

# Metformin-Associated Lactic Acidosis

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Metformin is a biguanide used to lower blood glucose levels in patients with non-insulin-dependent diabetes mellitus (NIDDM). Metformin notably has certain advantages over sulfonylureas because it does not cause hypoglycemia, nor does it promote weight gain or hyperinsulinemia.<sup>1</sup> It also appears to have beneficial effects on blood lipid levels.<sup>2</sup> Because of these advantages, metformin use is widely promoted, particularly to primary care physicians, and it will likely be used extensively in this country for treatment of NIDDM.

Nevertheless, a potential complication of metformin use is its rare association with lactic acidosis, a condition that has a mortality rate of approximately 50 percent.<sup>3,4</sup> Accordingly, it is instructive to describe a case of metformin-associated lactic acidosis. This condition developed in a patient who had no obvious risks for lactic acidosis (eg, renal failure). Several teaching points emerge from this case report that have important implications for metformin use, including altered physiology secondary to patient comorbidity, and potential for metformin-drug interactions. This case underscores important patient considerations related to metformin prescribing.

## Case Report

A 76-year-old, 65-kg woman was admitted to the hospital for progressive fatigue, shortness of breath, and persistently elevated blood glucose levels as documented by home monitoring. Her family reported that the patient experienced episodes of lethargy, somnolence, and progressive confusion during the preceding week. Her medical history

included NIDDM for 15 years, hypertension, coronary artery disease, hypercholesterolemia, congestive heart failure, and paroxysmal atrial fibrillation. An echocardiogram 3 months before admission showed left ventricular hypertrophy, mitral regurgitation, and an ejection fraction of 35 percent. The patient's home medications included glipizide 10 mg twice a day, digoxin 0.125 mg daily, prazosin 2 mg twice a day, furosemide 20 mg twice a day, aspirin 325 mg daily, and metformin 2500 mg daily. She reported no history of ethanol abuse. The patient had started metformin therapy 2 months before admission, which was gradually titrated to this dose. The most recent change in dosage was made 1 week before admission from 2000 to 2500 mg daily.

Although findings from a physical examination on admission were essentially unremarkable, the patient had complaints of generalized fatigue. She had no evidence of retinopathy. Her vital signs included a heart rate of 100 beats per minute, blood pressure 176/70 mmHg, respiratory rate 18/min, and temperature 37.9°C. Her lungs were clear to auscultation. An electrocardiogram on admission confirmed atrial fibrillation with a ventricular rate of 100 beats per minute. Her admission laboratory values included sodium 138 mEq/L, potassium 4.4 mEq/L, chloride 95 mEq/L, carbon dioxide 20 mEq/L, blood urea nitrogen 30 mg/dL, and creatinine 0.9 mg/dL. The patient's blood glucose was 288 mg/dL. Her total white cell count was 9600/ $\mu$ L, and glycosylated hemoglobin was 11.4 percent.

She had no indications of cardiac (jugular venous distention, S<sub>3</sub> gallop, marked peripheral edema) or pulmonary decompensation. Her chest radiograph was clear and had no evidence of congestive heart failure or infiltrate. An anion gap was 23, and because of the known association of metformin with lactic acidosis, a serum lactate concentration was measured, which was elevated to 4.1 mEq/L (normal 0.7 - 2.1 mEq/L). Serum and urine ketones were not elevated, and there was no proteinuria. Arterial blood gas was not analyzed,

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so metabolic acidosis could not be confirmed.

Metformin was recognized as the potential cause of lactic acidosis and was discontinued. The presumed acidosis resolved as the anion gap normalized, and a second lactate measurement obtained 24 hours later was 1.9 mEq/L. Because the patient remained in atrial fibrillation, she was transferred to a telemetry unit and was given amiodarone. Her subsequent hospitalization was uneventful, and she was discharged home.

## Discussion

### *Clinical Features of Lactic Acidosis*

Physicians prescribing metformin should be familiar with the clinical manifestation of lactic acidosis, particularly when prescribing the drug for elderly patients or those with predisposing factors. Signs and symptoms vary in actual case reports but tend to be nonspecific and include nausea, vomiting, altered consciousness, fatigue, abdominal pain, and thirst.<sup>1,3,5</sup> Treatment of lactic acidosis is supportive. Metformin is readily removed by hemodialysis, which would be appropriate for severe, life-threatening acidosis. In the case we described, the patient's symptoms included progressive fatigue, lethargy, and confusion, which prompted her hospital admission. On laboratory analysis, our patient had a decreased serum bicarbonate level, an elevated anion gap, and elevated lactate concentration in the absence of other factors known to be associated with an anion-gap metabolic acidosis. The laboratory abnormalities as well as the associated symptoms resolved promptly after discontinuation of metformin. Fortunately, this episode was mild, and no permanent sequelae developed. The omission of an arterial blood gas was an oversight, as it is an important part of the work-up for lactic acidosis.

