Special Feature
CASE REPORT/FOCUSED REVIEW

Metformin-Associated Lactic Acidosis

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Abstract: Metformin is the most commonly prescribed oral antidiabetic agent. Despite a good safety profile in most patients with diabetes, the risk of metformin-associated lactic acidosis is real if safety guidelines are ignored. Experience with 3 cases of metformin-associated lactic acidosis is reported. Two cases were caused by inappropriate use of metformin in the presence of renal, cardiac and hepatic failure and 1 case followed an intentional overdose. The literature was reviewed on the clinical presentation, prevalence, pathogenesis, prognosis and management of metformin-associated lactic acidosis. This report highlights the importance of proper patient selection, clinical and laboratory monitoring and recommendation on when to stop the drug in ambulatory and hospitalized patients to prevent this unusual but potentially lethal complication.

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Metformin is the most commonly prescribed oral antidiabetic agent for the management of type 2 diabetes (T2D).[1] The mechanism of action is not completely understood, but experimental and human data have shown that metformin reduces hepatic glucose production by inhibiting key enzymes in the gluconeogenesis pathway and by mitochondrial depletion of the energy necessary for gluconeogenesis.[2] In addition, it improves islet cell responsiveness to a glucose load through the correction of glucose toxicity and improves peripheral glucose utilization by enhancing muscle uptake of glucose.[3] Metformin also seems to modulate components of the incretin axis, increasing glucagon-like peptide 1 levels and the expression of genes encoding receptors for both glucagon-like peptide 1 and glucose-dependent insulinotropic peptide.[4,5]

Despite its introduction in Europe and Canada in 1957, metformin was not licensed in the United States until 1995 because of fear of lactic acidosis, a rare but fatal complication associated with phenformin.[6] The risk of lactic acidosis during metformin therapy has been the matter of continuous debate.[7–12] Data from comparative trials, cohort studies and meta-analyses have reported a frequency of lactic acidosis in 2 to 5 cases per 100,000 patients receiving metformin, a similar risk observed in patients with diabetes not receiving the drug.[8,13–15] Impaired kidney function is the most important risk factor for metformin-associated lactic acidosis. In the United States, the use of metformin is contraindicated in men and women with serum creatinine concentrations $\geq$1.5 mg/dL and $\geq$1.4 mg/dL ($\geq$132 and $\geq$123 μmol/L), respectively. The National Institute for Health and Clinical Excellence in the United Kingdom recommends that metformin may be continued (or initiated) with estimated glomerular filtration rates (eGFR) $<$60 mL/min per 1.73 m^2; to reduced dose when the eGFR falls below 45 mL/min per 1.73 m^2 and stopping when the eGFR is less than 30 mL/min per 1.73 m^2.[7] Similarly, the Canadian Diabetes Association and the Australian Diabetes Society recommend as contraindication to metformin use when the eGFR is $<$30 mL/min per 1.73 m^2.[7,16] A history of heart failure was also considered a contraindication to the use of metformin; however, the Food and Drug Administration removed heart failure as contraindication from the packaging label in 2006[17] after several observational studies reported lower morbidity and mortality in stable patients with a history of heart failure compared with other antidiabetic medications.[18–21]

There is lack of randomized studies on the safety and efficacy of metformin in the hospital setting. Metformin is commonly used for the management of inpatients with hyperglycemia,[7,8] and it is estimated that up to 1/4 of hospitalized patients with T2D are treated with metformin, even in the presence of contraindications.[22] The inpatient use of metformin seems to be well tolerated, in particular in those who were receiving the drug before admission, with few patients experiencing serious adverse effects or pH changes

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during the hospital stay.[22] These reports have raised questions about restrictions to prescribe metformin.[7,8]

The excellent efficacy and safety profile of metformin use in patients with diabetes have resulted in poor patient selection and ignoring safety guidelines, with recent reports suggesting increasing numbers of cases of metformin-associated lactic acidosis around the world.[23–30] To highlight the need of caution, we report our experience of 3 patients presenting with metformin-associated lactic acidosis and review the clinical presentation, prognosis and recommended approaches for managing metformin-associated lactic acidosis.

