Case Report

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Succesful Resusication with Veno-arterial Extracorporeal Membrane Oxygenation in Cardiac Arrest After Metformin Overdose: A Case Report and Current Literature Review

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Abstract

Metformin can cause gastrointestinal system symptoms, hyperlactatemia, and lactic acidosis even at therapeutic doses, and toxicity can result in serious complications and high mortality with massive infections. The prognosis for undifferentiated lactic acidosis is poor, with an expected case fatality rate of 30-50%. We present the case of a patient who was admitted to the emergency department with a large intentional metformin overdose. The patient was initially asymptomatic, but deteriorated rapidly during the observation period, developed cardiac arrest, and required extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy. Considering this case, we aim to emphasize that metformin overdoses may worsen in the late stages and that the follow-up period should be performed in a monitored setting that can provide, if needed, advanced cardiac support therapies such as ECMO.

Keywords: Metformin overdose, suicide, lactic acidosis, extracorporeal membrane oxygenation, continuous renal replacement therapy

Introduction

Metformin is a biguanide-derived drug and is the most commonly used oral antidiabetic drug for treating type 2 diabetes worldwide (1). Biguanides lower blood glucose levels by decreasing glucose absorption in the intestine by decreasing gluconeogenesis, and peripheral use of glucose. Because biguanides do not enhance insulin release, disorders of glucose homeostasis are rare with metformin, as occurs with the sulfonylurea and meglitinide classes of medications (2). Metformin can cause gastrointestinal symptoms, hyperlactatemia, and lactic acidosis even at therapeutic doses. Toxicity can lead to serious complications and high mortality with massive ingestion. The prognosis for undifferentiated lactic acidosis is poor, with an expected case fatality rate of 30-50% (3).

In this case report, we present the case of a patient admitted to the emergency department with a large intentional metformin overdose. The patient was initially asymptomatic but deteriorated rapidly during the observation period, developed cardiac arrest, and required extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy. Considering this case, we would like to emphasize that metformin overdose may worsen in the late stages, and the follow-up should be performed in a monitored setting that can provide advanced cardiac support therapies, such as ECMO, if needed.

Case Report

A 55-year-old, 90-kg male patient with a medical history of diabetes and hypertension was admitted to the emergency department because of an intentional

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ingestion of 90 g of metformin (90 tablets of Glifor® 1000 mg, Bilim Pharmaceuticals) approximately 8 hours prior to presentation. On arrival, he had a Glasgow Coma Scale of 15 and was cooperative and oriented. He expressed only slight discomfort in his abdomen. The vital signs of the patient were recorded as follows: blood pressure of 166/95 mmHg, heart rate of 95 beats/min, respiration rate of 20 breaths/min, temperature of 36.7 °C, and oxygen saturation of 97% on room air. The patient's physical examination did not reveal any significant findings. The electrocardiogram indicated sinus rhythm. The blood gas analysis was normal except for the lactate level, which was 9.0 mmol/L. The biochemical parameters were unremarkable except for the creatinine level (Table 1). The other laboratory results were normal. The patient was admitted to the medical toxicology intensive care unit (ICU) for close monitoring and treatment. A jugular vein dialysis catheter and a subclavian central venous catheter were placed. Intra-arterial catheterization was performed for invasive blood pressure monitoring. Based on the amount of metformin consumed and the lactate elevation at the time of admission, the patient was determined to have severe toxicity. The patient's oral intake was stopped, and a low-dose dextrose treatment was administered to prevent the development of hypoglycemia. 200 cc/h isotonic maintenance fluid and 50 cc/h %5 dextrose therapy were started. During follow-up, urine output was 200 mL/h. Blood gas was checked at regular intervals, and the results are shown in Table 1.

At the 12th hour of admission, sudden hypotension (65/40 mmHg) occurred on intra-arterial monitoring. Intravenous bolus fluid administration was performed using the Trendelenburg position. As the blood pressure did not increase, maximum doses of norepinephrine and dopamine were started, respectively. Despite this, blood pressure was 65-70/40-45 mmHg. At the 15th minute of hypotension development, the blood gas control showed a pH of 7.40, bicarbonate of 19.6 mEq/L, glucose of 98 mg/dL, and lactate of 8.4 mmol/L. A seizure lasting 5 seconds occurred in the 20th minute of an unstable condition. Bradycardia and sudden cardiac arrest occurred after the seizure. Endotracheal intubation was performed, and advanced cardiac life support was performed by administering 50 mEq of bicarbonate of soda every 5 minutes. After 9 cycles of cardiopulmonary resuscitation, spontaneous circulation was achieved in the 18th minute. In the follow-up period, he had three more seizures that lasted for approximately 10 seconds each. The patient

Table 1. Clinical course, arterial blood gas results and inotropic support of the patient during hospitalization.

