CASE REPORT

Continuous veno-venous hemodiafiltration in metformin-associated lactic acidosis caused by a suicide attempt: A report of two cases

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ABSTRACT

Lactic acidosis is the most important and life-threatening side effect of metformin that is widely used in the treatment of type 2 diabetes mellitus. In this case report, two cases who were treated in our intensive care unit for lactic acidosis due to high-dose metformin intake for suicidal purposes are presented. The first patient could be successfully treated with continuous venous-venous hemodiafiltration (CVVHDF) and supportive therapy. The second case required endotracheal intubation and mechanical ventilation in addition to CVVHDF and supportive therapy due to delay in treatment.

Keywords: Continuous veno-venous hemodiafiltration; lactic acidosis; metformin poisoning.

INTRODUCTION

Metformin-associated lactic acidosis (MALA) is a fatal side effect of metformin that is widely used in the treatment of type 2 diabetes mellitus.[1,2] The incidence of MALA is rather low, but when untreated appropriately, mortality is high (30–50%). The majority of cases occur when a predisposing condition leads to dehydration and/or reduced renal clearance while under therapeutic metformin levels. It may also occur in patients, intentionally receiving high-dose metformin for suicide.[3–13] Early diagnosis and treatment with clearance of lactate/metformin from plasma and correction of acidosis in addition to supportive treatment are essential in this life-threatening clinical condition.[14]

Herein, we present two cases with MALA due to high-dose metformin ingestion for suicidal attempt. The first patient was successfully treated with continuous venous-venous hemodiafiltration (CVVHDF) and supportive therapy, while the other case required endotracheal intubation and mechanical ventilation in addition to CVVHDF and supportive therapy due to delay in treatment. Written consent for publication was obtained from both of the patients.

CASE REPORT

Case 1– A 35-year-old female was brought to the emergency department by her relatives with nausea, vomiting, and abdominal pain 3.5 h after a suicide attempt with 30 metformin tablets (1000 mg metformin in one tablet) for suicidal purpose. She was drowsy with a Glasgow Coma Score (GCS) of 12 ($E_4M_5V_3$), blood pressure (BP) of 79/47 mmHg, heart rate (HR) of 88/min, and respiratory rate (RR) of 20/min. Arterial blood gas analysis revealed a metabolic acidosis with pH: 7.27, pCO_2: 36 mmHg, pO_2: 216 mmHg, BE: −10.4 mmol/L, HCO_3−: 16.5 mmol/L, and anion gap: 14.5 mEq/L. Laboratory findings were as follows: blood glucose level: 115 mg/dl, urea: 21 mg/dL, creatinine: 1.09 mg/dL, sodium: 140 mmol/L, potassium: 4.33 mmol/L, and chloride: 10^9 mmol/L. Intravenous (IV) 0.9% NaCl infusion was started and gastric

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lavage was performed via a nasogastric catheter, in addition to activated charcoal treatment. The patient was transferred to the intensive care unit (ICU). Sodium bicarbonate, dopamine, and noradrenaline infusions were started and an emergency dialysis was planned. A femoral catheter was placed and CVVHDF (blood flow 150 ml/min, flow rate of dialysate 1000 ml/min, pre-replacement 1000 ml/h, post-replacement 450 ml/h, heparin infusion of 750 IU/h, and ultrafiltration) was started. IV glucose-containing fluid was also administered to the patient in order to avoid hypoglycemia during CVVHDF. Arterial blood gas, HS-troponin, and CK-MB values of the patient during CVVHDF are presented in Table 1. During this period, acidosis, consciousness, and vital parameters of the patient were improved and inotropic and vasopressor support was gradually discontinued with no need with mechanical ventilation. She was transferred to the ward on the 4th day of admission to the ICU and discharged home without problem.

