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Case Report / Olgu Sunumu

Two cases of euglycemic diabetic ketoacidosis caused by dapagliflozin

Necla Güngörler[1], **Leyla Seyhan**[1], **Zafer Pekkolay**[2]

1 Dicle University Faculty of Medicine, Department of Internal Medicine, Diyarbakır, Turkey.

2 Dicle University Faculty of Medicine, Department of Endocrinology, Diyarbakır, Turkey.

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Abstract

Hyperglycemia (Glucose> 250 mg/dL), metabolic acidosis (pH <7.3), ketosis (ketonemia or ketonuria) are stated as diagnostic criteria for diabetic ketoacidosis. Diabetic ketoacidosis can rarely be seen in blood glucose below 250 mg/dL. This condition is called euglycemic diabetic ketoacidosis. Although it is a rare condition, since a normal glucose level may exclude the diagnosis, it may cause a delay in treatment and consequently increase morbidity and mortality. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are new generation oral anti-diabetic drugs used in the treatment of diabetes mellitus. It can cause rare but serious complications, such as euglycemic diabetic ketoacidosis. With these case reports, we aimed to raise awareness about euglycemic diabetic ketoacidosis.

Keywords: Dapagliflozin, euglycemic ketoacidosis, sodium-glucose co-transporter 2 (SGLT-2) inhibitors

Dapagliflozinin neden olduğu iki öglisemik diyabetik ketoasidoz olgusu

Öz

Hiperglisemi (Glukoz> 250 mg/dL), metabolik asidoz (pH <7,3), ketozis (ketonemi veya ketonüri) diyabetik ketoasidozun tanı kriterleri olarak belirtilmektedir. Nadiren kan şekeri 250 mg/dL'nin altında diyabetik ketoasidoz görülebilmektedir. Bu durum öglisemik diyabetik ketoasidoz olarak adlandırılmaktadır. Nadir bir durum olmasına rağmen normal bir glukoz düzeyi tanıdan uzaklaştırabileceği için tedavinin gecikmesine ve bunun sonucunda artmış morbidite ve mortaliteye sebep olabilir. Sodyum-glukoz ko-transporter 2 (SGLT2) inhibitörleri, diabetes mellitus tedavisinde kullanılan yeni kuşak oral antidiyabetik ilaçlardır. Öglisemik diyabetik ketoasidoz gibi, nadir fakat ciddi komplikasyonlara neden olabilir. Bu olgu sunumları ile, öglisemik diyabetik ketoasidoz hakkında farkındalık yaratmayı amaçladık.

Anahtar kelimeler: Dapagliflozin, öglisemik ketoasidoz, sodyum-glukoz ko-transporter 2 (SGLT-2) inhibitörleri.

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Correspondence / Yazışma Adresi: *Zafer Pekkolay, Dicle University Faculty of Medicine, Department of Endocrinology, Diyarbakır, Turkey e-mail: drpekkolay@gmail.com*

INTRODUCTION

Diabetes Mellitus (DM) is a severe disease with a high mortality and morbidity rate[1]. Diabetic ketoacidosis is a serious complication of DM and is considered among endocrine emergency. Hyperglycemia (glucose> 250 mg/dL), metabolic acidosis (pH <7.3), ketosis (ketonemia or ketonuria) are among the diagnostic criteria of diabetic ketoacidosis[2]. Approximately 6% of adults presenting with DKA have a blood glucose level of <250 mg/dl. In euglycemic ketoacidosis, the glucose level is not at the level of ketoacidosis[3]. Although euglycemic diabetic ketoacidosis is a rare condition, a normal blood glucose level can result in delayed treatment and ultimately increased morbidity and mortality[4]. SGLT 2 inhibitors, including dapagliflozin, have been associated with rare cases of euglycemic diabetic ketoacidosis[5].

We planned to present the follow-up and treatment process of two patients with Type 2 DM in these case reports. In our intensive care units, they were diagnosed with euglycemic diabetic ketoacidosis and used dapagliflozin.

