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Metformin-Associated Lactic Acidosis: A Case Report

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Abstract

Metformin is a widely prescribed and effective oral antidiabetic agent used in the treatment of type 2 diabetes mellitus (DM). Although generally well tolerated, metformin-associated lactic acidosis (MALA) is a rare but potentially fatal complication, especially in the presence of predisposing risk factors. Here in, we present a case of MALA that developed after volume depletion related to bowel preparation for endoscopic procedures.

A 56-year-old male patient with type 2 diabetes mellitus who was taking metformin presented with nausea, vomiting, and decreased urine output following endoscopy preparation. Laboratory tests revealed severe metabolic acidosis (pH: 7.05; HCO_3^-: 8.9 mmol/L; lactate: 21 mmol/L) and severe renal dysfunction (creatinine: 11.91 mg/dL). The patient was diagnosed with MALA based on clinical and biochemical findings and underwent emergency hemodialysis and intensive intravenous hydration. After treatment, the patient's metabolic parameters improved rapidly and the need for dialysis disappeared. Outpatient follow-up revealed that renal function had returned to normal.

This case underscores the potential risk of continuing metformin therapy during peri-procedural periods associated with volume depletion. The omission of pre-procedural discontinuation of metformin in our patient likely contributed to the development of life-threatening lactic acidosis. Early diagnosis and timely initiation of renal replacement therapy are critical for reducing mortality in MALA cases.

Key Words: Metformin, Lactic acidosis, MALA, Acute kidney injury, Hemodialysis, Endoscopic preparation

Metformin İlişkili Laktik Asidoz: Bir Vaka Sunumu

Özet

Metformin, tip 2 diyabetes mellitus (DM) tedavisinde yaygın olarak kullanılan etkili ve güvenli bir oral antidiyabetiktir. Ancak nadir görülen fakat mortalitesi yüksek bir komplikasyonu olan metformin ilişkili laktik asidoz (MALA), özellikle predispozan risk faktörlerinin varlığında hayatı tehdit edici bir tabloya yol açabilir. Bu çalışmada, endoskopik işlem hazırlığı sırasında gelişen hipovolemi sonrası akut böbrek hasarı ve ağır laktik asidoz gelişen bir MALA olgusu sunulmaktadır.

Tip 2 DM nedeniyle metformin kullanan 56 yaşındaki erkek hasta, endoskopi hazırlığı sonrası gelişen bulantı, kusma ve idrar çıkışında azalma ile başvurdu. Laboratuvar testlerinde ağır metabolic asidoz (pH: 7,05; HCO_3^-: 8,9 mmol/L; laktat: 21 mmol/L) ve ciddi böbrek fonksiyon bozukluğu (kreatinin: 11,91 mg/dL) saptandı. Klinik ve biyokimyasal bulgularla MALA tanısı konulan hastaya acil hemodiyaliz ve yoğun intravenöz hidrasyon uygulandı. Tedavi sonrası hastanın metabolic parametreleri hızla düzeldi ve diyaliz gereksinimi ortadan kalktı. Poliklinik kontrollerinde renal fonksiyonlarının tamamen normale döndüğü gözlendi.

MALA, özellikle renal fonksiyonları etkileyebilecek durumlarda metformin kullanımının devam ettiği olgularda ciddi sonuçlara yol açabilir. Bu vaka, invaziv işlem hazırlığında metforminin kesilmemesinin potansiyel risklerini ortaya koymakta ve işlem öncesi dönemde metformin tedavisinin durdurulmasının önemine dikkat çekmektedir. MALA şüphesi bulunan olgularda erken tanı ve tedavi, mortaliteyi azaltmada kritik rol oynamaktadır.