		Laboratory Values	pH	Bicarbonate (mEq/L)	Lactate (mmol/L)	Glucose (mg/dL)	Creatinine (mg/dL)	CK (U/L)
	Reference Values		7.35-7.45	22-26	0.5-2	74-106	0.7-1.2	0-190
Time	**Course of events**	**Treatment**						
-8 h	Metformin ingestion	-						
0	Admission	-	7.37	20	9	160	1.22	171
2 h	Stable clinic	-	7.31	24.1	7.6	243	-	-
6 h	Stable clinic	-	7.37	20.6	9.4	161	-	-
10 h	Stable clinic	-	7.39	21.6	7.7	104	1.42	174
12 h	Hypotension	N/D	7.40	19.6	8.4	98	-	-
13 h	Cardiac arrest	N/D/E	**7.04**	12.3	**21**	138	-	-
14 h	ECMO + CRRT	N/D/E	7.12	**10.7**	**19**	135	-	-
18 h	ECMO + CRRT	N/D/E	7.13	12.6	**15**	161	-	-
30 h	ECMO + CRRT	N/D	7.34	18.3	**14**	167	-	-
36 h	ECMO	D	7.36	27.5	6.8	161	0.97	**830**
48 h	ECMO	D	7.47	33	4.5	157	-	-
54 h	ECMO	-	7.48	37.2	2.1	135	-	-
72 h	-	-	7.44	37.1	1.9	153	0.67	**5498**
96 h	-	-	7.46	33.6	1.5	164	0.83	**8630**
144 h	Extubation	-	7.47	23	1.6	165	0.95	**5033**
240 h	Discharge	-	7.40	24.9	1.3	145	0.71	685

CK, creatine kinaz; CRRT, continuous renal replacement therapy; D, dopamine; E, epinephrine; ECMO, extracorporeal membrane oxygenation; N, norepinephrine.

was initiated on a sodium bicarbonate drip at a rate of 30 milliequivalents per hour. The arterial blood gas analysis revealed a pH of 7.05, a bicarbonate level of 13.3 mEq/L, a glucose level of 208 mg/dL, and a lactate level of 19.0 mmol/L. Despite the administration of a full dose of noradrenaline and an adrenaline infusion, no hemodynamic improvement was observed. The patient's blood pressure was 60/40 mmHg. A consultation for cardiovascular surgery was performed, and the patient was placed on venoarterial ECMO in the ICU. Continuous renal replacement therapy was initiated promptly. Based on the bedside ultrasonography, the diameter of the inferior vena cava was 14 mm, so fluid therapy was continued at the same infusion rate.

In the first 2 hours of ECMO, blood pressure remained at 70-75/45-50 mmHg. From the second hour of ECMO, the blood pressure progressively increased every hour, with a systolic blood pressure of 10 mmHg/h and a diastolic blood pressure of 5 mmHg/h. The heart rate was in the range of 65-70/min. Blood pressure reached 140/90 mmHg at the 10th hour of triple (adrenalin, noradrenalin, and dopamin) inotropic support and ECMO. Starting from the 10th hour of ECMO, inotropic support was gradually reduced. Adrenaline infusions at the 16th hour of ECMO, neuradrealin infusions at the 24th hour, and finally dopamine infusions at the 36th hour of ECMO were stopped. Table 1 displays the times for the initiation and discontinuation of inotropic support therapy. At the 58th hour of treatment, the patient was successfully weaned off ECMO. On the 6th day, the patient's laboratory values improved and no additional pathology developed, leading to successful extubation. There was no pathology in the vital parameters or system examinations. Psychiatric recommendations were made. On the 10th day of follow-up, the patient was discharged without any sequelae. Informed consent was obtained from the patient for the publication of this case at the time of discharge.

Discussion

Despite stable conditions, metformin overdose can result in unexpected and sudden cardiopulmonary arrest in the late stages. So, earlier extracorporeal elimination methods like hemodialysis can be thought about even when there are no symptoms and only a mild rise in serum lactate in a metformin overdose.

Metformin overdose causes symptoms such as nausea, vomiting, abdominal pain, and myalgia in mild cases; in severe toxicity, lactic acidosis, renal failure, respiratory failure, liver failure, and ventricular dysrhythmias may occur. Hypoglycemia due to the use of antidiabetic drugs and hyperglycemia due to the underlying disease can be seen. However, metformin does not cause hypoglycemia. In this study, the amount of metformin taken and the high lactate level at the time of admission were predictive of a poor outcome. Therefore, the oral intake of the patient was stopped, and a low-dose dextrose treatment was administered to prevent the development of hypoglycemia in the follow-up period. The most common and life-threatening complication of metformin toxicity is lactic acidosis. Lactic acidosis occurs because of the activation of anaerobic metabolism when mitochondrial oxygenation cannot be achieved. The etiology of lactic acidosis includes several disease processes. These include sepsis, hemorrhagic shock, cardiac arrest, trauma, intoxication, burns, diabetic ketoacidosis, cancer, intense muscular activity, and mitochondrial toxicants such as cyanide (4). Metformin overdoses can cause type B lactic acidosis in the early period, and type A lactic acidosis can be seen in the late period due to hypotension and hypoxia due to its cardiovascular effects.

