Abstract

Metformin is commonly used in type 2 diabetes mellitus and accounts for approximately one third of all prescriptions for oral hypoglycemic agents in the US [2]. The United Kingdom Prospective Diabetes Study demonstrated impressive reductions in diabetes-related endpoints and mortality in overweight patients with type 2 diabetes who used this drug [3]. A rare but extremely serious adverse effect of this medication is lactic acidosis, which carries a staggering 50% mortality rate [4].

Metformin is renally cleared and is known to accumulate in patients with chronic kidney disease [4]. Current guidelines stipulate that it be used with caution in estimated glomerular filtration rates (eGFRs) of less than 60 mL/minute and not at all in eGFRs of less than 30 mL/minute [5]. Identified risk factors for MALA include acute kidney injury (AKI), hypoxemia, sepsis, alcohol abuse, liver failure, myocardial infarction, and shock [6]. Medications that interfere with renal hemodynamic autoregulation (that is, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and non-steroidal anti-inflammatory drugs) and volume depletion are frequently implicated in generating the AKI leading to MALA [4]. The incidence of MALA is quoted at 1 to 5 cases per 100,000 patient-years but may be as high as 30 cases per 100,000 patient-years [4].

The mainstay of MALA therapy is supportive care. Particular attention should be paid to normalizing the acid-base imbalance, eliminating offending medication, and treating concomitant disease [4]. Activated charcoal may also have a role, especially in cases of metformin overdose [6]. Intravenous sodium bicarbonate is commonly used to correct blood pH. Renal replacement therapies, including conventional hemodialysis and continuous venovenous hemofiltration, have been successfully employed in MALA [6-11]. These allow for both isovolemic correction of the metabolic acidosis as well as removal of metformin and lactate [4].

Peters and colleagues [1] performed a 5-year retrospective review of all patients admitted to their intensive care unit presenting with MALA. They defined MALA as lactic acidosis (lactate of greater than 5 mmol/L and bicarbonate of less than 22 mmol/L) occurring in a patient who was chronically taking metformin or in the setting of a metformin overdose. No patients actually had MALA as their admission diagnosis. Most were admitted for management of shock or acute renal failure. MALA was part of the clinical presentation in this patient cohort rather than an admission diagnosis. MALA

AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; MALA = metformin-associated lactic acidosis.
accounted for 0.84% of all admissions and demonstrated a 30% mortality rate. Eighty percent of these patients developed acute renal failure and 62.5% required hemodialysis. Only one patient with normal renal function was dialyzed because of severe acidosis.

The definition of MALA in this study did not duly account for people presenting primarily with tissue hypoperfusion as the likely cause of their lactic acidosis. Although metformin may interfere with lactate clearance in a shock state, it is not thought to be the primary cause of the acidosis. Restoration of hemodynamic stability rather than dialysis is the goal of therapy in these cases. Most of the patients who died in this study were admitted with shock, suggesting that hypoperfusion, rather than metformin, was the principal cause of their lactic acidosis. However, MALA itself can present with hypotension due to negative inotropic effects and increased systemic vascular resistance with acidosis [4,6].

The mortality rate in MALA was not altered by hemodialysis. This may be a reflection of the small size of this study. Upon closer inspection of the data, those patients who were dialyzed were more acutely ill as they had higher values on the SAPS II (Simplified Acute Physiology Score II). Furthermore, those who were dialyzed trended toward having a larger burden of comorbidity (Charlson index) and more severe acidosis. These data strongly suggest that hemodialysis may be of benefit in MALA. This is in keeping with the available literature.

Competing interests
The author declares that he has no competing interests.

References