Anahtar kelimeler: Metformin, Laktik asidoz, MALA, Akut böbrek hasarı, Hemodiyaliz, Endoskopi hazırlığı

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INTRODUCTION

Metformin is the most commonly prescribed oral antidiabetic drug used in the first line of treatment for type 2 DM. It has been in use for many years, so its side effects are well known, and it is generally considered safe. The most common side effects are gastrointestinal (GI) side effects such as nausea, vomiting, and diarrhea. A rare but potentially life-threatening side effect of metformin therapy is lactic acidosis. This typically occurs in patients for whom metformin use is contraindicated. Examples include patients with kidney or liver failure, very elderly patients, and those with circulatory disorders such as congestive heart failure (1). Despite its rarity, metformin-associated lactic acidosis (MALA) remains a clinically significant concern, with an estimated incidence ranging from 3.3 to 9 cases per 100,000 patient-years. Nevertheless, new cases continue to be reported in the literature. The associated mortality is considerable, with rates reported between 30% and 50%. Historically, phenformin, a biguanide predecessor of metformin, was withdrawn from the market in the 1970s due to its strong association with fatal lactic acidosis. The estimated incidence of phenformin-induced lactic acidosis was approximately 129 cases per 100,000 patient-years, which is markedly higher than that observed with metformin (2).

Our case describes the diagnosis and treatment process of a patient with MALA. We aim to draw attention to this rare complication and contribute to its treatment.

CASE REPORT

A 56-year-old male patient presented with nausea and vomiting that had been ongoing for 4 days. He had no accompanying abdominal pain. He had gas and bowel movements. However, he had not urinated at all in the last day. He had a history of type 2 DM and hypertension (HT). He was taking metformin 2x1 g and valsartan+hydrochlorothiazide. It was learned that the patient had undergone upper GI endoscopy and colonoscopy 5 days prior to presentation. In preparation for the procedure, the patient had been on a liquid diet for three days prior to the procedure and had two enemas on the morning of the procedure. The patient's complaints began after the procedure and continued uninterrupted. It was learned that the patient had been taking metformin continuously before, on the day of, and after the procedure.

Vital signs were measured as follows: blood pressure 110/70 mmHg, respiratory rate 28/min, pulse 105/min, oxygen saturation 98. Physical examination revealed that the patient was conscious and in fair general condition. There was retractions in breathing. Lung sounds were normal, and no edema was detected. On admission, blood urea nitrogen (BUN) was 47 mg/dL, creatinine was 11.91 mg/dL, pH was 7.05, pCO2 was 31 mm/Hg, pO2 43 mm/Hg, bicarbonate (HCO3) 8.9 mmol/L, actual base deficit -20.5 mmol/L, lactate 21, anion gap (AG) 52, and basal creatinine was normal. The patient's test results at admission are shown in Table 1. When a small amount of urine was collected, no leukocytes or erythrocytes were observed in the urine tests. Proteinuria and urine sediment were not detected. A non-contrast urinary system tomography and ultrasound were performed to rule out postrenal acute kidney disease (AKI), and no pathology was detected. The patient was placed on hemodialysis due to the need for dialysis with the preliminary diagnoses of AKI and MALA associated with acute tubular necrosis. After dialysis without ultrafiltration for 2 hours, the patient's follow-up and treatment continued in the intensive care unit. The intravenous (IV) hydration initiated at the beginning was continued at 500 ml/hour of normal saline for the first 8 hours. However, the patient's follow-up tests showed BUN 37.8 mg/dL, creatinine 9.29 mg/dL, pH 7.12, pCO2 21.3 mm/Hg, pO2 108 mm/Hg, bicarbonate (HCO3) 6.9 mmol/L, actual base deficit -20.6 mmol/L, lactate 17, anion gap (AG) 43, and K 7.38, the patient underwent hemodialysis again. After hemodialysis, IV hydration was continued at 200 ml/h, and the infusion rate was adjusted according to urine output, central venous pressure (CVP), and physical examination. Subsequently, the patient began to urinate, had no electrolyte abnormalities, and her blood gas levels normalized, and she did not require further dialysis. Tests performed to determine the etiology of ABH revealed no proteinuria or erythrocyte sedimentation in the control urine. Complement (C3, C4), antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA), anti-glomerular basement membrane (anti-GBM) were negative. Urinary system ultrasound revealed normal kidney sizes and no additional structural abnormalities. Blood culture, urine culture, sputum culture, and viral markers tested for infectious pathologies were negative. The patient was discharged with creatinine 0.95 mg/dL, BUN 13 mg/dL, K 3.51 mmol/L, pH 7.43, pCO2 41 mmHg, pO2 61 mmHg, HCO3-27.2 mmol/L, and lactate 0.8. No issues were identified during subsequent outpatient follow-ups.

