When a friend can become an enemy! Recognition and management of metformin-associated lactic acidosis

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CASE PRESENTATION

Patient 1: A 78-year-old woman presented with a 3-day history of abdominal pain, nausea, vomiting, and anorexia. Past medical history included type 2 diabetes mellitus, autoimmune hepatitis, hypertension, and ulcerative colitis with colectomy. Medications included metformin 1500 mg twice daily (6 months), glyburide, rofecoxib, furosemide, levothyroxine, prednisone, azathioprine, and propanolol. On admission, she was hypothermic (34.4°C), had blood pressure, 115/51 mm Hg, pulse 104 beats/min, and trace of lower extremity edema. The rest of the physical examination was unremarkable. Arterial blood gases showed pH 7.0, pCO_2 7 mm Hg, tCO_2 2 mEq/l. She was transferred to the intensive care unit and intubated for respiratory failure. Serum creatinine was 8.9 mg/dl (baseline, 1.0 mg/dl; estimated glomerular filtration rate (eGFR) 57 ml/min/1.73^2 by the Modification of Diet in Renal Disease Study (MDRDS) formula); serum lactate 9.6 mg/dl; serum metformin 17 μg/ml (therapeutic level 1–2 μg/ml). Liver enzymes were normal. Urinalysis: protein 2+ and moderate blood. Renal ultrasound ruled out obstruction. Echocardiogram showed normal left ventricular function and all fluid cultures were negative. Pertinent laboratory findings are shown in Table 1.

Patient 2: A 64-year-old woman presented with nausea and vomiting. Past medical history included type 2 diabetes mellitus, hyperlipidemia, and hypertension. Medications included metformin 500 mg twice daily (3 months), lisinopril, and ibuprofen for arthritis. On admission, she was hypothermic (34.5°C), hypotensive (blood pressure, 85/38 mm Hg), and tachypneic (28 breaths/min). The rest of the physical examination was unremarkable. Arterial blood gases showed pH 6.78, pCO_2 15 mm Hg, and tCO_2 3 mEq/l. She was transferred to the intensive care unit and intubated for respiratory failure. Serum creatinine was 5.9 mg/dl (1.0 mg/dl 8 months earlier and eGFR 59 ml/min/1.73^2 by the MDRDS formula); serum lactate 22 mg/dl; serum metformin 31 μg/ml. Liver enzymes were mildly elevated. Urinalysis: blood 3+ and protein negative. All cultures and toxicology tests were negative. Non-contrast computer tomography showed no intra-abdominal or pelvic abscesses. Cardiac enzymes and electrocardiogram were not suggestive of myocardial injury. Pertinent laboratory findings are shown in Table 1.

CLINICAL FOLLOW-UP

Both patients were elderly women with type 2 diabetes mellitus taking metformin, presenting with volume depletion, acute kidney injury, and an elevated anion gap metabolic acidosis. Lactic acidosis was considered the most probable cause of the acidosis, although the initial source was not apparent. Metformin-associated lactic acidosis (MALA) was suspected and serum metformin level was measured and found elevated. Intravenous bicarbonate was used initially in the intensive care unit in an attempt to stabilize the patients before dialysis access placement. In patient 1, intermittent hemodialysis was initiated with an F70NR dialysis membrane (Fresenius, polysulfone), blood flow rate 250 ml/min, and dialysate containing bicarbonate 28 mEq/l. Serum lactate and metformin levels decreased (1.5 mg/dl and 4.4 μg/ml, respectively) after a 4-h dialysis session and the acidosis was corrected (Figure 1). Another 4-h dialysis session was performed the following day because of persistent renal dysfunction. Eventually, her kidney function recovered (serum creatinine 1.1 mg/dl and eGFR 51 ml/min/1.73^2) and she was discharged without need for further dialysis.

