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Case Report

Metformin-Associated Lactic Acidosis Developed as a Result of a Suicidal Attempt

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Abstract

Metformin is a biguanide group drug commonly used in the treatment of Type 2 DM. Even though Metformin- Associated Lactic Acidosis (MALA) is not seen very frequently, MALA has a high mortality rate. This case is presented to draw attention to efficiency of hemodialysis and CVVHDF tin the treatment of MALA.

A 25-year-old female patient was brought to the emergency service with abdominal pain and confusion. In her detailed history, it was learned that she took 100 tablets of metformin (1000 mg per tablet). Hemodialysis initiated because of severe metabolic acidosis, elevation of blood urea and hyperkalemia were seen in laboratory results. After that, patient was intubated because of low Glasgow Coma Scale (GCS:3) and vasopressor agent were started due to hypotension. In the intensive care unit, blood glucose was seen 44 mg dl^{-1} and treated with 10% dextrose solution. CVVHDF treatment was started because of anuria and metabolic acidosis. Patient who underwent CVVHDF treatment for 12-days transferred to nephrology service on the 23rd day of the ICU admission with full consciousness and stabilized vitals.

In conclusion, hemodialysis and CVVHDF should be the first treatment methods to be considered in patients with metformin-associated lactic acidosis. Renal replacement therapies, initiated rapidly and maintained for an adequate time period are promising in this high mortality rate cases.

Keywords: Hemodialysis; lactic acidosis; metformin intoxication.

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Metformin is a biguanide antidiabetic agent frequently used in the treatment of type-2 diabetes mellitus.[1] Metformin is an anti-hyperglycemic agent used to achieve euglycemia. Lactic acidosis can be seen in acute and chronic use of biguanides. Although the incidence of acidosis is 5-9 per 100.000,[3] metformin-associated lactic acidosis (MALA) has high mortality rates.[4, 5] Plasma half-life of metformin is approximately six hours. Its small molecular weight (165.8kD) and insignificant binding to plasma proteins increase the distribution volume of the drug (63-276 L).[6] Its sequestration in blood cells, such as erythrocytes and platelets, can extend its elimination half-life up to 17 hours.[7, 8]

The major mechanism in the excretion of metformin is tubular secretion, and metformin is largely excreted unchanged in the urine. Its estimated renal clearance is 507±129 ml/min which is more than three times its creatinine clearance. However, in cases, such as the presence of underlying chronic renal failure and/or high doses of metformin used for suicidal intent, renal clearance is exceeded

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and drug excretion decreases. As a result of this situation, lactic acidosis with high anion gap occurs.[9, 10]

Lactic acidosis seen in human beings is divided into two forms as type A and type B. Type A lactic acidosis arises from the cells' orientation to non-oxidative breathing for energy production as a result of poor perfusion of tissues. Type B, on the other hand, occurs with an external agent that may cause intoxication in tissues without initial perfusion defect or with a decrease in lactate clearance.[10, 11]

Metformin intoxication may present with nonspecific symptoms, such as nausea, vomiting, abdominal pain, hypoglycemia, hypothermia, tachypnea, tachycardia/bradycardia, hypotension/hypertension, agitation, somnolence, stupor and coma. Therefore, anamnesis is important to make differential diagnosis.[12, 13]

The classical triad of metformin toxicity can be listed as acute renal failure, high plasma metformin concentration and severe lactic acidosis.[7] Concerning its mechanism of action, metformin inhibits the complex necessary for hepatic gluconeogenesis and oxidative respiration in mitochondria and directs cells, primarily hepatocytes and intestinal cells, to anaerobic respiration (Fig. 1).