CASE 1 PRESENTATION

A 52-year-old male patient diagnosed with DM for 20 years presented with complaints of dysuria. He had been using dapagliflozin, metformin, vildagliptin, and glimepiride for two years in his history. In physical examination, consciousness was clear, and orientation and cooperation were present. Glasgow Coma Scale (GCS); 15 (E4M6V5) Body Temperature; 36.7^{o}C, Blood pressure; 110/56 mmHg, Respiratory Rate; 20/min, heart rate was 98 beats/min. The patient with positive leukocytes in the urine was diagnosed with urinary infection. The patient's blood glucose measured was 162 mg/dL. Blood gas parameters were: Ph:7.31, pCO2: 24, PO2: 58.8, HCO3: 14, Lactate: 1.3. Biochemical parameters were: Na: 127 mmol/L, Potassium: 3.72 mmol/L, Chlor: 100 mmol/L. Anion Gap: 18, the patient had metabolic acidosis with an increased anion gap.

Euglycemic diabetic ketoacidosis was considered because of the patient's metabolic acidosis in blood gas, ketone positivity in urine (2+) and use of dapagliflozin, an SGLT 2 inhibitor drug. For urinary system infection, the patient was started on meropenem 3 gr/day IV. On the first day of the patient's treatment due to euglycemic diabetic ketoacidosis; fluid therapy was started with 0.9% saline at a dose of 15-20 ml/kg/hour. Insulin infusion was started at a 0.1 U/kg/hour dose, following 24×1 blood glucose monitoring. The insulin dose was adjusted to the blood glucose was 150-200 mg/dL. Daily blood gas, biochemistry, and ketone levels in the urine were monitored. Fluid therapy with insulin and 0.9% saline was continued on the second day of the treatment. During the follow-ups, daily potassium replacement was applied to the patient for hypokalemia due to insulin therapy. Hourly blood glucose monitoring was continued. The patient's metabolic acidosis and urine ketone positivity (2+) continued. 4th day of treatment; The patient whose metabolic acidosis improved had ketone positivity (2+) in the urine, and fluid therapy was continued. Insulin therapy of the patient whose blood sugar returned to normal levels was discontinued. Antibiotherapy continued during this period. The patient was conscious, oriented, and cooperative, and his GCS was 15 (E4M6V5). On the fourth day of the treatment, the patient, whose blood gas acidosis improved, was followed by subcutaneous insulin therapy. After the patient's ketoacidosis improved, blood gas parameters were: Ph:7.38,

pCO2: 35, PO2: 20, HCO3act: 20,3, Lactate: 1.2. His blood sugar was 152 mg/dL.

CASE 2 PRESENTATION

A 55-year-old male patient diagnosed with DM for five years was being followed in the COVID-19 clinic due to COVID-19 pneumonia. In his history, it was learned that he had been using dapagliflozin for one year and metformin, vildagliptin, and gliclazide for two years. There was no consciousness, stupor, orientation, or cooperation in physical examination. Glasgow Coma Scale (GCS); 7 (E2M4V1), Body Temperature; 36.8^{o}C, Blood pressure: 150/90 mmHg, Respiration Rate; 22/min, kussmaul breathing was present, heart rate was 130 beats/min. The patient was being followed in the COVID clinic with the diagnosis of COVID-19 pneumonia. The patient's blood glucose measured was 205 mg/dL.

Blood gas parameters were: Ph: 6.95, pCO2: 26.3, PO2: 53.6, HCO3 act: 7 BE: - 27, Lactate: 1. Biochemical parameters were: Na: 138 mmol/L, Potassium: 4.58 mmol/L, Chlor: 106 mmol/L. Anion Gap: Calculated as 23, the patient had metabolic acidosis with an increased anion gap.

Euglycemic diabetic ketoacidosis was considered because of the patient's deep metabolic acidosis in blood gas, ketone positivity in urine (3+) and use of dapagliflozin, an SGLT 2 inhibitor drug. The patient was started on dexamethasone 8 mg IV, heparin 0.6 ml sc, and meropenem 3gr/day IV for COVID-19 pneumonia. On the first day of the patient's treatment due to euglycemic diabetic ketoacidosis; Fluid therapy was started with 0.9% saline at a dose of 15-20 ml/kg/hour. Insulin infusion was started at a 0.1 U/kg/hour dose, following 24×1 blood glucose monitoring. Fluid and insulin doses were adjusted to blood glucose was 150-200 mg/dL. Daily blood gas, biochemistry, and ketone levels in the urine were monitored. In the daily neurological examination of the patient, consciousness was lethargic, orientation, uncooperative, and GCS 7 (E2M4V1). Fluid therapy with insulin and 0.9% saline was continued on the second day of the treatment. Daily potassium replacement was applied to the patient for hypokalemia during the follow-up due to insulin therapy. Hourly blood glucose monitoring was continued. The patient's metabolic acidosis and urine ketone positivity (2+) continued. 5th day of treatment; The patient whose metabolic acidosis improved had ketone positivity in the urine (1+), and fluid therapy was continued. Insulin therapy of the patient whose blood sugar returned to normal levels was discontinued. Antibiotherapy continued during this period. The patient's consciousness was confused, orientation and cooperation were moderate, and GCS was 12(E3M5V4). On the fifth day of the treatment, the patient, whose blood gas acidosis improved, was followed by subcutaneous insulin therapy. After the patient's ketoacidosis improved, blood gas parameters were: Ph:7.56, pCO2: 23, PO2: 41, HCO3act: 24, BE:19.1 Lactate: 1.7. His blood sugar was 217 mg/dL.