Table 1. Test results from the application.

Variables Result	Variables Result
Glucose	89 mg/dL
BUN	47 mg/dl
Creatinine	11.91 mg/dL
Cl	89 mmol/L
Na	150 mmol/L
K	5.19 mmol/L
Ca	10.21 mg/dL
P	9.81 mg/dL
PH	7.05
PCO_2	31 mm/Hg
PO_2	43 mm/Hg
HCO_3	8.9 mmol/L
ABE	-20.5 mmol/L
Lactate	21
CRP	50 mg/dL
WBC	18.7 x 10^9/L
NEU	16.2 x 10^9 /L
HGB	15.5 g/dL
PLT	376 x 10^9/L

Na: Sodium, K: Potassium, Cl: Chloride, P: Phosphorus, CRP: C-reactive protein,
WBC: White blood cell, NEU: Neutrophil, HGB: Hemoglobin, PLT: Platelet, ABE: Actual Base Excess

DISCUSSION

Metformin is widely used as a first-line agent in the treatment of type 2 DM and is generally well tolerated. However, MALA, a rare but serious complication, is a condition that clinicians should approach with caution due to its high mortality risk. MALA is often seen in conjunction with predisposing conditions such as renal dysfunction, hypoperfusion, tissue hypoxia, or sepsis (3-5).

The presented case is a case of MALA that developed in a patient with previously normal renal function, following severe vomiting and enema administration after an endoscopic procedure, against a background of prerenal ABH. The patient's continued use of metformin during the pre-procedure period impaired drug elimination, leading to severe lactate accumulation and life-threatening metabolic acidosis. Another possible cause of renal dysfunction was phosphate nephropathy associated with enema.

The literature reports that the incidence of MALA is quite low, but when it does occur, mortality ranges from 30% to 50% (1,6). Its predecessor, phenformin, was withdrawn from the market in the 1970s due to the high risk of lactic acidosis (7). Metformin is considered safer, but it should be used with caution in cases of renal insufficiency, hepatic dysfunction, or hypovolemia.

The use of metformin prior to invasive procedures or surgical interventions has been a topic of debate in recent years, and many guidelines include recommendations on this issue. Guidelines such as NICE and the British National Formulary (BNF) recommend discontinuing metformin prior to procedures in patients with an eGFR <60 mL/min/1.73 m² or at

risk of volume loss (8,9). The American Diabetes Association (ADA) and the Australian Diabetes Society similarly recommend discontinuing metformin 24–48 hours before contrast imaging and surgical procedures and not restarting it in the postoperative period without evaluating renal function (10,11).

In our case, the patient was fed only liquids for three days during endoscopy preparation, and the resulting hypovolemia due to severe vomiting after the procedure and the administration of an enema reduced the renal elimination of metformin, leading to a severe case of lactic acidosis (lactate 21 mmol/L, pH 7.05, anion gap 52). The clinical picture was evaluated in favor of MALA, with high anion gap metabolic acidosis and marked lactate elevation. Early hemodialysis and intravenous hydration administered to the patient resulted in rapid renal and metabolic improvement. As noted in the literature, hemodialysis is an effective treatment method in severe cases of MALA, both for clearing metformin and correcting acidosis (12–15).

CONCLUSION

In conclusion, this case highlights an issue that is often overlooked in routine clinical practice: the need to discontinue metformin therapy prior to planned endoscopic or surgical procedures. Especially in cases where fluid restriction is applied, continued use of metformin may predispose to the development of latent renal dysfunction and MALA. Therefore, discontinuation of metformin therapy prior to such procedures and assessment of renal function before resuming treatment in the post procedural period is recommended.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report.

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