As a result, lactate accumulates in the body. Lactate formed may lead to high anion-gaped metabolic asidois even in patients with normal renal function.[7] Severe metabolic acidosis may disrupt the neurological condition and endanger the patient's airway. In addition, since metabolic acidosis may cause cardiovascular instability at a high rate,

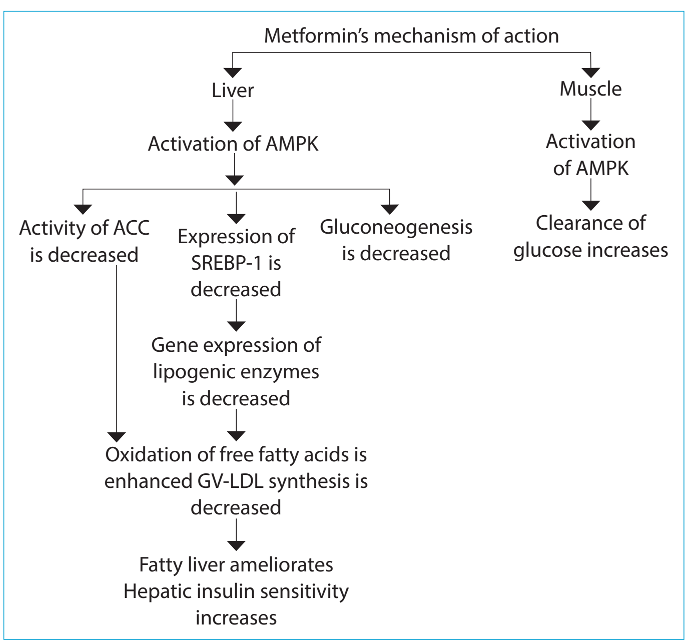

Figure 1. Metformin's mechanism of action.

AMPK: AMP –activated protein kinase; ACC: Acetyl -CoA carboxylase; SREBP-1. Sterol regulatory element –binding protein -1; GV-LDL, Group V LDL.

patients are usually followed up in controlled mechanical ventilation.

Given that metformin preparations are cheap and sold without a prescription makes access to the drug quite easily. In addition, metformin has become a drug that can be easily accessed by the young population due to its use in the treatment of obesity in type 2 diabetes mellitus and nondiabetic patients. This easily available drug can be used for suicidal purposes like many other drugs that are easily available.

In this case, we aimed to draw attention to acute metformin intoxication treatment protocols in people without additional disease history by sharing the intensive care follow-up process of a patient who received a total of 100 g (1530mg/kg) of metformin to commit suicide and brought to our hospital emergency room.

Case Report

A 25-year-old female patient without additional disease history was brought to the emergency room of our hospital with complaints of nausea, vomiting, abdominal pain and confusion. It was learned from her family that the patient who had received 100 tablets of 1000 mg metformin was sent to hemodialysis unit by the emergency clinic after being consulted with nephrology upon the presence of severe lactic acidosis in the arterial blood gas, urea-creatinine elevation and hyperkalemia in blood biochemistry. The consultation was requested by our clinic in the emergency room for the patient whose inotropic support was initiated due to closure of consciousness and hypotension after hemodialysis. The general health condition of the patient was poor. Besides, loss of conscious IR -/-, fixed and dilated pupillas accompanied by GKS: E1 M1 V1 and hypotension (68/42 mmHg) were detected despite inotropic treatment. Then, the patient was taken to the intensive care unit after orotracheal intubation.

The patient was started to undergo invasive mechanical ventilation, and after the development of hypoglycemia (44 mg dL^{-1}), 10% dextrose IV was administered. In addition, despite the infusion of dopamine, her mean arterial pressure was <60 mmHg, so noradrenaline infusion together with continuous treatment with veno-venous hemodiafiltration (CVVHDF) was initiated (Table 1). The patient who was hypothermic (33.2 ºC) was heated with a blow heater. Despite CVVHDF treatment, her blood pH remained at <7.15. Then, sodium bicarbonate infusion was initiated. When her pH was >7.15, sodium bicarbonate infusion was stopped. The patient regained consciousness on the 4th day of her intensive care stay. However, as a result of spontaneous ventilation attempts, sufficient ventilation capacity could not be seen, and mechanical ventilation was continued under the infusion of dexmedetomidine. In the intensive care follow-up, liver function parameters (AST, ALT) increased (Table 2) and platelet counts decreased, therefore consultations from departments of internal medicine and gastroenterology were requested.

