Case Report

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Single Dose Metformin-Induced Severe Metabolic Acidosis

Kemal Şener[1], İnan Beydilli[1], Tamer Çolak[1], Adem Çakır[2], Giray Altunok[1], Raşit Baysal[1], Ertuğrul Altuğ[3]

[1]Department of Emergence Medicine, Republic of Turkey, Mersin City Hospital, Mersin, Türkiye

[2]Department of Emergency Medicine, Ministry of Health of Turkey; Canakkale Mehmet Akif Ersoy State Hospital, Canakkale, Türkiye

[3]Department of Emergence Medicine, Republic of Turkey, Ministry of Healthy Başaksehir Cam and Sakura State Hospital, Istanbul,Türkiye

Abstract

Metformin, a member of the biguanide family, is one of the most widely used drugs in the treatment of diabetes worldwide. It was first commercialized in 1957, and its use has steadily increased since then. Metformin is recommended as the first pharmacological agent in the treatment of type 2 diabetes. 29-year-old female patient presented to our emergency department due to nausea and vomiting. In her history, she denied diarrhea, urinary symptoms suggestive of urinary tract infection, ingestion of any unusual food, use of any other medications or substances, and reported spending the entire day at home. Upon presentation, the patient was in good general condition, awake, alert, and cooperative. Vital signs were as follows: arterial blood pressure 110/70 mmHg, pulse rate 78 beats/min, respiratory rate 19 breaths/min, oxygen saturation 98%, and body temperature 36.5°C. Physical examination did not reveal any pathological findings. Recently, metformin has been used for weight loss as well as for therapeutic purposes. It is seen that even a single dose of metformin can cause serious side effects. People who use metformin both within and outside the indication should be careful.

Keywords: Lactic acidosis, MALA, metformin, single dose

Introduction

Metformin, a member of the biguanide family, is one of the most widely used drugs in the treatment of diabetes worldwide (1). It was first commercialized in 1957, and its use has steadily increased since then. Metformin is recommended as the first pharmacological agent in the treatment of type 2 diabetes. There is even literature suggesting its use in patients with prediabetes (2). Additionally, it is used to reduce insulin resistance in gestational diabetes and pregnant women with type 2 diabetes (3). However, the American Diabetes Association does not recommend its use as first-line therapy due to its feto-placental transfer (4). Metformin acts through various mechanisms aimed at reducing serum glucose, including increasing insulin sensitivity, antagonizing gluconeogenesis, and enhancing intracellular glucose uptake. However, it also has several significant side effects, including gastrointestinal symptoms (nausea, vomiting, and diarrhea), increased lactate production, decreased lactate clearance, and the potential to induce acidosis (5). Metformin-associated lactic acidosis (MALA) emerges as a cause of high mortality and morbidity (6). MALA occurs in the presence of conditions such as kidney injury, a history of liver or heart failure, or in cases of shock, acute or chronic medical comorbidities (7). Hyperlactatemia arises through several mechanisms. Metformin levels above the therapeutic dose lead to the inhibition of complex 1 in the mitochondrial respiratory chain, resulting in impaired oxidative phosphorylation. Metformin also inhibits pyruvate carboxylase, leading to reduced pyruvate metabolism and increased conversion of pyruvate to lactate. Impaired oxidative phosphorylation and pyruvate utilization result in decreased ATP production. This situation leads to increased AMP levels, which affect the inhibition of fructose-1,6-bisphosphatase, a rate-limiting enzyme in gluconeogenesis. Impaired gluconeogenesis results in decreased hepatic clearance of lactate. Additionally, metformin inhibits glucose-6-phosphatase, disrupting glycogenolysis. Decreased gluconeogenesis and glycogenolysis, reliance on glycolysis, and increased glucose utilization can trigger hypoglycemia observed in some MALA cases (8-10).

Our literature review revealed numerous cases of metabolic acidosis due to metformin overdose or secondary causes such as renal dysfunction and sepsis. However, no case of profound metabolic acidosis due to a single dose of metformin was found in the literature. In this case, we

Corresponding Author: Kemal Şener
e-mail: drkemalsener@hotmail.com
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aim to highlight the potential for profound lactic acidosis in patients using a single dose of metformin and contribute to the literature. Necessary consents were obtained from the patient for this case report, and they were adequately informed about the process.