Case 2– A 24-year-old female patient was brought to our ICU 13 h after the ingestion of 100 metformin tablets (1000 mg metformin in one tablet) for suicidal purpose. Emergency treatment was provided in another hospital and it was learned that IV 0.9% NaCl and 5% dextrose infusion was started, but activated charcoal was not administered due to the patient's refusal. On admission to ICU, she was unconscious with a GCS of 12 ($E_2M_2V_1$). BP was 80/50 mmHg, HR was 121/min, RR was 48/min, and peripheral oxygen saturation (SpO_2) was 82%. Arterial blood gas analysis revealed a severe lactic acidosis with pH: 6.90, pCO_2: 14.0 mmHg, pO_2: 69 mmHg, HCO_3- <3 mmol/L, and anion gap: 24 mEq/L. Laboratory

Table 1. Arterial blood gas, HS-troponin and CK-MB values of patients during treatment

	Emergency department	Intensive care unit					
		On admission	CVVHDF				At discharge
			6th h	12th h	24th h	48th h	72th h	
Case 1								
pH	7.30	7.27	7.16	7.33	7.44	7.46	7.48	7.49
$PaCO_2$ (mmHg)	34	36	25	31	38	45	44	40
PaO_2 (mmHg)	97	216	113	85	120	63	73	87
HCO_3 (mmol/L)	16.7	16.5	8.9	16.3	25.8	30.7	31.6	29.2
BE (mmol/L)	-9.7	-10.4	-19.8	-9.6	1.6	8.2	8.5	4.7
O_2 saturation (%)	97	100	97	96	99	93	96	98
Lactate (mmol/L)		9.1	14.4	5.9	1.4	0.8	0.4	0.5
Anion gap (mEq/L)	14.3	0.5	16.1	14.7	5.2	1.0	0.4	2.8
Urea (mg/dL)	21				21		19	21
Creatinine (mg/dL)	1.09				0.78		0.5	0.82
HS-troponin I (pg/mL)		3.1						3.4
CK-MB (ng/mL)		2.2						0.8
Case 2								
pH	7.05	6.90	7.14	7.25	7.37	7.40	7.47	7.42
$PaCO_2$ (mmHg)	19.4	41	38	36	38	46	37	44
PaO_2 (mmHg)	131	72	65	67	86	105	136	95
HCO_3 (mmol/L)	7.6	8.0	12.9	15.8	22.0	28.5	26.9	29.2
BE (mmol/L)	-23.3	-24.9	-16.1	-11.4	-3.3	-3.7	-3.2	4.7
O_2 saturation (%)	78.0	78.0	84	89	96	98	98	98
Lactate (mmol/L)	19	>15	>15	10.9	5.3	1.7	0.8	0.5
Anion gap (mEq/L)	30.4	24	26.1	21.2	14.0	8.5	2.1	2.8
Urea (mg/dL)	23	30				42	45	28
Creatinine (mg/dL)	1.57	2.46				2.28	2.41	0.91
HS-troponin I (pg/mL)		34.6					405	9.6
CK-MB (ng/mL)		7.1					11	1.5

CVVHDF: Continuous venous-venous hemodiafiltration; HS-Troponin: High-sensitivity troponin; CK-MB: Creatine kinase myocardial band; Partial pressure of carbon dioxide pH: Potential Hydrogen.

findings were as follows: blood glucose level: 95 mg/dL, urea: 30 mg/dl, creatinine: 2.46 mg/dL, sodium: 128 mmol/L, potassium: 5.78 mmol/L, and chloride: 96 mmol/L. The patient was entubated and mechanical ventilatory support was initiated. Vasopressor and inotropic support including noradrenaline and dopamine infusion was started because her BP dropped to 60/20 mmHg. Simultaneously, sodium bicarbonate infusion and CVVHDF (blood flow rate 150 ml/min, dialysate flow rate 1000 ml/h, pre-replacement 1000 ml/h, post-replacement 450 ml/h, and 750 IU/h heparin infusion) were started following insertion of a dialysis catheter. Immediately after, her arterial blood gas analysis showed severe metabolic acidosis with pH: 6.80, pCO_2: 72 mmHg, pO_2: 65 mmHg, and HCO_3: <3 mmol/l. Ultrafiltration (50 ml/h) was added and dialysate flow rate was increased to 2000 ml/h due to her low urine output. Arterial blood gas, HS-troponin, and CK-MB values of the patient during CVVHDF are presented in Table 1. During CVVHDF, acidosis and vital parameters of the patient were improved, plasma lactate levels were decreased, and inotropic and vasopressor support was gradually discontinued. IV sedation was terminated and the patient was extubated 78 h after admission to the intensive care unit. During the follow-up, dialysis was required on the 6th day of the ICU because of progressive increase in plasma creatinine levels. After a single dialysis, plasma creatinine levels returned to normal values and the patient required no further dialysis again. She was transferred to the ward on the 11th day of intensive care with a plasma creatinine of 0.9 mg/dl and discharged home without problem.