CASE PRESENTATIONS

Case 1

A 70-year-old patient with T2D treated with metformin (500 mg twice daily), dilated cardiomyopathy (ejection fraction of 10%) and stage III chronic kidney disease (serum creatinine: 1.5 mg/dL, eGFR: 59.4 mL/min per 1.73 m^2) presented with chest pain and progressive shortness of breath. On admission, his blood pressure was 149/77 mm Hg and heart rate was 60 beats per minute with Kussmaul respiratory pattern. Examination revealed bilateral lung crackles in the bases and the presence of S3 and S4 gallops, but no peripheral edema. Admission laboratory tests showed acute kidney injury with creatinine of 2.8 mg/dL, a lactic acid level of 11.1 mmol/L (normal $<$ 2.2 mmol/L), an arterial pH of 7.03, a serum bicarbonate of 3.8 mmol/L, an anion gap of 26 mEq/L, blood glucose of 206 mg/dL and negative serum ketones. Chest x-ray showed no evidence of pulmonary edema. The patient underwent emergent hemodialysis. The patient's high gap metabolic acidosis promptly resolved after dialysis. Predialysis metformin level was 25 μg/mL (therapeutic range: 1–2 μg/mL), and postdialysis metformin was 1.5 μg/mL (Table 1).

Case 2

A 56-year-old male patient with T2D, cirrhosis, hepatitis C and hepatocellular carcinoma presented after a syncopal spell. One-day before admission, he underwent liver biopsy and paracentesis with removal of 4 L of ascitic fluid. On admission, his blood pressure was 86/64 mm Hg (mean arterial pressure 71 mm Hg), heart rate was 95 beats per minute and saturation was 100%. Examination revealed the presence of jaundice, ascites and pretibial pitting edema. Lungs were clear to auscultation, and no jugular venous distention was noted. Laboratory results revealed acute kidney injury with a creatinine of 2.1 mg/dL (baseline 1.1 mg/dL), bicarbonate of 18 mEq/L and anion gap of 12 mEq/L. Diuretics and lisinopril were held but metformin (500 mg twice daily) was continued. On day 3, the patient developed altered mental status and respiratory failure. Laboratory results revealed worsening renal function with a serum creatinine of 3.2 mg/dL, a lactic acid level of 10.6 mmol/L, an arterial pH of 7.0, P_{CO_2} of 21 mm Hg, bicarbonate of 4 mEq/L, anion gap of 47 mEq/L, aspartate aminotransferase of 3598 U/L, alanine aminotransferase of 898 U/L and international normalized ratio of 7.0. He underwent emergency hemodialysis with correction of the high anion gap metabolic acidosis. Predialysis metformin level was 31 μg/mL (therapeutic range: 1–2 μg/mL), and postdialysis metformin level was 5.4 μg/mL.

Case 3

A 60-year-old man with T2D treated with a combination of metformin and neutral protamine Hagedorn and regular insulin presented after an intentional metformin overdose. The patient reported ingesting more than 10 metformin tablets (500 mg) in the setting of alcohol use. On arrival, he was in mild distress with stable vital signs. He was treated with activated charcoal and intravenous hydration. Laboratory studies showed a serum creatinine of 0.8 mg/dL, pH of 7.35, anion gap of 22 mEq/L and a lactic level of 7.4 mmol/L. The patient was admitted to the medical intensive care unit with a plan for hemodialysis; however, his clinical status improved with conservative measures with resolution of metabolic acidosis during the next 24 hours.

DISCUSSION

Metformin is the most commonly prescribed oral antidiabetic agent for the management of patients with T2D. Metformin is safe when used correctly, and in properly selected patients, there is no increased risk of lactic acidosis compared with non-metformin–treated patients.[13,31] The risk of metformin-associated lactic acidosis is remarkably low with a frequency similar to that reported in patients with diabetes not receiving metformin treatment.[8,13] The COSMIC trial evaluated the risk of serious adverse events including lactic acidosis with metformin therapy among 7,227 patients with T2D treated with metformin for more than 1 year.[31] This trial reported no significant differences in the frequency of serious adverse events compared with patients not receiving metformin therapy. A 2010 Cochrane systematic review reported no increase in the

TABLE 1. Characteristics of patients with metformin-associated lactic acidosis

	Case 1	Case 2	Case 3
Age, yr	70	56	60
Risk factor for lactic acidosis	CKD stage III, AKI, heart failure	Cirrhosis, AKI	Alcohol abuse, metformin overdose
Diabetes treatment	Metformin monotherapy	Metformin monotherapy	Metformin, NPH/R insulin
Serum creatinine before admission, mg/dL	1.5	1.1	0.8
Admission serum creatinine, mg/dL	2.8	2.1	0.8
Admission eGFR	30.3	40	>60
Serum bicarbonate, mEq/L	3.8	4	9
Anion gap	26	47	22
Arterial pH	7.03	7.0	7.35
Lactic acid level, mmol/L	11.1	10.6	>10
Serum metformin level, U/L	25	31	N/A
Therapy	Hemodialysis	Hemodialysis	Activated charcoal, hydration

CKD, chronic kidney disease; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; N/A, data not available; NPH, neutral protamine Hagedorn insulin; R, regular insulin.

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