Pseudotrombocytopenia was excluded based on the results of the peripheral smear test performed by the department of internal medicine, and thrombocytopenia was associated with metformin overdose and no recommendation was made except for replacement with pooled platelet suspension. Gastroenterology suggested avoidance of hepatotoxic drug use.

Nasal discharge, sputum, and urine samples of the patient whose infection parameters (CRP, procalcitonin) tended to increase were sent for antibiotic susceptibility tests and broad-spectrum antibiotherapy (meropenem, teicoplanin) was initiated by the department of infectious diseases. Contact isolation was applied, and colistimethate sodium was added to antibiotherapy in accordance with culture antibiogram sensitivity.

CVVHDF was terminated in the patient who had spontaneous urine output on the 17th day of the intensive care stay was started on intermittent diuretic therapy (furosemide).

In addition, the patient whose pneumonia improved and had adequate spontaneous breathing was intubated and noninvasive mechanical ventilation was performed intermittently according to arterial blood gas results.

Nephrology consultation was requested for the patient (Table 2) who did not have sufficient urine output and had high urea and creatinine value despite diuretic treatment. Then, the patient was included in the hemodialysis program by nephrology. On the 23rd day of the intensive care stay, the patient was in good general condition, conscious, cooperative, orientated, hemodynamically stable, so non-invasive mechanical ventilation was not required. However, her urea-creatinine level remained at high levels, so she was transferred to the nephrology service for the maintenance of her treatment.

Discussion

Metformin, which is a frequently used agent in the treatment of type 2 diabetes mellitus, may rarely cause lactic acidosis.[3] Lactic acidosis occurs due to the development of chronic kidney failure or acute kidney failure in people using normal doses of metformin. In addition, severe lactic acidosis, which may be life-threatening, can be observed in cases of acute intake of high doses of the drug for suicidal intent.

Metformin toxicity causes atypical symptoms and signs. As we encountered in our case, most of the patients apply to the emergency department with gastrointestinal symptoms (nausea-vomiting, diarrhea, epigastric pain), hypotension/hypertension, bradycardia/tachycardia, hypoglycemia, hypothermia, tachypnea, neurological changes (convulsion, somnolence, stupor, coma). Therefore, a detailed anamnesis constitutes a special place in terms of differential diagnosis.[12, 13]

The resulting metabolic acidosis affects the cardiovascular system negatively by depressing the calcium channels that open slowly. As a result of cardiovascular system depression, decreased systemic vascular resistance, severe arrhythmias (with the effects of hyperkalemia), profound

Table 1. Parameters of the blood gas and infection

	Emergency service	ICU 1. hr	ICU 24. hr	ICU 2. day	ICU 4. day	ICU 10. day	ICU 17. day	ICU 23. day
pH	7.03	7.11	6.90	7.26	7.30	7.37	7.40	7.42
pCO_2	30.4	32.5	56.7	36.3	38.5	49.5	41.4	35.3
pO_2	93.6	204	79	114	90.4	96.5	151	109
HCO_3	7.8	10	10.6	15.9	26.9	28	25.5	28.4
BE	-20.7	-17.6	-19.7	-9.8	1.2	3.1	1.3	5.2
sO_2, %	91.9	98.9	90	97.9	95.6	96.9	99.4	99.7
Lac	19	17	22	8	6.2	1.2	1	1.1
PCT	0.20	0.35	0.50	4.1	4.0	1.2	0.75	0.39
CRP	0.5	0.3	1.3	7.9	168.1	134	27.2	21.1
Hb	11.8	8.1	9.6	10.6	8.5	10.5	8.3	7.5
Hct	36.7	25.9	30.7	32.6	24	29.5	23.9	22.1
WBC	10.94	27	31.52	33.71	31.98	27.69	10.54	8.46
Neu, %	51.4	80.5	90.8	88.1	96.8	87.4	79.3	75
Plt	272	195	124	41	18	48	140	225

PCT: procalcitonin; Lac: lactate.