Case Report

29-year-old female patient presented to our emergency department due to nausea and vomiting. In her history, she denied diarrhea, urinary symptoms suggestive of urinary tract infection, ingestion of any unusual food, use of any other medications or substances, and reported spending the entire day at home. Upon presentation, the patient was in good general condition, awake, alert, and cooperative. Vital signs were as follows: arterial blood pressure 110/70 mmHg, pulse rate 78 beats/min, respiratory rate 19 breaths/min, oxygen saturation 98%, and body temperature 36.5°C. Physical examination did not reveal any pathological findings.

The patient had no chronic illnesses or surgical history other than cesarean section. She did not take any regular medications. Symptom-directed treatment was initiated after physical examination (intravenous infusion of 500 ml saline containing 40 mg pantoprazole and 4 mg ondansetron), and blood tests were requested. Before the test results were fully available, the patient expressed a desire to be discharged due to clinical improvement. After receiving appropriate information, the patient left the hospital. Laboratory results of the patient's application are given in Table-1. Venous blood gas analysis performed upon arrival showed pH 7.45, PCO_2 27 mmHg, HCO_3 18.4 mmol/L, and lactate level 4.9 mmol/L.

Later the same day (approximately 8 hours later), the patient was brought back to the emergency department via emergency medical services with decreased level of consciousness. Paramedics reported administering 50 mg intravenous dextrose due to a blood sugar level of 30 mg/dL. The patient was evaluated while dextrose infusion continued. On repeat physical examination, the Glasgow Coma Scale was 8, indicating decreased orientation and cooperation. Apart from this, no pathological findings were observed on examination. Vital signs at arrival were arterial blood pressure 90/50 mmHg, pulse rate 98 beats/min, respiratory rate 25 breaths/min, oxygen saturation 99%, and body temperature 36.5°C. Electrocardiography revealed normal sinus rhythm.

Following dextrose therapy, the patient's blood sugar levels rose, consciousness improved, and orientation and cooperation began to normalize, reaching a Glasgow Coma Scale of 15 after some time. Venous blood gas analysis performed upon arrival showed pH 6.96, PCO_2 22 mmHg, HCO_3 4.7 mmol/L, lactate level 15.6 mmol/L, and blood sugar level 33 mg/dL. Thirty minutes after regaining consciousness, repeat blood gas analysis showed worsening metabolic acidosis and increased lactate levels. Based on the patient's history and investigations, toxicological evaluation was initiated.

According to the patient's history, she had taken a single 1000 mg metformin tablet before breakfast that morning with the intention of losing weight. Apart from this, there was no history of alcohol or herbal medicine use, suicidal attempts, or ingestion of any other substances. During follow-up, venous blood gas analysis results were obtained (Table-2). Hourly urine output was normal, and renal function tests were within normal limits. Urine analysis was negative for ketones and showed no signs of infection. Serum ethanol and paracetamol levels were negative. Brain computed tomography did not reveal any pathology explaining the patient's altered mental status. Apart from metformin use, no other etiological cause was identified, and metformin-induced severe metabolic acidosis was considered primary in the etiology of deep metabolic acidosis.

Due to ongoing metabolic acidosis and lactic acidosis during follow-up, the patient received a 50 mEq sodium bicarbonate (Na^+ HCO_3) bolus and maintenance therapy at 20 mEq/hour. Additionally, she received hourly 500 cc saline infusion and 100 cc/hour 5% dextrose infusion. Preparation for hemodialysis began due to the possibility of persistent severe metabolic acidosis. However, as the acidosis began to decrease with medical treatment, hemodialysis was deferred upon normalization of blood gas parameters at the 8th hour of admission.

The patient remained stable during the 12-hour observation period in the emergency department, with stable vital signs and normalization of blood gas parameters. Subsequently, she was admitted to the internal medicine service for further monitoring and investigations. On the 2nd day of hospitalization, no additional etiological cause was found, and the patient was discharged in good condition.

