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【 CASE REPORT 】

A Case of Cardiac Dysfunction Due to Thiamine Deficiency after Hemodialysis for Biguanide-related Lactic Acidosis

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Abstract:
Biguanide is an ideal drug for the treatment of type 2 diabetes mellitus. When used appropriately, the incidence of lactic acidosis is reported to be very low. Risk factors associated with biguanide-related lactic acidosis include chronic kidney disease, congestive heart failure, alcohol use, severe dehydration, shock, hypoxic states, sepsis, and advanced age. We herein report a case of cardiac dysfunction due to thiamine deficiency after hemodialysis in a patient with suspected biguanide-related lactic acidosis. Patients who develop severe lactic acidosis while taking biguanides should be given a large dose of thiamine without delay, given the possibility of thiamine deficiency as a complication.

Key words: lactic acidosis, metformin, thiamin deficiency, cardiac dysfunction

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Introduction

Metformin improves insulin resistance by increasing the glucose uptake in muscle and adipose tissue and by decreasing hepatic gluconeogenesis. It is widely prescribed to obese patients with diabetes (1). Of note, biguanides inhibit mitochondrial respiration and promote the conversion of glucose to lactate, thereby increasing lactate production and leading to lactic acidosis (2). However, when biguanides are used appropriately, the incidence of biguanide-related lactic acidosis is reported to be very low (3). It is important to consider thiamine deficiency in the differential diagnosis of lactic acidosis.

We herein report a case of cardiac dysfunction due to thiamine deficiency after hemodialysis for biguanide-related lactic acidosis.

Case Report

An 82-year-old man was brought to our hospital with complaints of weakness and malaise. He had been undergoing treatment with metformin (2,000 mg/day), sitagliptin (50 mg/day), and gliclazide (20 mg/day) for the past several years. On day X-28, his blood test showed a serum creatinine (SCr) level of 1.7 mg/dL, and an estimated glomerular filtration rate (eGFR) 29.5 ml/min/1.73 m^2; the metformin dose was therefore reduced to 1,000 mg/day. He was a picky eater, and his usual diet had been white rice with little vegetables and meat for several years. He had not consumed alcohol since he was 50 years old. On day X-7, he suffered heat stroke after being exposed to heat for a long time outside; although he could barely eat, he continued to take his medication until day X-1.

The patient had the following vital signs: level of consciousness, E3V4M4 on the Glasgow Coma Scale; respiratory rate, 24 breaths/min; blood pressure, 76/42 mmHg; pulse rate, 100 beats/min; saturation of percutaneous oxygen (SpO_2), 97% (room air); and body temperature, 36.2°C. His body mass index was 17.9 kg/m^2. There were no symptoms suggestive of polyneuropathy or Wernicke's encephalopathy, and no abnormalities were observed on magnetic resonance imaging.

His physical findings showed dry mouth and dry axillae. Arterial blood gas findings showed a pH of 6.581, HCO_3^- of 1.0 mEq/L, base excess of -34.6 mEq/L, and lactate level of 12.4 mmol/L, indicating severe lactic acidosis (Table). In addition, an SCr level of 7.61 mg/dL, eGFR of 5.9 ml/min/1.73 m^2, K level of 6.6 mEq/L, renal dysfunction, and hyperkalemia were observed.

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Table. Laboratory Data at the First Visit to Our Hospital.

Biochemistry		Complete blood count		Arterial blood gas analysis	
TP	7.1 g/dL	WBC	13400 /μL	pH	6.6
Alb	4.1 g/dL	Hb	8.5 g/dL	pCO2	11.2 mmHg
BUN	59.8 mg/dL	Ht	28.7 %	pO2	150.7 mmHg
Cr	7.61 mg/dL	MCV	111.2 fl	HCO3-	1.0 mmol/L
eGFR	5.9 ml/min/1.73m2	Plt	17.1 /μL	AG	35.5
CCr	5.2 ml/min	Neu	90.2 %	lactate	12.4 mmol/L
Na	138 mEq/L	Lymph	6.2 %		
K	6.6 mEq/L				
Cl	104 mEq/L				
Ca	9.2 mg/dL	Coagulation test		Urinalysis	
P	6.4 mg/dL	PT-INR	1.48	gravity	1.016
Glu	98 mg/dL	PT%	51.7 %	pH	5.0
AST	22 IU/L	APTT	32.9 sec	protein	(1+)
ALT	11 IU/L	D-dimer	5.2 μg/mL	glucose	(+/-)
CK	99 IU/L	Fib	383 mg/mL	occult blood	(-)
CRP	2.2 mg/dL			ketone body	(-)
HbA1c	5.7 %				
BNP	467 pg/mL				
Vitamin B1	23 ng/mL				