Table 2. Biochemical tests and blood parameters

	Emergency service	ICU 1. hr	ICU 24. hr	ICU 2. day	ICU 4. day	ICU 10. day	ICU 17. day	ICU 23. day
Urea	15.83	10.65	11.36	31	42	122.09	90	107.62
Cre	2	1.63	1.34	1.33	1.15	1.79	2.93	3.79
eGFR	34	47	57	58	67	43	26	20
AST	21	59	106	308	501	64	20	27
ALT	13	37	74	148	223	85	11	11
T. Bil	0.80	0.96	1.02	1.42	1.83	3.26	1.16	0.89
D.Bil	0.16	0.74	0.72	0.75	0.80	1.05	0.41	0.26
Albumin	3.75	3.02	2.61	3.41	3.31	2.74	2.80	2.94
PT	32.2	22.2	23.6	14.4	12.9	13.3	12.7	13.3
aPTT	178	38.7	59.5	33.8	31.5	32.4	28.9	30.1
INR	2.9	1.95	2.01	1.22	1.08	1.12	1.05	1.14
Glucose	49	241	139	147	158	89	115	108
Na^+	140	139	154	146	132	140	138	139
K^+	4.29	3.21	2.88	4.35	4.14	2.86	3.64	3.75
Ca^{+2}	9.70	7.10	7.80	8.60	8.40	7.10	9.30	8.50
Cl^-	105	92	97	95	101	101	102	100
CK-MB	18.20	14.30						
Trop I	0.010	0.020						
β-hCG	0.48	0.44						

Trop: Troponin; T, bil: Total bilirubin; D.bil: Direct bilirubin.

hypotension and cardiac arrest can be seen. These cardiac effects may cause organ hypoperfusion, leading to multi-organ failure, especially renal failure.

We also encountered multi-organ failure, particularly renal failure in our patient. Arıkan et al.[14] stated that they applied sodium bicarbonate and diuretic therapy to MALA patients with the normal state of consciousness, hemodynamically stable, good renal functions, and pH >7.20, and achieved successful results. However, the treatment for the cause of metabolic acidosis was incomplete.

Indeed, the decrease in plasma bicarbonate value is the body's response to metabolic acidosis; in other words, bicarbonate deficiency is a result of a decrease in arterial blood gas values. In addition, sodium bicarbonate applied without eliminating metformin and lactate from plasma may cause excessive sodium burden and vasodilation. In addition, the pH value that shifts towards alkaline level after application of sodium bicarbonate increases the displacement of the hemoglobin-oxygen dissociation curve to the left and increases the oxygen affinity of hemoglobin and causes development of hypoxia at the tissue level. As a result, intracellular acidosis increases paradoxically. Therefore, when pH >7.15 was seen in this case, bicarbonate infusion was stopped and treatment was continued with CVVHDF until hemodynamic stability was achieved. In addition, the frequency of coagulopathy has increased in patients with MALA.[15] Akıncı et al.[15] explained the situation of developing coagulopathy with a decreased synthesis of coagulation factors produced in the liver. Indeed, in our case, the coagulation parameters measured at the beginning were above the normal values (Table 2). Hemodialysis or continuous renal replacement treatments (e.g., CVVHDF) are preferred to eliminate drug overdose, normalize serum potassium level and eliminate lactate, which is the cause of metabolic acidosis.[16, 17] Renal replacement therapies are generally preferred primarily because they provide better stability in hemodynamic parameters. Relative hemodynamic stability is a positive condition for the patient, although it takes a longer time for toxin and lactate elimination in continuous renal replacement therapies. However, any significant difference was not seen between both methods in terms of their effects on mortality.[5] Long-term and/or intermittent renal replacement therapies may be required, as in our case, because of the large distribution volume of metformin and its accumulation in blood cells in MALA.[18–21] In our patient, CVVHDF was applied for a total of 12 days all along with her hospital stay. Informed consent was obtained from our patient for this case presentation.

Conclusion

In conclusion, hemodialysis or continuous renal replacement therapies should be considered firstly in patients diagnosed with MALA caused by metformin, which can also be used without requiring a prescription for slimming purposes. Renal replacement therapies, which are started quickly and maintained for a sufficient period, continue to give hope even in this condition with high mortality rates.

Disclosures

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

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Conflict of Interest: None declared.

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