Table 1: Laboratory results of the patient at the time of first admission

WBC	HBG	PLT	Glukoz	Üre	Cr	ALT	AST	Na^+
5,54	11,4	263	80	24	1,0	15	34	140
K^+	**Cl^-**	**Amilaz**	**Lipaz**	**GGT**	**CRP**	**Aptt**	**INR**	**HsTrop**
5,0	111	51	29	12	0,39	18	1,09	Negatif

WBC: Leukocyte ($x10^3/mm^3$); **HGB:** Hemoglobin (mg/dL); **PLT:** Platelet ($x10^3/mm^3$); **Glucose, Urea** (mg/dL); **Cr:** Creatinine (mg/dL); **ALT:** Alanine transaminase (IU/L); **AST:** Aspartate transaminase (IU/L); **Na^+**: Sodium (mEq/L); **K^+**: Potassium (mEq/L); **Cl^-**: Chlorine (mEq/L); **Amylase, Lipase** (IU/L); **GGT:** Gamma Glutamyl transferase (IU/L); **CRP:** C-reactive protein (mg/dL); **INR:** International Normalized Rate; **HsTrop:** High sensitivity troponin

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Table 2: Venous blood gas follow-up results of the patient

Parametre	1. Admission	2. Admission	2. Admission 30th min	2. Admission 60th min	2. Admission 2nd h	2. Admission 4th h	2. Admission 8th h	2. Admission 12th h
pH	7.45	6.95	6.75	6.84	6.97	7.11	7.42	7.45
PCO_2 (mmHg)	27	22.2	21	30.9	35	30	28.7	27
HCO_3 (mmol/L)	18.4	4.7	4.1	5.1	7.9	14	18.2	19.3
Laktate(mmol/L)	4.8	15.8	20.8	22.3	19.9	8.2	4.9	3.3
Na^+ (mmol/L)	141	146	143	142	143	140	138	139
K^+ (mmol/L)	4.1	4.1	4.0	4.5	5.1	4.2	3.5	3.6
Cl^-(mmol/L)	108	116	111	103	102	104	101	100
Glukoz (mg/dL)	80	33	115	272	279	185	176	124

PCO_2: Partial Carbon Dioxide; **HCO_3**: Bicarbonate; **Na^+**: Sodium (mEq/L); **K^+**: Potassium (mEq/L); **Cl^-**: Chlorine (mEq/L); **min**: Minute; **h**: Hour

Discussion

MALA is a rare complication of metformin use. In the literature, it is often associated with high single doses or therapeutic doses in patients with renal or hepatic dysfunction (11,12). Lactic acidosis in patients taking metformin can occur in three different clinical scenarios: metformin-induced, metformin-associated, and unrelated to metformin (13). In cases of metformin-induced lactic acidosis, symptoms typically manifest within 6-12 hours after ingestion, and hemodialysis is considered the gold standard treatment in cases involving renal insufficiency or overdose (14).

In our case, the patient took a single therapeutic dose of metformin without any renal impairment, thus treatment did not require hemodialysis. However, hemodialysis would have been considered if there had been no improvement in severe metabolic acidosis. Considering metformin's half-life of 18 hours, the patient's recovery period aligns with this timeframe (15). Mild compensated metabolic lactic acidosis was observed in our patient during the initial presentation. History of alcohol and substance use was negative, and no chronic illnesses or regular medication use were reported. During the second presentation, the presence of severe metabolic acidosis, elevated lactate levels, and hypoglycemia supports the clinical association with metformin. Therefore, clinicians should consider that even a single therapeutic dose can lead to severe metabolic and lactic acidosis in cases presenting with severe metabolic acidosis (16).

This case presentation could serve as an important guide indicating that even a single dose of metformin can induce severe metabolic acidosis in patients. However, a significant limitation of our study is the inability to measure metformin levels in the patient.

Conclusion

Recently, metformin has been used for weight loss as well as for treatment purposes. It is seen that metformin is not a very innocent drug and even a single dose of metformin can cause serious side effects. People who use metformin both on and off-label should be careful. It should not be forgotten that life-threatening side effects may occur.

Patient consent form-Ethics

The case report has written in an anonymous characteristic, thus secret and detailed data about the patient has removed.

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