TP: total protein,Alb: albumin, BUN: blood urea nitrogen, Cre: creatinine, eGFR: estimated glomerular filtration rate, CCr: creatinine clearance, Glu:glucose, AST:aspartate aminotransferase, ALT: alanine aminotransferase, CK:creatine kinase, CRP:C-reactive protein, HbA1c:hemoglobin A1c, BNP: denotes brain natriuretic peptide, WBC:white blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, Neu:neutophil, Lymph:lymphocyte, PT-INR:prothrombin time International normalized ratio, PT%:prothrombin activity, APTT:activated partial thromboplastin time, Fib:fibrinogen, pCO2: partial pressure of carbon dioxide, pO2: partial pressure of oxygen, AG:anion gap

Abdominal ultrasonography showed no hydronephrosis, both kidneys were atrophied, and the inferior vena cava was collapsed. His blood pressure was low, but echocardiography showed a left ventricular ejection fraction (LVEF) of 65%, indicating that his cardiac function was well preserved, and cardiogenic shock was unlikely. Based on the medical history, ultrasonography, and physical findings, the cause of the decrease in blood pressure was considered to be hypovolemic shock. At the same time, it was considered that the decrease in the reactivity of catecholamines in the myocardium and peripheral blood vessels due to severe metabolic acidosis was also involved in the decrease in blood pressure.

In the present case, lactic acidosis was thought to have been caused by metformin and microcirculatory impairment due to a decreased body fluid volume. The patient received 2 L of extracellular fluid, but no auturia was observed. He was started on noradrenaline because of circulatory instability, followed by continuous hemodiafiltration (CHDF). After the start of dialysis, his acidosis gradually improved, and his lactate level decreased (Fig. 1). As his acidosis improved, his blood pressure also increased, and noradrenaline was discontinued 36 h after admission. As the blood pressure increased, the microcirculation improved, and the metabolic acidosis further improved. Intravenous administration of glucose was started on day X+3. The patient's respiratory status worsened on day X+5, and chest radiography showed pulmonary congestion, bilateral pleural effusions, and elevated level of brain natriuretic peptide (BNP) (1,997 pg/dL). Echocardiography showed diffuse hypokinesis, his LVEF decreased to 28%, and electrocardiography showed ST depression at V3-6. Oxygenation worsened, but his systolic blood pressure remained unchanged at 100 mmHg.

There was a possibility of ischemic heart disease as a cause of the sudden decline in THE cardiac function, but coronary angiography could not be performed because of his poor general condition. Interviews with his family revealed that the patient's diet before admission had consisted mainly of white rice, which may have contributed to his chronic thiamine deficiency. The decrease in his blood thiamine concentration due to dialysis and the administration of glucose in the absence of thiamine administration were considered to have manifested the decrease in his cardiac function due to thiamine deficiency. From day X + 19, thiamine chloride hydrochloride (500 mg/day) was intravenously administered for 3 days. From day X+22, the dose was reduced to 100 mg/day intravenously. After administration for 5 days, the dose was switched to 75 mg/day orally. On day X+23, echocardiography showed that the LVEF had improved to 47%, and on day X+36, it was similar to that on admission (Fig. 2).

As the cardiac function improved, the BNP levels decreased, pulmonary congestion improved, and bilateral pleural effusions decreased. The serum concentration of vitamin B1 was 23 ng/mL (reference value: 24-66 ng/mL) in the blood test taken before the first dose of thiamine. The renal function eventually improved to an eGFR of 28.5 ml/min/1.73 m^2, and the patient was transferred to the hospital for rehabilitation on day X+37.

Discussion

Metformin has been regarded as the first-line drug for the treatment of type 2 diabetes mellitus because it attenuates macrovascular diseases and is available at a low price (4). However, lactic acidosis is a serious adverse effect of metformin use, requiring attention. The mechanism of