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Table 1 | Laboratory data of the patients on admission

Initial presentation	Patient 1	Patient 2	Reference values
Arterial blood gas			
pH	7	6.78	7.35–7.45
pCO_2 (mm Hg)	7	15	35–45
tCO_2 (mEq/l)	2	3	—
Serum Electrolytes			
Na^+ (mEql/l)	133	146	136–145
K^+ (mEq/l)	6.7	6.6	3.5–5.5
Cl (mEq/l)	102	100	96–110
HCO_3 (mEq/l)	5	5	24–32
Anion Gap	26	41	8–12
Corrected Ca^{2+} (mEq/l)	9.1	9.0	8.5–10.5
Phosphate [PO_4^-] (mg/dl)	8.1	13.6	2.5–4.5
Serum blood urea nitrogen (mg/dl)	120	32	10–26
Serum glucose (mg/dl)	184	143	70–100
Serum creatinine (mg/dl)	8.9	5.9	0.7–1.5
Serum lactate (mg/dl)	9.6	22	0.7–2.1
Serum metformin level (μg/ml)	17	31	1–2
Aspartate aminotransferase (AST) (U/l)	36	242	8–50
Alanine aminotransferase (ALT) (U/l)	27	87	15–75
Complete blood count			
White Blood Cells K/cmm	11.7	40	4–10.4
Hemoglobin (gm/dl)	10.5	12.1	13.8–17.3
Platelets K/cmm	220	486	141–320

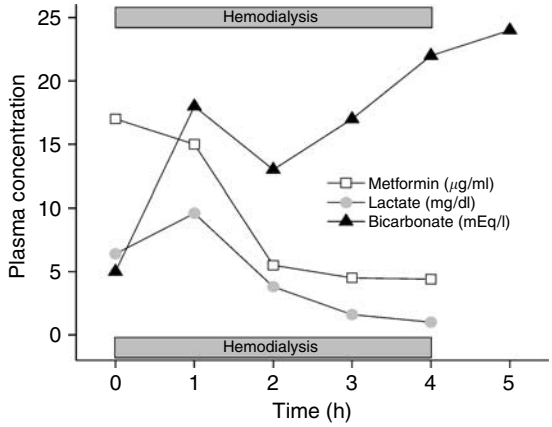

Figure 1 | Effect of intermittent hemodialysis for 4 h on serum lactate, metformin, and bicarbonate levels. Note the rapid decrease of both metformin and serum lactate level and the reciprocal increase of the bicarbonate level.

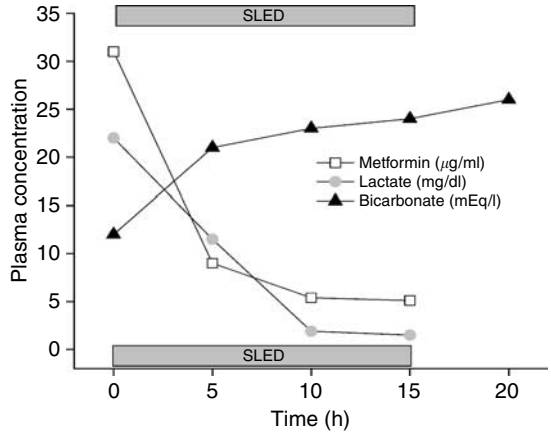

Figure 2 | Effect of sustained low-efficiency dialysis (SLED) over 15 h in the serum lactate, metformin, and bicarbonate levels. Note the rapid decrease of both metformin and serum lactate levels and the reciprocal increase of the bicarbonate level.

In patient 2, sustained low-efficiency dialysis (SLED) was initiated with an F5 dialysis membrane (Fresenius, polysulfone), blood flow rate 200 ml/min, and dialysate containing bicarbonate 28 mEq/l. SLED was discontinued 15 h later. Serum lactate and metformin levels decreased and the acidosis was corrected (Figure 2). The patient received four additional intermittent hemodialysis sessions because of slow renal function recovery. Ten days later, her kidney function improved and she was discharged without need for further dialysis.

DIAGNOSIS

Both patients were diagnosed with acute kidney injury and metabolic acidosis with an elevated anion gap, thought to be due to MALA.

DISCUSSION

In 1995, the Food and Drug Administration approved the use of metformin, the only biguanide currently available in the United States. Phenformin, its congener, was withdrawn in 1977 because of an association with fatal lactic acidosis.