### *Biguanide Mechanism of Action and Lactic Acidosis Development*

Metformin is thought to work by a combination of different mechanisms that include increasing glucose transport into glucose-utilizing cells and decreasing hepatic gluconeogenesis.<sup>1,4,6</sup> Metformin might have an important effect of increasing glucose transport across the cell membrane in skeletal muscle.<sup>7</sup>

The exact mechanism by which metformin and phenformin cause lactic acidosis is uncertain. Biguanides reduce pyruvate dehydrogenase activ-

ity and mitochondrial transport of reducing agents, and thus enhance anaerobic metabolism.<sup>1</sup> This subsequent shift to anaerobic metabolism, in the presence of reduced insulin, increases production of precursors for the Krebs cycle.<sup>6</sup> The inhibition of pyruvate dehydrogenase results in a decreased ability to channel those precursors into aerobic metabolism, which, in turn, results in increased metabolism of pyruvate to lactate and increases the net lactic acid production. Additionally, increased glucose utilization in the small intestine caused by biguanide drugs could theoretically increase portal vein lactate levels.

Phenformin, another biguanide introduced into the market around 1950, has a mechanism of action similar to that of metformin, but a much greater propensity to cause lactic acidosis.<sup>6</sup> Because of the high incidence of lactic acidosis associated with phenformin, it was removed 20 years ago from clinical use in this country. Compared with metformin, patients taking phenformin have a 10 to 20 times greater risk of developing lactic acidosis.<sup>4</sup> The chemical structure of phenformin includes a long side chain, which enhances its lipophilicity and results in a greater affinity for binding to mitochondrial membranes, which could account for its greater ability to inhibit aerobic metabolism than metformin.<sup>1</sup>

Additionally, after phenformin was withdrawn from the marketplace, it was found that certain patients (eg, about 10 percent of white patients) have an inherited defect in hydroxylation of the drug.<sup>8</sup> This defect could have resulted in phenformin accumulation. Metformin, in contrast, is not metabolized. The overall average estimated incidence of metformin-induced lactic acidosis is rare: 0.03 cases per 1000 patient-years.<sup>1,3,4</sup> This statistic is also cited by the manufacturer of the drug and is based upon worldwide surveillance data. The frequency with which lactic acidosis develops in patients with risk factors is unknown and might be much higher.

### *Predisposition to Metformin-Associated Lactic Acidosis*

Renal insufficiency results in lowered clearance of both lactate and metformin, increasing the risk of lactic acidosis.<sup>6</sup> Additionally, any state that results in tissue hypoperfusion can lead to tissue hypoxia, because pyruvate is converted to lactate (the alternative pathway in the Krebs cycle) during tissue hypoxia. Thus, in addition to renal failure, the fol-

lowing comorbid conditions can contribute to lactate accumulation: pulmonary disease, liver failure, cardiac impairment, shock states, severe dehydration, and microvascular disease. It is worth noting that some of the conditions (eg, renal insufficiency, microvascular disease, and dehydration) develop in poorly controlled or advanced stages of diabetes. Some clinicians have suggested that metformin would also be inappropriate for someone with chronic obstructive airway disease, ischemic heart disease, or severe infection, in which lactate production might be increased or tissue perfusion decreased.<sup>4,9</sup>

In the case described, our patient had a normal serum creatinine level (0.9 mg/dL). Using the corrected Cockcroft-Gault method of calculating creatinine clearance,<sup>10,11</sup> this patient's estimated glomerular filtration rate was approximately 60 mL/min. The manufacturer of metformin states that metformin should not be used in patients with serum creatinine values greater than 1.5 mg/dL for men, 1.4 mg/dL for women. These values, however, are less reliable as indicators of renal function in elderly or chronically debilitated patients. Metformin should be prescribed with great caution in any patient with moderate renal impairment (estimated creatinine clearance 30-60 mL/min).

