is presented as a ketosis; indeed, without proper management the natural history of a diabetic ketosis is to evolve to DKA which is a life threatening situation.

Normoglycemic DKA has been associated with periods of stress (surgery) or fasting¹⁶. Our patient had an average intake of 210 ± 60 g of carbohydrates (CH) during the month prior to the ketosic event; however, the day prior to the ketosis when she had no symptoms, she had an intake of 105g of CH and

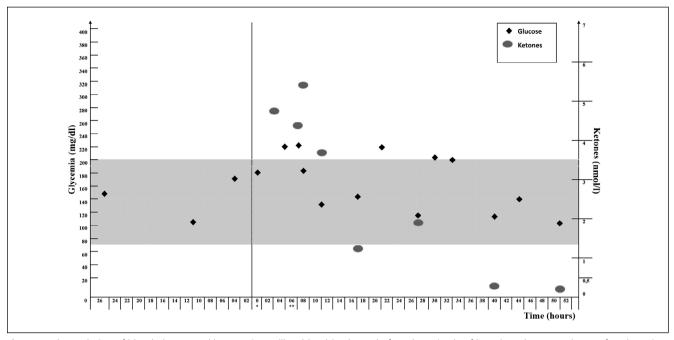


Figure 2. The evolution of blood glucose and ketones in capillary blood (26 hours before the episode of ketosis and up to 51 hours after the episode) is shown. *The zero hour (0) indicates the clinic begins with metallic taste, thick saliva, undetermined malaise. After 2 hours, nausea, vomiting, decay and weakness are added to the picture. **Hour six (6) indicates the time the patient enters the emergency room with generalized weakness, decay, severe dehydration and drowsiness. Relatively low glycemia (223-183 mmol/L) is evident, with marked ketosis (4.9-5.4 nmol / l). Treatment with intravenous hydration is initiated. The scored area indicates the target glycemia range for an adolescent with Type 1 Diabetes (70-200 mg/dl), including fasting and postprandial glycemia. Normal capillary ketone levels are undetectable (< 0.1 nmol/L). In cases of fasting it can rise to levels ≤ 0.4 nmol / L.

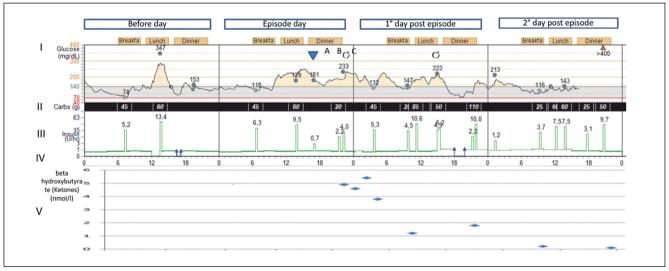


Figure 3. Original log download of the Medtronic 640G insulin pump with sensor embedded in the Medtronic Pro program. The record of the before day, the day that the symptoms are started and the ketosis and the evolution of two days later are shown. The inverted triangle symbol indicates the moment symptoms appear. I: Continuous monitoring of interstitial glucose. The dark circles are the capillary glycemia levels (mg/dl) measured with glucometer at that time. II: Dark band under the graph showing the amount of carbohydrates (CH) and the moment they were ingested. III: Insulin administered as basal infusion and the columns correspond to insulin boluses administered through the pump. The numbers indicate the number of units of insulin. The periods in which the basal insulin is discontinued between two arrows corresponds to automatic stopping of the basal by prediction of future hypoglycemia. IV: Time in hours (24 hours format). V: Not part of the pump registry. It is a graph showing the levels of beta hydroxybutyrate in capillary blood (ketones) (nmol/L) measured at the times indicated by line IV. It is observed that on the day of the ketosis episode, the blood glucose levels were maintained in a suitable range between 118 and 233 mg/dl in contrast to elevated ketones up to 5.4 nmol/L. With hydration plus insulin and glucose supply, the ketones drop to 0.1 nmol/L at 48 hours post-episode. A and C indicate the administration of syringe-administered extra bolus of subcutaneous insulin that does not appear in the pump records. A = 4 IU, B = 7 IU, C = 5.5 IU. Administration of rapidly absorbed carbohydrates by oral route (sugary juices).

the day she had the symptoms, she ingested 125 g of CH. It is reasonable to suspect that the low CH intake and the consequent lack of prandial insulin boluses and the reduction of the total insulin dose that reached 0.6 IU/kg/day might have favored the onset of the ketosis.

