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EUGLYCEMIC KETOACIDOSIS DIAGNOSIS AND TREATMENT PROTOCOL IN TYPE 1 DIABETES PATIENT

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Abstract

Introduction. *The introduction of sodium glucose cotransporter 2 inhibitors in the management of diabetes was an innovation in the treatment of this disease, considering the protective cardiovascular effect not only the ability of decreasing the plasma glucose. In Europe, this class of medication is approved for the treatment of type 2 diabetes and some of them (dapagliflozin and sotagliflozin) are also approved for use in certain patients with type 1 diabetes mellitus. These patients must have inadequate control of their blood glucose levels despite optimal insulin therapy. One of the adverse effects is diabetic ketoacidosis.* ***Case report.*** *This case report presents a diabetic patient whose treatment was changed from insulin therapy to oral therapy. Within 10 days after the initiation of the new treatment her condition gradually worsened and she arrived at the emergency room with nausea, vomiting and altered general condition. She was admitted for euglycemic ketoacidosis and treated according to the protocol.* ***Conclusions.*** *This case reveals the importance of continuing the insulin therapy when adding a sodium glucose cotransporter 2 inhibitor in type 1 diabetes patients.*

key words: *type 1 diabetes, euglycemic ketoacidosis, SGLT2 inhibitors*

Background and aims

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of prescription drugs that are FDA and EMA approved for use in type 2 diabetic (T2D) patients to lower blood glucose levels along with diet and exercise. In Europe, some of them are currently approved for overweighed type 1 diabetes (T1D) patients who could not achieved glycemic control. In Dubai, SGLT2 inhibitors are NOT approved for type 1 diabetes treatment.

The mechanism of action of these drugs is to inhibit Sodium Glucose cotransporter 2 so that the renal glucose reabsorption does not take place. As this occurs, glucosuria is increased and serum glucose levels decline, particularly in hyperglycemic patients. This process take place in the early proximal tubule of the kidneys [1].

Diabetic ketoacidosis (DKA) is one of the main concerns related to using SGLT2 inhibitors, particularly in type 1 diabetic patients [2]. After the first year of post marketing surveillance in the United States, a warning was released by the Food and Drug Administration that reported 20 cases of DKA or ketosis. Although some cases occurred in patients with

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T1D receiving off-label therapy against indication, an unexpected finding was that most cases occurred in patients with T2D [1].

When insulin dosage is lowered too much, SGLT2 inhibitors can enhance ketogenesis to the extent that the risk of diabetic ketoacidosis increases, particularly in type 1 diabetic patients. One of the proposed mechanisms of the DKA in type 1 diabetes patients treated with insulin and SGLT2 inhibitors is that a lower level of insulin and a high glucagon level are responsible for enhancing lipolysis and releasing of more free fatty acids from adipose tissue, which are then used for ketogenesis by the liver. At high levels of plasma ketone bodies, SGLT2 inhibitors may also facilitate the renal retention of ketone bodies by lowering glomerular filtration rate (GFR) and thereby reducing the filtered amount of ketone bodies below the renal tubular reabsorption capacity [3]. Hence, increased ketonemia and DKA can occur in response to SGLT2 inhibition in the absence of hyperglycemia [4]. Potential triggers for DKA in T1D patients are infections, increased physical activities, reduced food and fluid intake, insulin dose reduction or omission.

Case report

A 39 years-old female patient presented to Emergency Room (ER) with complains of sever dizziness, nausea, vomiting, generalized body ache and diplopia in the last 2 days. During this time the symptoms gradually aggravated. Her medical history revealed a T1D with the onset at the age of 29 and hypothyroidism. Her current medical treatment is: Gliclazide 120 mg/day, Empagliflozin 25 mg/day, Sitagliptin/Metformin 50/1000 per day and Levothyroxine 150 mcg//day. It is worth mentioning that she stopped insulin treatment 10-day prior ER admission, probably on her own initiative. Her A1c hemoglobin value was 7.5 % at admission time and the weight 68 kg, height 160 cm and BMI 26.5 kg/m2.

Initial physical and laboratory evaluation in ER

BP- 115/70 mmHg, Temp-39 Celsius, HR-119 b/min, SpO2-99% on room air, RR-28 breaths/min, fully orientated to time, place and person, no signs of neurological deficits.

Laboratory results

Sever metabolic acidosis (*p*H-6.9, HCO_3-2.5), with very high anion gap: 25, plasma glucose: 130 mg/dl, Urine ketones: +++, Magnesium: 1.03 mg/dl (low), ionized Calcium:5.1 mg/dl (low)

Hospital course

She was admitted to Intensive Care Unit (ICU) where the DKA management was initiated as per the internal protocol (see below the DKA protocol) but omitting the initial bolus of insulin (10 U iv bolus before starting the infusion) as she was euglycemic. She was started on continuous infusion of iv fast acting insulin alongside with continuous infusion of iv glucose products for a target plasma glucose around 200 mg/dl. Potassium levels where check 4 hourly and corrected with IV KCL. Low Mg and low ionized Ca++ levels were corrected in the next 24 hours with iv $MgSO_4$ and Ca gluconate.