The therapeutic adult dose of metformin is a maximum of 2.550 mg/day (5). In this study, 90 g of metformin intake at one time constitutes the expectation that severe toxicity will develop. However, an asymptomatic course was observed for several hours, with abdominal pain that regressed from the time of admission to the emergency department. Isolated serum lactate elevation was accompanied by an asymptomatic course without acidosis with normal hemodynamic and laboratory findings. However, in the late period (20th hour) after ingestion, the hemodynamic status suddenly deteriorated, and cardiac arrest developed with a seizure. In our case, although adequate fluid (200 mL/h) resuscitation was performed after hospitalization, the hypotension that developed at the 20th hour was controlled with inotropes, and ECMO was performed at the 21st hour after the sudden cardiac arrest that developed. Considering the case of a patient who developed pulseless electrical activity and cardiac arrest approximately 25 hours after ingestion in the late period of ingestion (2), in addition to focusing on metabolic acidosis for treating metformin poisoning, it is necessary to be prepared for hemodynamic instability and sudden cardiac arrest that may occur in the late period and to develop preventive treatment protocols.

Extracorporeal methods are used for treating metformin overdoses. However, hemodialysis is mainly applied for correcting metabolic acidosis and not for the removal of metformin in overdoses. The clearance of metformin by renal replacement therapies is controversial because of the high volume of distribution of metformin, up to more than 3 L/kg (63-646 L/kg), as it is predominantly located in the intracellular compartment (6). There is no prognostic correlation between serum lactate levels and metformin-induced lactate acidosis, even at lactate

levels up to 35.5 mmol/L (7). The focus of treatment is to correct metabolic acidosis.

Hemodialysis with bicarbonate replacement fluid has been successfully used for treating metformin-induced acidosis because it not only corrects the acidosis but also efficiently removes metformin from plasma, preventing further lactate overproduction. The EXTRIP criteria for extracorporeal methods of metformin dosage therapy are recommended (8). According to EXTRIP, hemodialysis is recommended in the presence of lactate concentrations >20 mmol/L (recommendation, 1D), >15 mmol/L (suggestion, 2D), or pH ≤7.0 (recommendation, 1D), or pH ≤7.1 (suggestion, 2D). However, in our case, despite high-dose metformin ingestion, the clinical and laboratory progress was mild, the pH level did not deviate from the normal range, and lactate levels did not rise above 9 mmol/L. However, in the following hours, both clinical and laboratory values deteriorated rapidly. The patient experienced cardiopulmonary arrest. Despite administering high-dose vasopressors and inotropes, there was no response. Therefore, the patient was connected to ECMO to stabilize hemodynamics and allow extracorporeal treatments to be applied for the treatment of acute hyperlactatemia and metabolic acidosis.

Recommendations for the management of metformin overdose include supportive care and the correction of metabolic acidosis (9). In our case, it was observed that creatinine values deteriorated in the early period and urine output decreased in the late period of clinical observation (a few hours before hypotension). Increased urea-creatinine values and decreased urine output can also be considered indicators of a poor prognosis. The follow-up period for metformin overdose should be at least 24 hours because the clinical status is normal in the early period, sudden hemodynamic instability and lactic acidosis may occur, and seizures may accompany the late period of clinical observation.

Conclusion

Note that hemodynamics may suddenly and rapidly deteriorate in the late phase of a metformin overdose, leading to severe lactic acidosis. Hemodialysis should be performed in patients with a large volume of ingestion who may experience an abrupt deterioration in condition due to severe metabolic acidosis. Preparation for initiating ECMO should be considered in cases of refractory hypotension and in cases of shock due to a severe metformin overdose.

Ethics

Informed Consent: Informed consent was obtained from the patient for the publication of this case at the time of discharge.

Authorship Contributions

Concept: I.A., R.C., Z.K., S.K., A.S., Design: R.C., Z.K., S.K., A.S., Data Collection or Processing: I.A., R.C., I.H.T., A.S., Analysis or Interpretation: I.H.T., Z.K., S.K., A.S., Literature Search: I.A., I.H.T., Z.K., A.S., Writing: I.A., Z.K., A.S.

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