

Metformin-Associated Lactic Acidosis: A Case Report

Metformin İlişkili Laktik Asidoz: Olgu Sunumu

ABSTRACT

A 65-year-old man was admitted to the emergency department with the complaints of general discomfort, nausea, vomiting, abdominal pain, dysuria and shortness of breath. Type II diabetes mellitus, essential hypertension, atrial fibrillation and chronic obstructive pulmonary disease were noted in his medical history. He was using metformin, warfarin and diltiazem besides inhaler medications. Laboratory test results were as follows: BUN 52 mg/dl, creatinine 2.9 mg/dl (one month ago it was 0.9 mg/dl), potassium 6.3 mmol/L, PT-INR 17.78, arterial blood pH 7.05, bicarbonate 5.3 mmol/L, partial carbon dioxide pressure 19 mmHg, and lactate level 175 mg/dl. The urine examination revealed pyuria and urinary density was 1028. The patient was considered to suffer from acute kidney injury, urinary tract infection and metformin-associated lactic acidosis (MALA). Metformin was withdrawn immediately and acute hemodialysis was planned. However, a central venous catheter could not be inserted because of high PT-INR values. Parenteral 0.9% NaCl, glucose – insulin solution infusions, sodium bicarbonate infusion as well as empirical intravenous ceftriaxone treatments were started. He dramatically responded to medical therapy and did not require any dialysis support. In the literature, hemodialysis has been proposed as the initial treatment modality of MALA. However, herein, we presented a favorable outcome without utilizing hemodialysis.

KEY WORDS: Metformin, Metformin-associated lactic acidosis, MALA, Acute kidney injury

ÖZ

Altmış beş yaşında erkek hasta genel durum bozukluğu, bulantı, kusma karın ağrısı, dizüri ve nefes darlığı yakınmaları ile acil servise başvurdu. Öyküsünden, hipertansiyon, tip 2 DM, kronik atriyal fibrilasyon ve KOAH tanıları olduğu; metformin, warfarin, diltiazem ve inhaler tedavileri almakta olduğu öğrenildi. Laboratuvar bulguları BUN: 52 mg/dl, Cr: 2,9 mg/dl (bir ay önce 0,9 mg/dl), K: 6,3 mmol/L, PT-INR: 17,78, arteriyel kan gazında pH: 7,05, HCO₃: 5,3 mmol/L, pCO₂: 19 mmHg, laktat düzeyi: 175 mg/dl idrar dansitesi: 1028, pyüri (+) şeklindeydi. Hastaya akut böbrek yetmezliği, idrar yolu enfeksiyonu ve metformin ilişkili laktik asidoz (MİLA) tanıları konuldu. Metformin derhal kesildi ve acil hemodiyaliz planlandı. Ancak yüksek INR düzeyleri nedeniyle santral venöz kateter takılamadı. Parenteral %0,9 NaCl, nötralize glukoz - insulin solüsyonu, NaHCO₃ infüzyonu ve ampirik seftriakson tedavisi başlandı. Hastanın izleminde dramatik düzelmeye kaydedildi ve diyaliz gereksinimi kalmadı. Literatürde, hemodiyalizin MİLA olgularında öncelikle tedavi yaklaşımı olduğu belirtilmekteyken, bizim olgumuzda hemodiyalize gerek kalmadan oldukça olumlu bir sonuç elde edilmiştir.

ANAHTAR SÖZCÜKLER: Metformin, Metformin ilişkili laktik asidoz, MİLA, Akut böbrek yetersizliği

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INTRODUCTION

Metformin is a widely prescribed biguanide for the management of patients with type II diabetes starting from the prediabetes period. It increases sensitivity to insulin action and improves glycemic control and lipid profile. The main excretion site is the kidney; however, the major adverse effects are related with the gastrointestinal system and include abdominal pain, diarrhea and vomiting (1). Lactic acidosis, a serious side effect with a high mortality rate, is a rarely reported complication in patients using this medication (2). Coexistence of some clinical conditions such as dehydration, hypoxemia and the use of nephrotoxic drugs might facilitate the development of lactic acidosis (3).

We present a patient using metformin with profound metabolic acidosis together with concomitant acute kidney injury and urinary tract infection. The clinical condition improved with supportive management and without dialysis therapy in this case

CASE REPORT

A 65-year-old man presented to the emergency department with general discomfort, agitation, nausea, vomiting, abdominal pain, dysuria and shortness of breath for the last two days. Type II diabetes mellitus, hypertension, mild congestive heart failure with atrial fibrillation and chronic obstructive pulmonary disease were noted in his medical history. He was on treatment with metformin (1000 mg twice a day), diltiazem (90 mg three times a day) and warfarin (5 mg once a day) besides the inhaler medications. He was also using flurbiprofen (100 mg twice a day) and clarithromycin (500 mg twice a day) for 7 days due to acute rhinosinusitis. At admission, mild mental confusion, agitation, and a deep and frequent breathing pattern were noted. Arterial blood pressure was measured as 100/70 mmHg, body temperature was 36.9°C, respiratory rate was 26 breaths per minute, pulse rate was 96 beats per minute and pulse oximetry showed 88% oxygen saturation. Physical examination revealed dry appearance of mucosa, decreased turgor of skin, tachypnea, prolonged expiration during breathing, few sibilant rhonchi, arrhythmia, and sensitivity at the epigastric and suprapubic regions.