Patients with T1D should receive a daily insulin dose enough to suppress lipolysis and ketogenesis²⁰. In clinical practice, this minimum dose is not calculated since capillary blood glucose and CGM are considered sufficient to guide the insulin doses adjustment.

Patients who adjust their insulin therapy to CH intake and especially those who use an insulin pump with CGM that stops the basal insulin infusion several times per day to prevent hypoglycemia, present a new challenge for the endocrinologist and the pediatrician who might eventually receive these patients at the emergency room. Some of them use very little basal insulin and a high percentage of the daily insulin is provided by the prandial boluses. These patients should be alerted that there is a minimum "threshold" of insulin needed to avoid ketosis. This concept is more relevant in patients on SGLT2-I because hyperglycemia might be lost as an alert for the lack of insulin. It would be important to take special care if the patient is inactive, if he is fasting for some procedure or if he decides to take a low CH diet. In these cases, the basal insulin supply should be temporarily increased and it would be advisable to suspend SGLT2-I²¹⁻²³.

In this case, our hypothesis is that the low CH intake associated with the use of Dapaglifozin could have trigger the ketosis. However, another reasonable possibility is that the low CH intake was a consequence of ketones that were already elevated the day before the onset of symptoms.

It should be noted that once the vomiting ceased, the patient was pressured to receive rapid-acting CH (sugary juices) and insulin, since transient anorexia can be induced by ketones. To suppress lipolysis it is necessary to have glucose and insulin available in the blood stream, therefore, if the patient does not receive oral CH, it would be necessary to administer an intravenous glucose infusion to suppress the ketones production.

In this case, we postulate the relationship between ketosis and SGLT2-I, since both infection and alcohol intake were ruled out¹⁸, there was no other intervention that could mask hyperglycemia and no other known factors that could favor ketosis were found.

The most frequent causes of ketosis in insulin pump users are technical problems such as cannula disconnection, shrinking or occlusion¹⁷. In this case, the patient maintained the insulin pump therapy before, during and the day after the ketosis episode, the infusion set was not changed and the day after, she

continued using the same cannula and reservoir with good metabolic control, therefore, a technical failure of the infusion system is ruled out.

Another frequent cause of ketosis in adolescents is the neglect of the patient and his/her family who tend to relax the metabolic control supervision in older children²⁴⁻²⁶. In this case, this hypothesis is also ruled out. This is the first episode of ketosis in 9 years with T1D. In addition, there are frequent reports of capillary blood glucose on previous days and on the day of the event, the patient had a good metabolic control with HbA1c 7.5% and there is evidence of administration of insulin boluses with adequate frequency in the pump records.

We also have interstitial CGM records consistent with adequate metabolic control in the previous weeks and the day before the event.

It should be noted that CGM was well calibrated and the records were concordant with capillary blood glucose, as shown in figure 3, where it is observed that interstitial glucose was only slightly elevated during the episode. The absence of hyperglycemia blinded the patient and her parents to suspect a DKA.

This case teaches us that the pediatrician should measure capillary ketones more frequently since blood glucose monitoring is not enough in children with diabetes. Our case emphasize the importance to have a glucose meter that also measures capillary ketones both in emergency rooms s and in patients' homes.

A recent study shows that only 17% of adolescents between 13 and 17 years of age achieve the recommended HbA1c target: in this group, the average HbA1c is 9%, and 35% of adolescents are overweight or obese¹. Therefore, it is a fact that insulin is insufficient as monotherapy and that new therapies are required as adjuvant to insulin in adolescents with T1D.

Treatment with SGLT2-I is not approved in T1D, nor in adolescents, however, it seems a promising alternative for young people with T1D. The use of these drugs appears to be increasing in young people with T1D despite not being approved^{1,27-30}. This case illustrates the risk of using these promising drugs when long-term safety studies are lacking.

Conclusion

We present an atypical case of an adolescent with T1D under treatment with insulin and dapaglifozin who developed a ketosis "without hyperglycemia". This life threatening condition may be difficult to recognize. It is important to alert pediatricians and patients to increase suspicion to allow timely management of this condition.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors state that any conflict of interest exists regards the present study.

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