As she presented with fever and high WBC empirical antibiotic therapy was started but stopped after 3 days as no source of infection could be identify (source south by: urine culture, blood culture, chest X ray, abdominal ultrasound).

After 12 hours of treatment her *p*H increased to 7.24, HCO3- 12 with minimal symptoms.

After 24 hours all her labs and vitals are in normal range and DKA management stopped and switched on subcutaneous insulin

(combination of long acting and short acting insulin) and shifted to general ward.

She stayed in the general ward for 24 more hours for optimization of her insulin treatment by endocrinologist, education and recommendations from nutritionist. She has been discharged with stable clinical condition after 48 hours of admission.

The evolution of the laboratory analysis and of the treatment in the first 24 hours after hospitalization are shown in Table 1.

Table 1. Labs and infusions in the first 24 hours. (D5NS- dextrose 5 % normal saline, NS- normal saline)

	Admission time	After 4 hours	8 hours	12 hours	16 hours	24 hours
pH	6.95	7.03	7.18	7.24	7.34	7.4
Urine ketones	+++	++	++	+	Negative	Negative
Blood ketones	5	Not done	Not done	Not done	Not done	Not done
Plasma glucose	130	200	260	220	275	240
Insulin	3u/h	5u/h	7u/h	5u/h	7u/h	5u/h
Dextrose 10 %	120 ml/h	NO	NO	NO	NO	NO
Dextrose 5% NS	NO	150 ml/h	NO	150 ml/h	NO	NO
Normal Saline	NO	NO	200 ml/h	NO	200 ml/h	150 ml/h
K	4.8	3.9	3.6	3.5	3.5	3.69
KCl	10 mmol in each 500 ml fluid	15 mmol in each 500 ml fluid	10 mmol in each 500 ml fluid	10 mmol in each 500 ml fluid	15 mmol in each 500 ml fluid	15 mmol in each 500 ml fluid

Medcare Hospital DKA protocol

This patient was treated according to Medcare Hospital DKA protocol. The most important aspect of DKA protocol is the Continuous Insulin Infusion, in order to keep blood glucose levels between 200 and 250 mg/dl.

1. Rapid acting insulin:

- initial IV bolus 10 U (usually in ER)
- Insulin Actrapid iv infusion sliding scale:

Table 2. Insulin infusion depending the blood sugar level

plasma glucose mg/dl	Insulin actrapid U/h
<100	0
101-150	1
151-200	3
201-250	5
251-300	7
301-350	9
351-400	10

2. Fluids will be adjusted as per patient's hydration status. Give more if severely dehydrated.

- Initial rapid infusion of 1-liter NS in the first hour (usually done in ER)
- After first hour

Table 3. Type of fluids and rate of administration depending on the blood sugar level

plasma glucose mg/dl	Type of fluid	Infusion rate ml/h
<180	Dextrose 10%	120
181-250	D5NS	150
>250	NS	200-250 (as per patient's hydration status)

3. Potassium levels correction

Table 4. KCl administration depending of K plasma level.

Serum K levels mmol/l	Action
<3.3	infusion of 10 mmol/h
3.3-4.9	10-15 mmol in each 500 ml

Serum K levels mmol/l	Action
	fluid
>5	none

4. Frequency of monitoring plasma parameters

Table 5. Monitoring for plasma parameters (ABG/VBG-arterial blood gases/venous blood gases)

Parameter	Frequency	Comments
plasma glucose	hourly	Every 15-30 min if hypoglycemic
K	Every 6 hours	Every 2 hours if less than 3.3 mmol/l
ABG/VBG	Every 6 hours	Every 2 hours if patient is deteriorating
Ca, Mg, phosphate, urea, creatinine	Every 12 hours	Every 6 hours if patient is deteriorating
Urine ketones	Each voiding	

5. Level of different parameters to consider resolution DKA

- plasma *p*H >7.3,
- plasma bicarbonate> 18 mEq,
- glucose < 200mg/dl,
- anion gap<12.

Discussion

This is a case of euglycemic DKA to a T1D patient in the context of stopping the insulin treatment. The patient was lost to follow up after this episode. Surely this patient needed more careful supervision regarding the administration of the insulin therapy and the necessity of this treatment. After this DKA episode, it is certain that she needs insulin therapy for controlling her blood glucose. The add on of empagliflozin will be possible if the legislation of United Arab Emirates will allow it, for the purpose of better glucose control and weight management. Because she was diagnosed 10 years ago and she is still not convinced that she needs insulin therapy, probably she is a good candidate for psychotherapy.

Conclusions

This is a case of an euglycemic ketoacidosis in a patient with type 1 diabetes who stopped insulin treatment (by her own decision) and administrated oral glucose lowering therapy. It is very important for a type 1 diabetic patient not to discontinue insulin treatment in order to prevent any complication like acidosis. SGLT2 cannot be used alone, without insulin therapy in type 1 DM.

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