His laboratory test results were as follows; blood urea nitrogen: 52 mg/dl (normal range (NR): 7-20) mg/dl, creatinine: 2.9 mg/dl (NR: 0.9-1.3 mg/dl; one month ago it was 0.9 mg/dl), serum glucose; 132 mg/dl (NR: 70-100 mg/dl), potassium: 6.3 mmol/L (NR: 3.5-5.3 mmol/L), sodium: 133 mmol/L (NR: 135-146 mmol/L), hemoglobin: 11.6 g/dl (NR: 13.5-17.5 g/dl), white blood cell count: 13000/mm³ (NR: 4500-11000 /mm³), thrombocytes: 437000/mm³ (NR: 130000-400000 /mm³), PT-INR: 17.78 (NR: 0.8-1.25), arterial blood pH: 7.05 (NR: 7.35-7.44), bicarbonate (HCO₃): 5.3 mmol/L (NR: 20-26 mmol/L), partial oxygen pressure: 74 mmHg (NR: 80-98 mmHg), blood oxygen saturation: 90%, partial carbon dioxide pressure: 19 mmHg (NR: 36-43 mmHg), lactate level: 175 mg/dl (NR: 5-22

mg/dl) and blood anion gap: 24 mEq/L (NR: 8-12 mEq/L). The urine examination revealed a density of 1028, pyuria, and a positive test for leukocyte esterase but not for glucose or ketone. Chest X ray revealed hyper inflated lungs, flattened diaphragm and ribs without a sign of infiltration in the parenchyma. Renal Doppler ultrasonographic examination revealed normal-sized kidneys with mild increase in parenchymal echogenicity.

The patient was considered to be suffering from acute kidney injury, lower urinary tract infection and metformin-associated lactic acidosis (MALA). Intravenous NaHCO₃ supplementation in 0.9% NaCl solution (every 5 ml containing 1 mEq NaHCO₃) at a rate of 2 ml/kg/hour and 10% dextrose solution (containing 1 unit regular insulin for every 5 gr of glucose) at a rate of 1 ml/kg/hour and nasal oxygen were started in the emergency room. Empirical 1 gr intravenous ceftriaxone treatment twice daily was introduced after sampling for urine culture. The urine output was monitored and the 20 ml per hour urine output increased to 70 ml per hour after 8 hours of treatment. The NaHCO₃ dosage was arranged closely with repeated pH measurements. Acute hemodialysis was planned due to the profound metabolic acidosis. However, central venous line placement could not be attempted due to the unexpectedly high PT-INR values. Three units of fresh frozen plasma were transfused and 10 mg intravenous vitamin K twice daily was started. On the following day, the patient was transferred to the nephrology clinic with values of pH: 7.19, HCO₃: 11.4 mmol/L and creatinine: 2.1 mg/dl. The general condition was somewhat improved and the agitation decreased. Dialysis support was not given even when PT-INR became near normal (1.28) on the third day of hospitalization since the laboratory values and clinical condition improved progressively.

He was discharged at the eighth day of hospitalization with the following laboratory results: pH 7.40, HCO₃ 28 mEq/L and creatinine 0.6 mg/dl. After metformin withdrawal, the patient was ordered repaglinide for diabetes management. Two weeks later, he was clinically stable with similar laboratory values on outpatient follow-up.

DISCUSSION

Metformin-associated lactic acidosis (MALA) should be kept in mind in the differential diagnosis of metabolic acidosis in elderly patients who have predisposing conditions (4). It should be noted that metformin is contraindicated in renal insufficiency (serum creatinine >1.4 mg/dl in women and >1.5 mg/dl in men), severe congestive heart failure and liver failure (4). Metformin should be used with further caution in clinical conditions like dehydration, hypoxemia and concomitant use of nephrotoxic agents, since lactic acidosis could develop more easily.

We have discussed a case of MALA in an elderly patient who had concomitant acute kidney injury and urinary tract infection. The blood metformin concentration could not be measured but the absence of clinical evidence for tissue hypoperfusion and

severely disturbed tissue oxygenation suggested metformin as the cause of the lactic acidosis. In our case, dehydration (due to excessive vomiting and decrease in oral fluid uptake) and nephrotoxicity of flurbiprofen seemed to be precipitating both the development of MALA and acute kidney injury. It should be noted that, acute kidney injury itself had probably contributed to the process by impairing the renal compensatory mechanisms, retarding the recovery of acidosis and causing a decrease in drug elimination.

The choice of initial treatment strategy in MALA cases can change depending on the hemodynamic and respiratory instability of the patients (4). Some reports have proposed hemodialysis as the initial treatment modality in order to ameliorate acidosis and to provide rapid drug elimination (5). We also planned emergent hemodialysis for our case. However, placement of a central venous line was not attempted and hemodialysis techniques could not be performed due to extremely high level of initial PT-INR value. Such a high level probably resulted from warfarin interaction with recently ordered flurbiprofen and clarithromycin. INR level was normalized on the third day. However, the patient did not require hemodialysis anymore with his clinical and laboratory evaluations at that time. Intravenous fluid resuscitation and sodium bicarbonate administration with close monitoring ended up with a favorable outcome in our case.

In conclusion, conservative approaches including appropriate parenteral hydration, controlling underlying infections and parenteral sodium bicarbonate administration under close monitoring might be a rescue strategy in patients who have special contraindications for invasive procedures, even when severe acidosis is present.

Declaration of Interest: We report no conflicts of interest. We alone are responsible for the content and writing of the paper.

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