DISCUSSION

Euglycemic Diabetic Ketoacidosis (DKA) is a clinical condition characterized by metabolic acidosis (pH <7.3), ketosis (ketonemia or ketonuria), and unlike diabetic ketoacidosis, there is no hyperglycemia (blood glucose <250 mg/dL). Metabolic acidosis with an increased anion gap is seen in our patients. Although the mechanism is not precise; It is thought that increased glucagon levels, resulting in increased ketone bodies, impaired insulin balance, increased lipolysis, and ketogenesis is caused. Its incidence increases in patients who use long-term fasting, carbohydrate-poor diet, physical activity, pregnancy, infection, alcohol, and insulin pump use. Although diabetic ketoacidosis is more common in the diabetic patient group, it is observed that the frequency of euglycemic diabetic ketoacidosis increases, especially in patients using SGLT 2 inhibitors[6,7].

Clinical findings such as nausea, vomiting, and abdominal pain are clinically similar to diabetic ketoacidosis.

In one of our cases, altered consciousness was the first finding. In the treatment, the drug that is thought to be the cause should be discontinued, saline-electrolyte therapy should be done first, and insulin therapy should be arranged so that the target glucose is 150-200 mg/dL with frequent blood glucose monitoring, and hypoglycemia should be avoided. In our cases, dapagliflozin treatment was terminated, and ketoacidosis treatment was administered.

SGLT2 inhibitors provide renal excretion of glucose and thus act by lowering elevated blood glucose levels in patients with type 2 diabetes. They usually do not cause hypoglycemia. Moderately reduce blood pressure and body weight[8].

It is known that SGLT2 inhibitors increase DKA risk[9]. SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin) have been associated with a higher risk of developing DKA compared to dipeptidyl peptidase 4 (DPP-4) inhibitors[10]. In several studies, "euglycemic" (usually meaning plasma glucose <250 mg/dL) DKA has been reported in patients with type 2 diabetes. Among the three SGLT2 inhibitors, canagliflozin was associated with the highest risk and empagliflozin with the lowest risk[11]. The absence of significant hyperglycemia in these individuals delays the recognition of ketoacidosis by both patients and clinicians. Serum ketones should be measured in any patient with nausea, vomiting, or malaise while taking SGLT2 inhibitors, and SGLT2 inhibitors should be discontinued if acidosis is confirmed[12]. Our patient is using dapagliflozin and metformin. Although metformin is a drug that causes metabolic acidosis by producing lactic acidosis, the mean lactate level in our cases excluded the diagnosis[13]. In the follow-ups of our patients, improvement of acidosis, negative ketone levels, and normalization of the anion gap are the findings showing the treatment response.

In some cases, although acidosis may occur, glucose may not increase. These situations can be explained as follows. Glucose levels may not be very high due to increased glucose consumption, nausea, and vomiting in infections. Glycogen storage is reduced during fasting. Alcohol consumption limits calorie intake, makes osmotic diuresis and facilitates ketogenesis. Trauma limits oral intake and increases glucose utilization[14].

In conclusion, Although SGLT 2 inhibitor drugs are newly introduced antidiabetic drugs, they can cause complications such as euglycemic ketoacidosis with high mortality. Even if the blood glucose level is normal in patients with diabetes and severe metabolic acidosis, this complication should be kept in mind, and the drugs used by the patients should be questioned carefully. Early diagnosis and early treatment of euglycemic ketoacidosis, a severe complication after SGLT 2 inhibitor use, reduce morbidity and mortality.

Informed Voluntary Consent Form: Consent form were taken from the patients.

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