CASE REPORT

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A Rare Case of Mortal Metformin Intoxication

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Abstract

Metformin is the first-line oral antidiabetic for treating type 2 diabetes mellitus (DM). Its major toxicity is lactic acidosis (LA). Metformin-induced LA (MILA) rarely develops in the absence of an acute overdose. However, LA is the most serious complication of metformin intoxication, and MILA is associated with high mortality rates. We presented a comparative evaluation of a mortal MILA case with the literature. A 47-year-old woman with type 2 DM and using metformin, admitted to the emergency department with abdominal pain and vomiting that started 4 h after taking 60 gr metformin for suicide. There was no abnormality on her initial hemogram, biochemical profile, or coagulation findings. However, her arterial blood gas analysis on admission was remarkable for pH: 7.025 and lactate: 20.32 mmol/L. HD was planned rapidly in the patient with high anion gap metabolic acidosis. Despite the aggressive therapy, the patient developed ventricular fibrillation and then cardiac arrest and died in the 4th hour of her admission to the emergency department. Under acute and high-dose metformin intoxication, metabolic acidosis can develop rapidly. Hemodialysis therapy should not be delayed, particularly in cases with MILA. It should be remembered that these cases are mortal despite aggressive treatment.

Keywords: Hemodialysis, lactic acidosis, metformin, mortality, suicide

Introduction

Metformin is the first-line oral antidiabetic for treating type 2 diabetes mellitus (DM) [1]. Although metformin is an antihyperglycemic agent, it does not induce hypoglycemia in a single-use [2]. It may cause kidney or hepatic insufficiency above the therapeutic dose, but its major toxicity is lactic acidosis (LA) [3]. Metformin-induced LA (MILA) rarely develops in the absence of acute overdose [4]. However, LA is the most serious complication of metformin intoxication, and MILA is associated with high mortality rates. Lalau and Race [5] reported a mortality rate of 45% in their case series of 49 metformin-treated and developed LA patients. In Vecchio et al.'s [6] case series consisting of 66 patients, the mortality rate was 26%.

We evaluated a rare case of metformin intoxication developed LA after drug overuse and resulted in death in a short time after the first admission to the emergency department.

Case Report

A 47-year-old woman with type 2 DM and using metformin, admitted to the emergency department with abdominal pain and vomiting that started 4 h after taking 60 tablets of 1000 mg metformin (60 g) for suicide. Her general condition became moderate upon admission. She was conscious and oriented, with a Glasgow Coma scale of 15/15. Vital signs were stable; blood pressure was 100/60 mmHg, pulse 110/min, respiratory rate was 20/min, and SpO_2 was 98% on room air. On physical examination, her pupils were isochoric and reactive. Except for tachycardia, no abnormality was detected on heart and chest examination. She had diffuse abdominal tenderness; however, there was no defense or rebound on abdominal examination. After the gastric lavage and activated coal (1 gr/kg) therapy, hydration with 0.9% isotonic NaCl and symptomatic treatment was started. There was no abnormality on her initial hemogram, liver function tests (aspartate aminotransferase, alanine transferase), blood urea nitrogen, creatinine, electrolyte values,

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Table 1. An initial, 1st, 2nd, and 4th hours blood gas results of the patient				
	0 hour	1st hour	2nd hour	4th hour
pH	7.025	7.012	6.921	6.881
pCO_2 (mmHg)	40.3	36.6	22.6	10.5
HCO_3 (mmol/L)	9.1	8.8	6.8	4.8
Lactate (mmol/L)	20.32	22.3	25.02	29.01
Anion gap (mmol/L)	18	20	23	24
Glucose level (mg/dL)	492	410	364	301

and coagulation findings. However, her arterial blood gas analysis on admission was significant for pH: 7.025, pCO_2: 40.3 mmHg, HCO_3: 9.1 mmol/L, lactate: 20.32 mmol/L, anion gap of 18 mmol/L, and glucose level: 492 mg/dL. The patient was observed to develop metformin-induced LA with a high anion gap. After administering 1.5 meq/kg intravenous bolus sodium bicarbonate ($NaHCO_3$), 1.5 meq/kg $NaHCO_3$ infusion was added to the treatment chart. Hemodialysis (HD) therapy was planned due to the progress of metabolic acidosis in the serial blood gas follow-ups (Table 1), and she was taken to the intensive care unit. The patient developed ventricular fibrillation and then cardiac arrest during HD. Despite the administration of defibrillation and cardiopulmonary resuscitation, a normal heartbeat could not be restored, and the patient died in the 4th hour of her patient to the emergency department.

Discussion

Metformin-associated LA (MALA) has been categorized in the literature as follows: 1) MILA: Cases where no known additional conditions that could lead to LA are present except for high-dose metformin use. 2) MALA: Cases where additional other conditions that will cause LA with metformin use. 3) Metformin-unrelated LA: Cases in which LA develops due to other conditions rather than metformin accumulation [7]. Our patient used high-dose metformin, and there were no abnormalities in the initial hemogram, biochemistry, and coagulation parameters. As well as there were no additional conditions that would cause LA in the patient. LA with a high anion gap was present in her blood gas findings on admission. Our patient was evaluated as MILA.

Gastrointestinal decontamination with activated charcoal, hydration, and intravenous $NAHCO_3$ is suggested in MILA. For patients with severe metabolic acidosis, HD is the preferred approach [8]. As well as there are no antidotes for metformin intoxication [9]. Our patient was admitted to the emergency department 4 h after taking the drug. Activated charcoal and gastric lavage was applied to the patient despite the late admission. Additionally, hydration and symptomatic treatment was initiated. HD was rapidly planned for the patient who was started on $NaHCO_3$ therapy because of severe metabolic acidosis during the follow-up. Biguanide group drugs are not antihyperglycemic agents, so hypoglycemia is not expected in single-use [2]. Similarly, hypoglycemia was not observed in our patient follow-up. Therefore, additional dextrose treatment was not necessary.

Metformin increases the conversion of glucose to lactate in the small intestine [10]. Additionally, it inhibits mitochondrial respiratory chain complex 1, leading to decreased hepatic gluconeogenesis from lactate, pyruvate, and alanine [6]. In this way, metformin increases the blood lactate level, but LA rarely occurs unless acute overdose taking. However, mortality is extremely high in patients with LA [11]. Mortality rates in multiple case series range from 26% to 48.3% [5,6,12,13]. In a systematic review, Dell'Aglio et al. [14] evaluated 22 metformin overdose cases and found a correlation between low pH and high lactate level and mortality [14]. In this study, the patient's pH was 7.025, and lactate level was 20.32 mmol/L on admission. High lactate levels and progressive metabolic acidosis were observed in the patient follow-ups. Similar to the literature, our patient developed a devastating condition, and despite early supportive therapy, she was mortal at the 4th hour of her admission to the emergency department.

Conclusion

In conclusion, LA is the cause of metabolic acidosis with an increased anion gap; it can develop rapidly in acute and high-dose metformin intoxication. HD should not be delayed, particularly in cases with MILA. Physicians should remember that these patients are mortal despite aggressive treatment.

Ethics

Informed Consent: Written informed consent obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., T.A., Concept: A.A., T.A., Design: A.A., T.A., Data Collection or Processing: A.A., T.A., Analysis or Interpretation: A.A., T.A., Literature Search: A.A., T.A., Writing: A.A., T.A.

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