Characteristics

Metformin hydrochloride is a dimethylbiguanide with molecular formula $C_4H_{11}N_5 \cdot HCL$.[1] It is an antihyperglycemic agent that improves insulin sensitivity without decreasing the glucose concentration below normal range. Metformin is 90–100% renally excreted as unchanged drug, and clearance is reduced with renal dysfunction.[2,3] The plasma half-life is 1.5–4.9 h in healthy volunteers. Metformin has high water solubility, molecular weight 165.63, negligible protein binding in serum, and a large volume of distribution (63–276 l), because it diffuses freely into the intracellular compartment and binds to microsomes.[4]

Benefits versus risks

The beneficial effects of metformin therapy for overweight and type 2 diabetic patients were demonstrated by the United Kingdom Prospective Diabetes Study (UKPDS),[5] and it has become the oral agent of choice for such patients. Nausea, vomiting, diarrhea, and anorexia are common side effects, but MALA, a potentially life-threatening metabolic disorder, can also occur. Diabetic patients, not taking metformin, are already at increased risk for developing lactic acidosis associated with hypoxemia because of atherosclerosis and microvascular disease, and/or in sepsis or volume depletion.[6] Metformin may increase this risk.

Pathogenesis of MALA

Several mechanisms have been postulated to explain this condition. Metformin may cause a shift in the intracellular redox potential away from aerobic to anaerobic metabolism. In experimental models of biguanide-associated lactic acidosis, this process has been observed in gastrointestinal tract cells, the site of metformin accumulation, and these cells appear as the main lactic acid production site in this condition.[7] The liver takes up approximately 60% and oxidizes the lactate to pyruvate, which is converted by pyruvate carboxylase to glucose via gluconeogenesis. Biguanides are known to decrease intracellular pH. This effect reduces lactic acid utilization by decreasing liver uptake of lactate, and suppression of gluconeogenesis by reduction in the hepatic activity of pyruvate carboxylase. Increased hepatocyte anaerobic metabolism also increases lactic acid production resulting in further decreases in lactate uptake. Furthermore, biguanides can have a negative inotropic effect on cardiac muscle, resulting in decreased cardiac output, decreasing further hepatic lactate clearance.[8] Increased production and decreased utilization of lactic acid predisposes patients taking biguanides to increased serum concentrations and may result in lactic acidosis. Metformin is less likely than phenformin to cause lactic acidosis because metformin concentrates in the cytosol, has less effect on mitochondrial glucose oxidation, less protein binding, shorter half-life than phenformin, and it is not metabolized by the liver.[6]

Clinical features

MALA can present with anorexia, nausea, vomiting, and abdominal pain. Other serious effects include hypotension, respiratory failure, arrhythmias, and hypothermia.[9,10] Laboratory tests suggesting lactic acidosis include serum lactate levels >4 mg/dl, serum pH <7.35, and an elevated anion gap. Our patients presented with gastrointestinal symptoms, hypothermia, and respiratory failure requiring intubation. Serum lactate and metformin levels were elevated. Although a correlation between serum lactate and metformin levels has been observed in both animal and human studies,[11] in the latter, it was only noted in patients with high metformin levels and the relationship was confounded by other lactic acid-promoting conditions.

Epidemiology

MALA is believed to be rare. A recent Cochrane review reported an incidence approximating 1–5 cases/100 000 patient-years. This study was looking at prospective comparative trials or observational cohort studies and concluded that, 'there is no evidence to suggest that metformin is associated with an increased risk of lactic acidosis, or with increased levels of serum lactate, compared to other glucose-lowering treatments if prescribed under the study conditions, taking into account the current suggested contraindications.'[12] However, a review of the literature, as well as our own clinical experience, suggests that MALA may be more prevalent (30 cases/100 000 patient-years).[13] Confidence generated by the UKPDS results[5] has possibly led to more frequent prescribing, and thus metformin may be used in patients with conditions that place them at risk for developing renal dysfunction and lactic acidosis. A recent study showed that 62% of 204 hospitalized patients taking metformin had one or more contraindications or precautionary conditions.[14]

