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Case Report

Acute Pancreatitis After a Late Period of Metformin Intoxication in a Non-Diabetic Patient

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ABSTRACT

Metformin, an oral antidiabetic drug, is the first-line treatment modality for the treatment of non-insulin-dependent diabetes mellitus. Metformin is more commonly associated with gastrointestinal side effects. Acute pancreatitis due to metformin is very rare. We present a case of acute pancreatitis after a late period of metformin intoxication in a non-diabetic patient. Because acute pancreatitis can appear in the late period of metformin intoxication, the emergency physician should be vigilant for this condition.

Keywords: Acute pancreatitis, metformin, intoxication

INTRODUCTION

Metformin, an oral antidiabetic drug in the biguanide class, is the first-line treatment modality for the treatment of non-insulin-dependent diabetes mellitus and the most widely prescribed antidiabetic drug in the world. It's also used in the treatment of polycystic ovary syndrome, non-alcoholic fatty liver disease, and premature puberty (1). Metformin is more commonly associated with gastrointestinal side effects, including diarrhea, cramps, nausea, vomiting, and increased flatulence. However, the most serious adverse effect and potentially life-threatening complication of metformin is lactic acidosis (2). Acute pancreatitis due to metformin is very rare and this adverse effect results from a combination of drug overdose and renal failure (3,4). Furthermore, there is limited knowledge regarding the course of metformin intoxication without renal failure in non-diabetic patients. Herein, we present a case of late edematous pancreatitis following metformin intoxication in a non-diabetic patient with normal renal function.

CASE

A 26-year-old man admitted to the emergency department with epigastric pain, nausea, and vomiting for one day. He had a history of hospitalization in the intensive care unit owing to a suicide attempt with 60 grams of metformin use one week before his admission to our clinic. He had been hospitalized for five days and was discharged after successful treatment with activated charcoal gastric lavage, intravenous hydration, and a single four-hour hemodialysis session without anyother organ failure for side effects of metformin overdose and lactic acidosis. He had no history of trauma, smoking, alcohol consumption, or use of herbal or illicit drugs. On physical examination, he was afebrile, with a blood pressure of 125/75 mm/Hg, and a pulse of 78 beats per minute. His abdominal examination revealed tenderness in the epigastric region, but no rigidity or rebound was detected. The remainder of the examination was normal.

Results of the blood tests were as follows; white-cell count: 9300 per cubic millimeter, hemoglobin level: 14.4 g/dl (reference range: 13.6-17.2 g/dl), platelet count: 20700/mm3, aspartate aminotransferase: 23 U/L (reference range: 0-34 U/L), alanine aminotransferase: 42 U/L (reference range: 10- 49 U/L), alkaline phosphatase: 61 U/L (reference range: 40-129 U/L), gama glutamyl transferase: 67 U/L (reference range: 8-73 U/L), total bilirubin: 0.7 mg/dL (reference range:0.3-1.2 mg/dL), direct bilirubin: 0.2 mg/dL (reference range: 0-0.2 mg/dL), total protein: 7.2 g/dl, albumin: 4.2 g/dl, glucose: 93 mg/dL, lactate dehydrogenase: 247 U/L (reference range: 120-246 U/L), pancreatic amylase: 303 U/L (reference range:13-53 U/L), lipase: 320 U/L (reference range: 6-51 U/L), creatinine: 1.1 mg/dL (reference range: 0.7-1.3 mg/dL), and urea: 32 mg/dL (reference range: 19-48 mg/dl). The electrolyte levels were in the normal range and arterial blood gases had a pH of 7.37 and a lactate level of 1.53 mmol/L (reference range: 0-1.8 mmol/L). The level of lipid profiles and thyroid-

stimulating hormone were normal. C-reactive protein level was 8.2 mg/L (reference range: 0-8 mg/L). Polymerase-chain-reaction tests were negative for hepatitis B, hepatitis C, and human immunodeficiency virus. An ultrasonographic examination of the abdomen showed that the vertical size of the liver was 12 cm. This examination also revealed a mild increase in liver echo density with no gall stones and splenomegaly and an increase in the pancreatic body with the hypoechoic pattern. An abdominal computed tomography scan detected a diffusely enlarged pancreas with low density from edema, and acute pancreatitis was confirmed by radiologic imaging. The patient was treated with intravenous fluids and a proton pump inhibitor. Within two days, the patient's abdominal pain improved and serum pancreatic amylase and lipase levels recovered. The patient was discharged three days after the hospitalization and tested well at the follow-up.

DISCUSSION

The patient was diagnosed with mild edematous pancreatitis after metformin intoxication in the late period due to the clinical presentation of epigastric pain, the lack of multi-organ failure, high levels of amylase and lipase, the lack of other known causes of acute pancreatitis, and the conformable radiological findings for the diagnosis of acute pancreatitis. The most important causes of acute pancreatitis are alcohol consumption and gallstones. Drug-induced acute pancreatitis is generally considered to be a rare condition, accounting for approximately 2% of all causes of acute pancreatitis (5). Furthermore, metformin accounts for a very small percentage of the drugs that induce acute pancreatitis. Hence, metformin's involvement in the complication is an extremely rare event.