Of particular importance was this patient's history of severe obstructive pulmonary disease, which was noted in her previous medical records. Although her clinical condition was not consistent with an exacerbation of this disease process, her chronic pulmonary impairment might be considered a risk factor for lactic acidosis. In addition, although this patient did not have symptoms of acute decompensated heart failure, she did have a history of left ventricular impairment (ejection fraction 35 percent) and was in atrial fibrillation, both of which could have predisposed her to lactic acidosis by means of decreased peripheral tissue perfusion.

We believe this case illustrates the potential for multiple risk factors to affect the overall risk of lactic acidosis associated with metformin use and emphasizes the need for more than a cursory review of associated conditions before implementing therapy.

#### ***Drug Interactions Contributing to Metformin-Associated Lactic Acidosis***

Metformin does not undergo hepatic metabolism; the main route of elimination is renal tubular se-

cretion. Metformin is a protonated cation at physiologic pH.<sup>1</sup> It has been hypothesized that certain drugs, such as cimetidine, might compete with renal tubular secretion of metformin at the site of organic cation transport.<sup>12</sup> In one report cimetidine decreased the renal clearance of metformin by 27 percent.<sup>12</sup> Examples of other drugs known to compete with organic cations for renal tubular excretion include digoxin, procainamide, quinidine, ranitidine, iodinated contrast media, and amiloride.<sup>1</sup> The effects of these drugs on metformin renal excretion are unknown, because studies have yet to be published. A recommendation to temporarily discontinue metformin before and after the administration of contrast media emphasizes the need for caution when concurrent administration of competing substances is required. In the case presented, the only medication that could theoretically compete for secretion was digoxin.

The patient described in this case was taking furosemide, which reportedly can alter metformin pharmacokinetics.<sup>1</sup> Metformin product information includes an unpublished report from a single-dose, normal volunteer study showing the ability of furosemide to increase the maximum serum concentration and area under the curve by 22 percent and 15 percent, respectively.

In addition to concurrent medications, it might also be wise to consider a patient's use of alcoholic beverages before prescribing metformin. Ethanol might reduce both the conversion of lactate to glucose and hepatic extraction of lactate.<sup>3</sup> Consequently, heavy alcohol consumption (eg, binge drinking) sufficient to cause hepatic impairment could represent a relative contraindication to metformin use. The patient described herein did not have a history of ethanol use.

#### ***Patient Selection Issues for Metformin Use***

It is imperative to evaluate a patient's renal function before prescribing metformin. Equally important, however, is the consideration of any comorbid state associated with tissue hypoxia. Recent reports<sup>13,14</sup> have confirmed that metformin-induced lactic acidosis is not necessarily due to metformin accumulation (as might be expected in renal failure), and that the clinical severity and prognosis of acidosis is more dependent on associated pathologic conditions. In retrospect, one could conclude that our patient was not an ideal candidate for

high-dose metformin therapy given her history of congestive heart disease, pulmonary disease, coronary artery disease, and atrial fibrillation.

The ideal candidate for metformin monotherapy is an obese patient with NIDDM who has no serious comorbidity and who has failed diet and exercise therapy.<sup>1</sup> Concurrent hyperlipidemia with poorly controlled NIDDM might also favor the use of metformin. Further studies are needed to establish the role of metformin for nonobese NIDDM patients and for those with serious comorbidity before prescribing the drug as a first-line therapy.

Patients should be instructed to recognize potential symptoms of lactic acidosis, and medications that can interfere with secretion should be avoided. Metformin should be temporarily withheld in patients receiving iodinated contrast media or any other condition in which an acute decline in renal function might occur (eg, aggressive diuresis, excessive fluid loss from gastroenteritis, surgery, etc). It is possible to learn which patients are at particular risk for developing metformin-associated lactic acidosis by applying general screening guidelines published in the American Diabetes Association clinical practice recommendations.<sup>15,16</sup>

### Conclusion

Metformin-associated lactic acidosis is a rare, preventable, but life-threatening, adverse event. Primary care physicians should profile a patient's risk for developing this side effect by considering comorbid diseases, concurrent diabetic complications, concomitant medical therapy, and anticipated diagnostic and surgical procedures. Patients who are taking metformin should be instructed to provide that information readily; the use of medical alert tags indicating metformin use might help reduce the incidence of lactic acidosis. Increased drug surveillance is necessary to define further the risk of developing lactic acidosis secondary to metformin use.

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