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Clinical Communications: Adults

OCCULT METFORMIN TOXICITY IN THREE PATIENTS WITH PROFOUND LACTIC ACIDOSIS

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□ **Abstract—There are 20.8 million Americans with diabetes, and metformin is the most commonly prescribed oral diabetes agent. A review of our metformin experience highlights common pitfalls that lead to life-threatening or fatal poisonings. We describe 3 patients with metformin toxicity; 2 of 3 patients were prescribed metformin despite end-stage renal disease (ESRD). Case 1: a 40-year-old woman presented after a polysubstance overdose. Within 8 h, vomiting and lethargy developed; a profound acidosis, pH 6.95, pCO_2 26, pO_2 195, and elevated serum lactate 21 mmol/L (ref 0.5–1.6 mmol/L) were noted. Further inquiry revealed that the patient had ingested metformin. She was intubated; bicarbonate therapy and hemodialysis were initiated; however, she became hypotensive and died. A metformin level was 150 μg/mL (therapeutic 1–2 μg/mL). Case 2: a 69-year-old woman with non-insulin-dependent diabetes mellitus (NIDDM) and ESRD presented to the Emergency Department (ED), having missed dialysis. She was sluggish and complained of abdominal pain; an acidosis, pH 7.37, pCO_2 20, pO_2 171; anion gap 38, and elevated serum lactate18.9 mmol/L were noted. Hemodialysis was initiated when it was revealed that she took metformin daily. She improved rapidly and a metformin level was 27.4 μg/mL. Case 3: a 57-year-old woman with a history of NIDDM and ESRD presented with dyspnea. Laboratory studies showed pH 7.03, pCO_2 21, pO_2 99; anion gap 36, and lactate 16 mmol/L. Bicarbonate therapy and hemodialysis were initiated after discovering that she had recently been prescribed metformin. She had a fatal cardiac arrest after dialysis was completed. We describe 3 ED patients with occult metformin toxicity diagnosed after laboratory results showed an anion gap metabolic acidosis and elevated lactate levels. All patients had lethargy, vomiting, or abdominal pain, also suggesting sepsis or mesenteric infarction. Despite sodium bicarbonate therapy and hemodialysis, metformin-associated lactic acidosis was fatal in 2 of 3 patients. Emergency Physicians must be vigilant to recognize metformin toxicity in patients at high risk for metformin-associated lactic acidosis.**

□ **Keywords—metformin; lactate; metabolic acidosis; poisoning; anion gap**

INTRODUCTION

Diabetes mellitus affects over 20 million Americans and is increasing by approximately one million new cases each year in the United States. Over 42 million prescriptions for metformin were written in 2005 (1). Metformin is relatively well tolerated, and hypoglycemia does not occur in therapeutic dosing. However, metformin-associated lactic acidosis (MALA) is a concern. The mechanism of production of MALA is not completely understood. Elderly patients or those with renal insufficiency are at highest risk. Other contributing factors include concomitant infections or illnesses leading to dehydration and poor renal perfusion. Diabetes is a common comorbidity in Emergency Department (ED) patients and they may present with illnesses that predispose them to the development of MALA. A review of the metformin toxicity cases in our ED patients highlights

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common pitfalls that lead to life-threatening or fatal metformin toxicity.

We describe 3 patients with metformin exposures; 2 of the 3 patients were prescribed metformin despite having end-stage renal disease (ESRD). In all of the cases, metformin toxicity was considered after markedly elevated lactate levels were measured. Metformin toxicity was confirmed by serum metformin levels or additional history, or both. We report these cases to describe the diagnosis and treatment of metformin toxicity in the ED, and to highlight the pitfalls that lead to these occult presentations.