DISCUSSION

Metformin, which acts by reducing hepatic glucose production and increasing peripheral glucose use, is the first step drug used in the treatment of diabetes mellitus type 2.[1] It reaches peak plasma concentration within 3 h after oral intake. Approximately 40% is absorbed in the upper small intestine and 10% in the ileum and colon. Oral bioavailability, although dose dependent, is 50–60%. Non-absorbed metformin accumulates in the intestinal mucosa and eliminated by feces.[2] The mean plasma half-life of the drug is 2–6 h. It is circulated freely in the plasma (unbound) and excreted unchanged from the body by glomerular filtration and tubular secretion. Therefore, it can accumulate in the body in renal failure.[3] The fact that some individuals using metformin are more susceptible to the development of lactic acidosis is explained by possible genetic variations associated with metformin and lactate carriers among individuals.[4] Blood levels of metformin are usually in the normal therapeutic range in most cases indicating that no linear relationship between metformin-related lactic acidosis and serum metformin levels exists. Additionally, when used as monotherapy, metformin does not cause hypoglycemia but has been shown to cause hypoglycemia when overdosed.[5] Therefore, detailed patient history is essential and other possible causes of lactic acidosis should be ruled out in the differential diagnosis of MALA.

Lactic acidosis is defined as a blood pH below 7.35 and a plasma lactate level above 2 mmol/L, with 2 types depending on the absence (Type A) or presence (Type B) of adequate tissue perfusion. MALA is classified as Type B lactic acidosis.[6] In the pathogenesis, it is thought that inhibition of mitochondrial respiration in tissues such as liver and muscle plays an important role. Metformin prevents formation of nicotinamide adenine dinucleotide (NAD) from NAD hydrogen (NADH) by the mitochondria via inhibiting oxidative phosphorylation. Increased NADH inhibits pyruvate dehydrogenase, causing more lactate to form than pyruvate. Furthermore, metformin directly inhibits the pyruvate carboxylase enzyme, resulting in the accumulation of pyruvate and reduced lactate metabolism. As a result, lactate production in the blood increases (Type B lactic acidosis).[7] Cardiovascular failure due to reduced myocardial response to catecholamines and arrhythmias due to lactic acidosis reduces tissue perfusion and further increases lactate production (superimposed Type A lactic acidosis). This is the most important potential cause of hypotension in both of our cases which required vasopressor and inotropic support at the beginning of treatment. During the treatment period, with the improvement of acidosis, the need for inotropic support decreased with no need after 72 h in both cases.

