CASE REPORT

Severe Lactic Acidosis and Acute Pancreatitis Associated with Cimetidine in a Patient with Type 2 Diabetes Mellitus Taking Metformin

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Abstract

An 82-year-old woman with type 2 diabetes mellitus, hypertension, and unstable angina presented with severe lactic acidosis and acute kidney injury (AKI) accompanied by acute pancreatitis. Her medical history revealed that she had taken cimetidine for two weeks while taking other medications, including metformin. Continuous veno-venous hemodiafiltration (CVVHDF) was initiated under diagnosis of lactic acidosis due to metformin and AKI caused by cimetidine-induced acute pancreatitis. In three days of CVVHDF, the levels of serum biochemical markers of lactic acidosis and AKI improved and the patient’s urine output reached over 1 L/day. The pancreatitis improved over time.

Key words: severe lactic acidosis, metformin, acute pancreatitis, cimetidine


Introduction

Metformin is commonly used to treat type 2 diabetes mellitus. Lactic acidosis is a very rare complication of metformin. The risk of lactic acidosis increases with age and the degree of kidney function impairment (1). Metformin is excreted by the kidneys, and begins to accumulate when the glomerular filtration rate is less than 50-60 ml/min (2). Acute kidney injury (AKI) often occurs in patients with acute pancreatitis due to a decreased circulating blood volume (3). The two most common causes of acute pancreatitis are gallstones and alcohol abuse, followed by hypercalcemia, hypertriglyceridemia, trauma and drugs (4). Drug-induced acute pancreatitis occurs in only approximately 2% of all cases of pancreatitis (5). Cimetidine, which is used to treat peptic ulcers and reflux esophagitis, has also been reported to induce acute pancreatitis. We herein report the rare case of a patient with metformin-induced severe lactic acidosis and AKI associated with cimetidine-induced acute pancreatitis that recovered with supportive treatment and continuous veno-venous hemodiafiltration (CVVHDF).

Case Report

An 82-year-old woman with type 2 diabetes mellitus, hypertension, and unstable angina presented to the emergency department after two weeks of nausea and vomiting. Her medication history included gliclazide, voglibose, fenofibrate, atorvastatin, lorazepam, thioctacid, and 2,000 mg of daily metformin. She had been taking metformin for two years. Three weeks prior to presentation, 600 mg of daily dexibuprofen and 600 mg of daily cimetidine were added to her medication regimen due to an L5 compression fracture caused by a fall. Six years prior to presentation, she had undergone low anterior colon resection for the treatment of sigmoid colon cancer. There had been no signs of cancer recurrence.

In the emergency room, the patient’s blood pressure was 80/50 mmHg, her pulse rate was 52 beats/min and her body temperature was 36.1°C. Her respirations were very deep, and her respiratory rate was 28 breaths/min. On physical examination, her head, eyes, ears, nose and throat were unremarkable. Clear breath sounds and normal heart sounds were heard. Abdominal distension and whole abdominal ten-
Figure 1. Contrast-enhanced abdominal CT. (A) Initial CT images showing mild swelling of the pancreas with peripancreatic infiltration (arrow). (B) Posttreatment CT images showing decreased pancreatic swelling (arrow).

derness were noted; however, bowel sounds were absent. The patient’s skin turgor was observed to have decreased.

The laboratory findings were as follows: white cell count: 23,900/μL, hemoglobin: 13.8 g/dL, platelet count: 306,000/μL, and erythrocyte sedimentation rate: 6 min/hour. Biochemistry showed a blood urea nitrogen level of 93.3 mg/dL, a creatinine level of 5.1 mg/dL, an aspartate aminotransferase/alanine aminotransferase level of 80/25 IU/L, an alkaline phosphatase level of 235 IU/L, a sodium/potassium/chloride/tCO₂ level of 136/6.5/90/1 mEq/L, a calcium level of 10.2 mg/dL, a phosphorus level of 15.8 mg/dL, an amylase/lipase level of 297/892 U/L, a LDH level of 874 IU/L, a creatinine phosphokinase level of 158 IU/L, a myoglobin level of 827.5 ng/mL, and a C-reactive protein level of 0.48 ng/dL. A urinalysis revealed a pH of 5.0, a SG level of 1.018, an albumin level of 2+, a WBC count of 0-1/HPF and a RBC count of 0-1/HPF with no evidence of eosinophil casts. Arterial blood gases showed a pH of 6.950, aHCO₃⁻ of 3.9 mmol/L and an anion gap of 42.1 mmol/L. The serum lactate level was 12 mmol/L, and ketones were negative.

Abdominal computed tomography (CT) demonstrated pancreatic swelling and peripancreatic infiltration without gallstones, a normal parenchyma, vasculature, and kidney size and normal anastomosis following left hemicolectomy for the treatment of sigmoid cancer (Fig. 1A). Based on the laboratory and radiographic findings, the patient was diagnosed with severe lactic acidosis and acute pancreatitis-associated AKI.