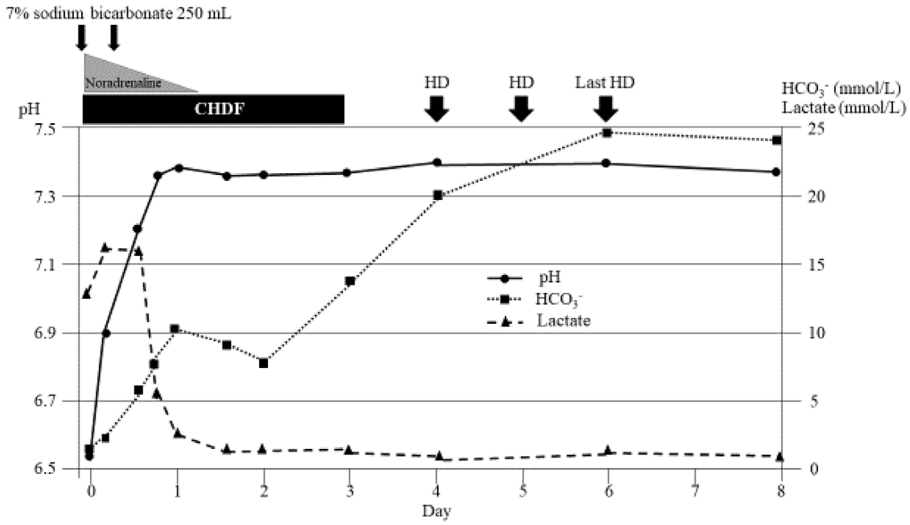

Figure 1. **Clinical course of the patient's lactic acidosis. With the start of CHDF, the lactate levels decreased rapidly, and the metabolic acidosis improved. HD on day 6 was the final dialysis procedure, as the amount of urine increased. HD: hemodialysis, CHDF: continuous hemodiafiltration**

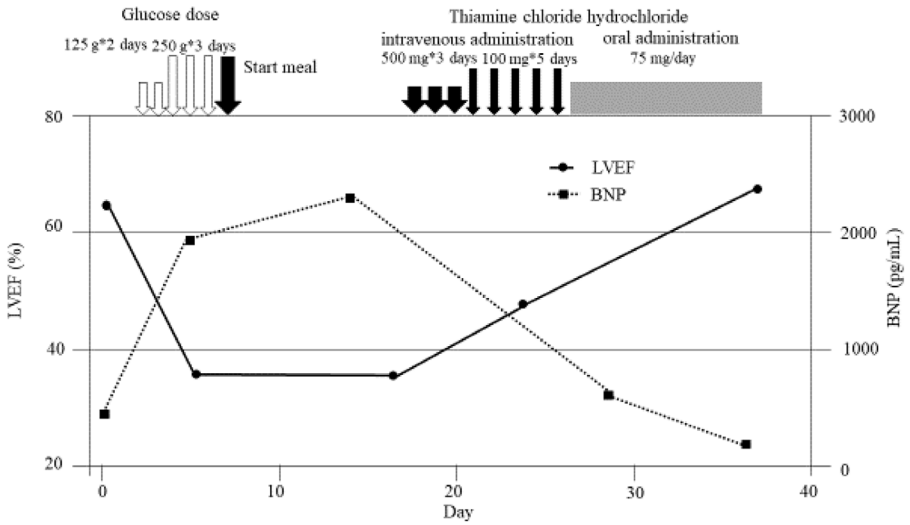

Figure 2. **Clinical course of the patient's cardiac function and serum BNP level. The patient's marked reduction in the left ventricular systolic function was reversed by the administration of high-dose thiamine. The serum BNP level decreased significantly. Each arrow indicates the intravenous administration of thiamine chloride hydrochloride. LVEF: left ventricular ejection fraction, BNP: brain natriuretic peptide**

biguanide-induced lactic acidosis is as follows: biguanides bind to the mitochondrial cell membrane of hepatocytes and inhibit oxidative phosphorylation, resulting in an increase in reduced nicotinamide adenine dinucleotide (NADH), a decrease in the tricarboxylic acid (TCA) cycle, and a decrease in pyruvate dehydrogenase, thereby leading to an increase in lactate production. In addition, an increase in lactate production due to the accumulation of pyruvate caused by the suppression of glycogenesis in hepatocytes is also thought to be a contributing factor (5). When biguanides are used appropriately, the incidence of biguanide-associated lactic acidosis is reported to be very low, but the mortality rate at the time of the onset is extremely severe, at 50% (6).

Risk factors associated with biguanide-related lactic acidosis include chronic kidney disease, congestive heart failure, alcohol use, severe dehydration, shock, hypoxic states, sepsis, and advanced age (2). Therefore, guidelines in various countries recommend cautious administration or contraindicate biguanides in patients with renal dysfunction or in the elderly because of the risk of lactic acidosis (7, 8). In the present case, chronic kidney disease and old age were the relevant risk factors associated with biguanide-related lactic acidosis. The treatment target for diabetes in elderly dementia patients in Japan is HbA1c <8.5% when taking

sulfonylurea drug (9). The HbA1c at admission in this case was 5.7%, which was considerably lower than the target value. Regarding metformin, a blood test 1 month earlier had shown that the renal function had already decreased to an eGFR of 29.5 ml/min/1.73 m^2, which was a contraindication. It is highly probable that inappropriate drug treatment for diabetes in this elderly dementia patient led to our patient's condition. Although 99% of metformin is excreted in urine from the kidneys, renal excretion of metformin is known to decrease with a worsening renal function (10). In addition, it has been suggested that metformin itself may cause renal tubular damage (10). In animal experiments, enlargement and vacuolar degeneration of proximal tubular cells after the administration of biguanides have been reported (11). In this case, because the patient also had mild dementia, metformin was not withdrawn during the sick days, which may have contributed to the development of lactic acidosis.