Metformin is more commonly associated with gastrointestinal side effects, but the most serious adverse effect and life-threatening complication of this drug is lactic acidosis, with mortality greater than 30% (2,6). The exact molecular mechanism underlying metformin-induced acute pancreatitis is still unknown. However, available evidence suggests that acute pancreatitis due to metformin is probably caused by the overexpression and prolonged activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK), by the drug overdose or/and with renal insufficiency (7).

Recommended daily dose of metformin is <2550 mg (2). If administered within these doses, metformin activates AMPK, a liver enzyme that plays an important role in insulin signaling and cellular energy homeostasis. This activation leads to hepatic fatty acid oxidation and ketogenesis, inhibition of lipogenesis, stimulation of skeletal muscle fatty acid oxidation and glucose uptake, and modulation of insulin secretion by pancreatic beta-cells. Additionally, this process suppresses hepatic glucose production, increases insulin sensitivity, enhances peripheral glucose uptake, increases fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract (8).

On the other hand, administration of metformin above the recommended daily dose (>2550 mg), can lead to pancreatic beta cell damage due to overstimulation of the AMPK signaling pathway. This is in line with a previous study where the pancreatic beta-cell function was shown to be impaired in vivo by overexpression of AMPK (9) (**Figure**). Prolonged activation and overexpression of AMPK will tend to decrease beta-cell function, leading to acinar cell damage and intracellular leakage of digestive enzymes from ductules. This leakage is associated with pancreatic inflammation

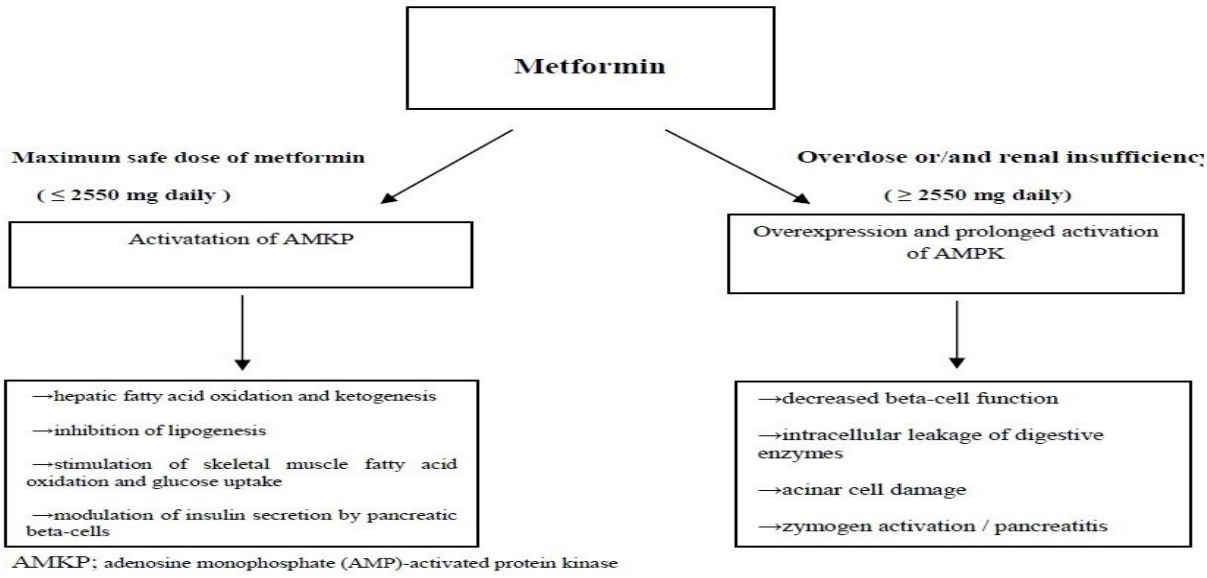

Figure. Dose-dependent effects of metformin on AMPK activation (adapted from Reference 9).

through zymogen activation. Dose-dependent effects of metformin on AMPK activation are shown in the Figure.

Metformin is cleared from the body by tubular secretion and excreted in the urine without any change. Therefore, overdoses of metformin and renal dysfunction will tend to cause an accumulation of the drug and trigger pancreatitis via the aforementioned prolonged activation of the AMPK signaling pathway.

A few cases of pancreatitis have been reported with metformin. Among the published case reports, metformin-induced pancreatitis was attributed to metformin overdose, patients' comorbidities, a combination of other drugs (angiotensin-converting enzyme inhibitor, non-steroidal anti-inflammatory), and renal failure (4,6,7,10).

There is no knowledge of the course of metformin intoxication without renal failure in non-diabetic patients in the late period. This is the first case of metformin-associated late-acute pancreatitis due to overdose-dependent side effects of metformin in a patient with non-comorbidities and no-renal impairment. Because acute pancreatitis can appear in the late period of metformin intoxication, the emergency physician should be vigilant for this condition.

DECLARATIONS

Acknowledgment: Not applicable
Ethics Committee Approval Number: Not necessary
Informed Consent: Not necessary
Referee Evaluation Process: Externally peer-reviewed
Conflict of Interest Statement: Authors declare no conflict of interest.

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