First, the patient’s previous medications, including cimetidine, dexibuprofen and metformin, were discontinued. On the first day of hospitalization, she was treated with inotropic agents, intravenous fluids, and bicarbonate without enteral feeding. On the second day of hospitalization, she was started on CVVHDF due to severe high anion gap metabolic acidosis with oliguria (<10 cc/hour) that was refractory to medical treatment. On the fourth day of hospitalization, her serum lactate level decreased to 4.3 mmol/L and her blood pH improved to 7.47. When her urine output increased to over 1 L per day and the serum creatinine level decreased to 0.9 mg/dL (baseline serum creatinine: 1.0 mg/dL), the continuous renal replacement therapy was discontinued. On the 14th day of admission, the serum amylase/lipase level was 33/39 U/L (Fig. 2), and the patient’s bowel sounds returned to normal. The pancreatic swelling and peripancreatic infiltration were also improved on follow-up abdominal CT (Fig. 1B). Oral intake was therefore initiated. However, two days after the initiation of oral intake, the patient suddenly made a grunting sound and developed a fever accompanied by coughing and impaired consciousness. The oral feeding, including the liquid diet, was immediately stopped. Over the next several days, the patient developed sepsis with aspiration pneumonia that did not improve. Although the initial acidosis, pancreatitis and AKI improved, she nevertheless died of infection on the 18th hospital day.

Discussion

Drug-induced pancreatitis accounts for 1.2% of all cases of acute pancreatitis (6). Eland et al. (7) reported that cimetidine, a histamine H₂-receptor antagonist used to treat peptic ulcers and reflux esophagitis, is associated with acute pancreatitis. The relative risk of developing acute pancreatitis in current cimetidine users is 2.1 (95% confidence interval: 0.6-7.2) (7). The risk is highest in the first 30 days of therapy (7). Dexibuprofen administered in combination with cimetidine is a nonsteroidal anti-inflammatory drug (NSAID). NSAIDs are the first-line therapy for the pain of acute pancreatitis and are used to prevent postendoscopic cholangiopancreatography acute pancreatitis (8). In the present case, cimetidine was more likely than dexibuprofen to be the causative agent. Our patient did not exhibit gallstones on abdominal CT and was not an alcohol abuser. We hypothesized that her acute pancreatitis had thus been caused by cimetidine, which had recently been added to her medication regimen.

Metformin is a biguanide that has been widely used to treat type 2 diabetes mellitus since 1957 (9, 10). Metformin
promotes mild weight loss, lowers the insulin level, and slightly improves the lipid profile. Metformin is used as initial therapy due to its efficacy, low rate of side-effects and relatively low cost (11). Although gastrointestinal tract problems, such as diarrhea, anorexia and nausea, are frequent side effects of metformin, lactic acidosis is rare. The incidence of metformin-associated lactic acidosis is not well known. Salpeter et al. (12) reported that the incidence of lactic acidosis associated with the use of metformin is 8.1 cases per 100,000 patient-years, although the mortality rate of metformin-associated lactic acidosis is approximately 50% (13). Metformin induces the production of lactic acid by interfering with glucose oxidase in the muscles and intestines (14). Serum lactate is used for gluconeogenesis in the liver or is eliminated via the kidneys (14). Therefore, metformin should not be administered to patients with renal insufficiency, any form of acidosis, congestive heart failure, liver disease or severe hypoxia due to the risk of lactic acidosis (11).

Reduced renal elimination of lactate also occurs in patients with AKI. Acute pancreatitis contributes to the development of AKI by reducing the renal elimination of lactate. Approximately 50% of patients with severe acute pancreatitis exhibit organ failure. Zhu et al. (3) reported that renal failure occurred in 16.2% of 74 patients with severe acute pancreatitis. However, dexibuprofen (a NSAID), which was prescribed for the patient’s L5 fracture in this case, is also a causative drug for the development of AKI. The second mechanism involves the development of acute interstitial nephritis. Schneider et al. (15) reported that approximately 3.4% of new NSAID users older than 65 years of age develop AKI. In addition, AKI secondary to rhabdomyolysis rarely occurs when statins are used in combination with fibrates (16). In this case, we were unable to find evidence of rhabdomyolysis, and the level of creatinine phosphokinase was normal at the time of admission. Therefore, cimetidine is more likely to have induced the pancreatitis than dexibuprofen, atorvastatin or fenofibrate as a cause of AKI.

Boehm et al. (17) first reported metformin- and cimetidine-induced lactic acidosis and acute pancreatitis in a patient with type 2 diabetes mellitus. Not only is lactic acidosis a rare side effect of metformin, acute pancreatitis is also a rare side effect of cimetidine. Our patient had type II diabetes mellitus and was taking metformin with no signs of renal dysfunction. After using cimetidine, she was diagnosed with high anion gap lactic acidosis and acute pancreatitis-induced AKI. She first stopped taking the metformin and cimetidine and underwent bowel rest while receiving emergent CVVHDF. After four days of treatment, the metabolic acidosis, acute pancreatitis and AKI improved, and the CVVHDF was discontinued.

In summary, we herein reported a case of lactic acidosis and AKI due to acute pancreatitis in a patient with type 2 diabetes mellitus taking metformin simultaneously with cimetidine. The development of acute pancreatitis was most likely the initial event leading to the subsequent onset of lactic acidosis. Cimetidine induced acute pancreatitis, which in turn reduced the renal excretion of metformin, thus resulting in the metformin toxicity that had caused severe lactic acidosis.

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

References