The mainstay of treatment for biguanide-related lactic acidosis is supportive care involving infusion of fluids and administration of sodium bicarbonate (12). However, metformin has a small molecular weight (165 Da) and a low protein-binding rate of 1.1-2.8%; therefore, it can easily pass through the dialysis membrane. There are many reports showing the efficacy of extracorporeal circulation therapy, including dialysis therapy (13-15). In 2015, a working group of the Society of Critical Care Medicine issued a recommendation for the use of metformin in extracorporeal circulation, including dialysis (12). In that report, extracorporeal circulation was recommended for patients with a serum lactate level of >20 mmol/L, pH of ≤7.0, and no improvement with supportive care. In contrast, because the distribution volume is large (1-5 L/kg), the rebound phenomenon of metformin distributed in the tissues is concerning (16), and hemodialysis should be continued until the lactate concentration is <3.0 mmol/L and pH >7.35.

The relationship between the blood metformin concentration and prognosis is controversial, and the blood metformin concentration has not been used as a criterion for initiating extracorporeal circulation therapy (12). In the present case, the urine volume was not determined despite massive infusion of fluids, and the lactic acidosis was severe; thus, CHDF was started to remove metformin and lactic acid and replenish bicarbonate ions. After the start of blood purification therapy, acidosis improved rapidly, the blood pressure increased, and the circulatory dynamics stabilized.

In addition, the patient developed congestive heart failure owing to a rapid decline in the cardiac function during the course of treatment. Echocardiography on admission showed a normal cardiac function, but echocardiography on day X+5 showed diffuse hypokinesia, and the LVEF had decreased to 28%. After thiamine supplementation was started, his cardiac function improved immediately, suggesting that thiamine deficiency had probably been involved in this decline in the cardiac function. The symptoms of heart failure due to thiamine deficiency include an initially high cardiac output heart failure and right heart failure, but gradually, this is accompanied by cardiomyocyte damage due to impaired glucose metabolism in the cardiomyocytes and a decrease in cardiac output, complicated by symptoms of left heart failure. Hyperemic heart failure is reportedly a characteristic finding of the pacing heart, but it is not absolute, and a normal or low cardiac output does not necessarily negate the presence of the pacing heart (17).

Thiamine is known to be removed by hemodialysis, and it has been reported that the concentration of thiamine in blood decreases by approximately 50% before and after dialysis (18). Regarding the relationship between dialysis duration and blood thiamine concentration, the blood thiamine concentration of patients on dialysis for a long duration is significantly lower than that of patients on dialysis for a normal duration (19). The fact that the patient's diet consisted mainly of white rice with no vegetables or meat suggests that thiamine stores may have been very low or insufficient. Prolonged use of hemodialysis in this patient may have further decreased thiamine levels in the body, resulting in a decreased cardiac function due to thiamine deficiency. In addition, the fact that glucose administration was started on day X+3 without thiamine administration is considered to be one of the causes of the manifestation of cardiac dysfunction due to thiamine deficiency.

Thiamine deficiency is also associated with lactic acidosis. Thiamine is involved in glucose metabolism as a cofactor for pyruvate dehydrogenase in the glycolytic system and α-ketoglutarate dehydrogenase in the TCA cycle. When thiamine is deficient, pyruvate is not oxidized to acetyl CoA, and lactic acid is produced in excess, resulting in lactic acidosis (20). In the present case, thiamine deficiency and metformin may have been the reasons for the severe lactic acidosis at the time of admission. The thiamine concentration in the patient's blood before thiamine administration was only slightly lower than normal. However, the vitamin B1 level in patients with thiamine deficiency is not always extremely low (21, 22). Current guidelines for parenteral nutrition recommend 100-300 mg/day of intravenous thiamine during the first 3 days of treatment for critically ill patients with possible thiamine deficiency (23). Thiamine supplementation is a safe, easily available, and well-tolerated treatment with few side effects other than anaphylaxis (22).

It was recently reported that diabetes patients taking metformin for a long time have an increased risk of serum vitamin B12 deficiency (24-26). However, not only vitamin B12 but also metformin may have anti-thiamine activity, as phenformin, the precursor of metformin, has shown anti-thiamine activity in experimental animals (27). In the present case, thiamine deficiency due to picky eating and oral administration of metformin may have contributed to thiamine deficiency.

Thiamine deficiency is not widely recognized and may be a diagnostic pitfall. In this case, we initially thought that the patient had biguanide-related lactic acidosis and started treatment. Subsequently, the deterioration of the cardiac

function due to thiamine deficiency became apparent. Suspicion of thiamine deficiency can be prompted by taking a detailed history of the alcohol intake and dietary habits. It is also important to start treatment without delay when thiamine deficiency is suspected, as thiamine supplementation can rapidly improve treatment.

The authors state that they have no Conflict of Interest (COI).

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