Indications and contraindications

Metformin use is currently contraindicated in people with serum creatinine $\geqslant 1.5$ mg/dl (men) and $\geqslant 1.4$ mg/dl (women), heart failure, liver failure, or older than 80 years of age. According to the manufacturer's product information, doses over 2000 mg daily can also cause lactic acidosis. Herein, both patients had serum creatinine of 1 mg/dl, and neither had known liver or heart failure. Patient 1 was younger than the contraindicated age and on a recommended metformin dose (1000 mg/day), whereas patient 2 was close to the age breakpoint and on an inappropriately high dose (3000 mg/day). Nonetheless, both patients suddenly developed volume depletion and acute kidney injury. In addition, patient 2 was taking an angiotensin-converting enzyme inhibitor for hypertension and over the counter ibuprofen, whereas patient 1 was on a diuretic and rofecoxib, regimens that predispose to renal dysfunction when effective volume depletion is present, and allow lactic acid accumulation. This suggests that the established contraindications for metformin use may not protect a large number of people who have common conditions that put them at risk, including elderly type 2 diabetic patients on angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, or diuretics. It may be advisable to patients temporarily discontinue these medications, as well as metformin, when acutely ill or on admission to a hospital.

Another important observation is that the serum creatinine of 1.5 mg/ml (men) and 1.4 mg/ml (women) is not a reliable measure of renal impairment. Chronic kidney disease (CKD) is best identified by the eGFR, easily calculated by the MDRDS formula[15] or the Cockcroft–Gault equation. According to the National Kidney Foundation Disease Outcomes Quality Initiative CKD staging, both our patients had CKD stage 3 (eGFR 30–60 ml/min/1.73m^2) before presentation despite 'normal' serum creatinine levels. This suggests that identification of patients at risk would improve if CKD staging were incorporated into routine clinical practice.

Treatment

MALA carries a mortality rate of 50% if not treated, and supportive care is the mainstay of treatment. This includes eliminating the medication, correcting the acid-base imbalance, and treating any concomitant disease.[8] Intravenous bicarbonate is often administered in an attempt to ameliorate the effects of the acidosis, particularly when there is ventilatory fatigue and hemodynamic instability,[16] although this treatment has not been shown to improve either hemodynamic stability or overall survival.[17] The ability of

bicarbonate to correct the acidosis is limited by complications from rapid administration of hypertonic fluid and by alkali-induced stimulation of lactic acid production.[6] Intermittent and continuous hemodialysis have been used for treatment of MALA, allowing correction of acidosis by isotonic and isovolemic bicarbonate supplementation and removal of metformin and lactate from the circulation.[18,19] Metformin's low molecular weight and lack of protein binding makes it possible for effective clearance with conventional dialysis modalities.[20] Extended treatment sessions are needed because of the rebound increase in serum lactate levels reported with short sessions, possibly due to increased lactic acid production from the high delivery of bicarbonate.[6] Total drug removal is difficult due to the large volume of distribution and intracellular binding. Patient 1 received intermittent hemodialysis for 4 h initially and 4 h the following day. In patient 2, SLED was used for 15 h. The serum lactate and metformin levels decreased, acidosis was corrected, and both recovered with normal or near normal kidney function (Figures 1 and 2).

Conclusions and suggestions

Patients without the established contraindications to metformin use remain at risk for developing potentially fatal lactic acidosis, if they have predisposing conditions for developing acute renal dysfunction. These include intercurrent illness that cause volume depletion in association with conditions or medications, which alter intrarenal hemodynamics such as advanced age, hypertension, diabetes, known CKD, and/or the use of angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, non-steroidal anti-inflammatory drugs, and diuretics. Metformin appears to decrease the risk of diabetes-related end points in overweight diabetic patients, and is associated with less weight gain and fewer hypoglycemic attacks than insulin and sulfonylureas making it the therapy of choice in these patients.[5] However, it should be used with the knowledge that these are the same patients who are vulnerable to acute and chronic changes in renal function, and thus there should be contingency plans to stop or adjust the dose if such conditions occur. Renal function should be measured in all persons with diabetes at least yearly, more often in those with proteinuria or known CKD, and at any time when renal function is threatened by an intercurrent illness. Calculating the eGFR using the serum creatinine level with either the MDRDS or Cockcroft–Gault equations is the best measure to use. Empiric decrements in the metformin dose should accompany reduction in renal function. Monitoring serum metformin levels has not been shown to be useful and is not recommended. Patients should be educated to contact a health care provider and hold metformin (as well as angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, diuretics, and non-steroidal anti-inflammatory drugs), if diarrhea or vomiting together with inability to take anything by mouth exists for several days. Finally, SLED or intermittent hemodialysis can provide an excellent and highly efficient treatment modality for MALA resulting in timely and favorable outcomes.

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