CASE REPORTS

Case 1

A 40-year-old woman was brought to the ED after a polysubstance overdose of risperidone, sertraline, and hydrochlorothiazide. Vital signs were: blood pressure 126/49 mm Hg, pulse 79 beats/min, and respiratory rate 14 breaths/min; fingerstick glucose was 140 mg/dL. Physical examination was significant for mild lethargy initially but otherwise unremarkable. A dose of activated charcoal was administered by mouth. Laboratory studies were normal, including a serum bicarbonate level of 25 mEq/L and anion gap of 12. Within 8 h of her arrival, the patient had vomited multiple times and had become more lethargic. She had several episodes of hypoglycemia requiring intravenous dextrose. Repeat laboratory studies revealed a severe metabolic acidosis: pH 6.95, pCO_2 26 mm Hg, pO_2 195 mm Hg; and a serum lactate of 21 mmol/L. With further inquiries to the home, it was disclosed that the patient may have also ingested her husband's diabetes medication, Glucovance, a metformin/glyburide combination agent (Bristol-Myers Squibb Company, New York, NY). The patient was intubated, given sodium bicarbonate therapy, and underwent emergent hemodialysis. Octreotide was added to manage the persistent hypoglycemia. Despite fluids and supplemental bicarbonate therapy, she became profoundly hypotensive and died approximately 24 h after ED presentation. A metformin level obtained from admission was 150 μg/mL (therapeutic 1–2 μg/mL). Other etiologies of anion gap acidosis were ruled out, including a negative aspirin level and a negative toxic alcohol screen for ethylene glycol and methanol. An autopsy was not performed.

Case 2

A 69-year-old woman with multiple medical problems and ESRD on hemodialysis presented to the ED having missed dialysis due to weakness. Upon paramedic arrival, she was found to have a fingerstick glucose level of 38 mg/dL. In the ED, vital signs were: oral temperature 36.2°C (97.1°F), blood pressure 151/85 mm Hg, pulse 100 beats/min, respirations 32 breaths/min, and 100% oxygen saturation. Fifty mL of a 50% dextrose solution was administered with improvement in her mental status. Her medications included amiodarone, clonidine, valsartan, gabapentin, glyburide/metformin, furosemide, atorvasatin, lisinopril, amlodipine, and omeprazole. Physical examination revealed an ill, elderly woman with a Kussmaul respiratory pattern, dry mucous membranes, and diffuse rhonchi in her chest. Her abdomen was soft with mild tenderness, and her neurologic examination was at her baseline after receiving glucose. Electrolytes showed sodium 140 mEq/L, potassium 6.7 mEq/L, chloride 88 mEq/L, bicarbonate 14 mEql/L, anion gap 38; blood urea nitrogen 40 mg/dL, creatinine 10.9 mg/dL; glucose $<$ 20 mg/dL; arterial blood gas (ABG) on 6 L oxygen: pH 7.37, pCO_2 20 mm Hg, pO_2 171 mm Hg; serum lactate 18.9 mmol/L. In the ED she was treated for hyperkalemia and was admitted to the Intensive Care Unit for emergent dialysis. She improved rapidly with hemodialysis. The metformin level was 27.4 μg/mL (therapeutic 1–2 μg/mL).

Case 3

A 57-year-old woman with a history of non-insulin-dependent diabetes mellitus (NIDDM), hypertension, and ESRD on hemodialysis was transferred from a rehabilitation facility with the chief complaint of dyspnea. In the ED, an ABG revealed: pH 7.03, pCO_2 21 mm Hg, and pO_2 99 mm Hg; anion gap 36, and lactate16 mmol/L. Further inquiries to the rehabilitation facility revealed that 3 days earlier she was noted to have hyperglycemia and had been started on metformin. With that information, emergent hemodialysis with sodium bicarbonate infusion was begun. Her ABG improved to pH 7.10, pCO_2 30, and pO_2 76, and her serum lactate decreased to 8.4 mmol/L. However, she required intubation due to ventilatory failure, and after intubation she developed hypotension requiring pressor support to continue hemodialysis. After hemodialysis was completed, continuous venovenohemofiltration with bicarbonate-containing fluid was started and her ABG improved to pH 7.22, pCO_2 30 mm Hg, and pO_2 456 mm Hg. A non-q-wave myocardial infarction occurred with a peak troponin of 46 ng/mL. Ventricular tachycardia and cardiac arrest ensued. She was resuscitated but later, care was withdrawn and she died. The family declined an autopsy.