The treatment of MALA, which has not an effective antidote, requires ICU care. Activated charcoal should be administered as soon as possible to prevent further absorption of the drug by the small intestine. The main goals of treatment include correction of lactic acidosis, removal of absorbed metformin from the body, and support of circulation and respiration.[8] Infusion of parenteral sodium bicarbonate alone has been shown to be insufficient in the correction of acidosis.[9] Moreover, the use of sodium bicarbonate is controversial due to its side effects such as left shift of oxyhemoglobin dissociation curve, excessive sodium load, and rebound metabolic alkalosis.[9] Both metformin and lactate are small molecules that do not bind to the proteins and can easily pass through hemofilters. Therefore, they can be easily cleared from blood by dialysis.[10] Although the efficacy of hemodialysis has been demonstrated in these cases, the superiority of intermittent hemodialysis or CVVHDF treatments has not been demonstrated.[11] However, there are several publications emphasizing the importance of CVVHDF in patients with hemodynamic instability and signs of tissue hypoperfusion who cannot tolerate hemodialysis.[12–14] In the first patient, metabolic acidosis with high anion gap was observed without signs of tissue hypoxia. Following early diagnosis, gastric lavage, and active charcoal treatment with immediate hemodynamic support and CVVHDF therapy, the patient did not require endotracheal intubation, organ failure did not develop, and she was discharged from the ICU on the 4th day of admission. In our second case, severe lactic acidosis and acute renal failure developed due to the lack of active charcoal treatment, late onset of hemodialysis, and inadequate supportive treatment despite early diagnosis.

Additionally, she admitted to ICU after 13 h of ingestion of large dose of metformin (100 metformin tablets). Endotracheal intubation, mechanical ventilation, hemodynamic support, and CVVHDF were simultaneously administered immediately after her admission to the ICU and she could be discharged on the 11th day.

It has been reported that 9/100.000 and 1% of patients admitted to the emergency services and ICUs were diagnosed with MALA, respectively. The mortality rate is around 30–50% in this complication, which is reported to be seen in 3.5% of the patients using metformin regularly. Additionally, only 16% of these cases are associated with a single excessive dose.[15] No significant relationship was found between serum metformin levels and the degree of lactic acidosis and/or mortality.[4,16] On admission, presence of hypotension, hypothermia, renal failure, pancreatitis, respiratory failure, coma, and cardiac arrest as well as non-specific symptoms such as confusion, abdominal pain, nausea, and vomiting indicates a poor prognosis.[16] We could not measure plasma metformin levels (measurement of plasma metformin level was not available in our center), but the diagnosis could be made because both of the patients have a history of metformin ingestion for a suicidal attempt. Both of the patients were hemodynamically unstable requiring vasopressor and inotropic support. Additionally, severe lactic acidosis could be corrected using CVVHDF with sodium bicarbonate infusion. However, plasma lactate levels increased immediately after the initiation of CVVHDF and then gradually reached normal levels in both patients. Possible explanations of this finding are initial higher lactate production rate than clearance by hemodiafiltration and Type A lactic acidosis associated with concomitant hypotension. Furthermore, increased intracellular glucose metabolism due to IV glucose-containing infusion solutions administered may have led to an increase in lactate production. In both cases, dopamine and noradrenaline infusion was required because of hemodynamic stability. In the second case, acute renal failure developed and improved after hemodialysis.

Conclusion

Lactic acidosis is a fatal complication of metformin intoxication. Early diagnosis, cardiovascular support, and immediate dialysis (intermittent hemodialysis or continuous renal replacement therapies) should be performed, especially before the occurrence of tissue hypoxia/hypoperfusion symptoms in order to save lives.

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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OLGU SUNUMU - *ÖZET*

Suisid girişiminin neden olduğu metformin-ilişkili laktik asidozda sürekli venö-venöz hemodiyafiltrasyon: İki olgu sunumu

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Tip 2 diyabetes mellitus tedavisinde yaygın şekilde kullanılan metforminin en önemli ve hayatı tehdit eden yan etkisi laktik asidozdur. Bu olgu sunumu ile intihar amaçlı yüksek doz metformin alımına bağlı laktik asidoz nedeniyle yoğun bakımımızda tedavi edilen iki olgu sunulmuştur. Olgulardan biri sürekli venö-venöz hemodiyafiltrasyon (CVVHDF) ve destek tedavisi ile başarılı bir şekilde tedavi edilebilmiştir. Diğer olguda gecikmiş tedavi nedeniyle CVVHDF ve destek tedavi yanında endotrakeal entübasyon ve mekanik ventilasyon gereksinimi olmuştur.

Anahtar sözcükler: Laktik asidoz; metformin zehirlenmesi; sürekli venö-venöz hemodiyafiltrasyon.

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