When a harmless procedure causes a life-threatening problem: a case report of metformin-associated lactic acidosis following a colonoscopy

Abstract
Metformin is the preferred initial pharmacologic agent for the treatment of adults with type 2 diabetes mellitus. Although considered safe, it carries a potential life-threatening risk of lactic acidosis. Metformin-associated lactic acidosis is believed to be a consequence of metformin inhibition of the mitochondrial respiratory chain, and has a mortality ranging between 10–50%. However, its outcome is better than lactic acidosis of other cause with similarly severe acid-base imbalance.

In this article, we describe the case of a 72-year-old woman with type 2 diabetes mellitus, presenting to the emergency department with gastrointestinal symptoms associated with severe lactic acidosis (arterial pH 6.6 and lactate 17 mmol/L) and acute kidney injury. Upon obtaining collateral history, the diagnosis of severe metformin-associated lactic acidosis following a colonoscopy preparation was made. The patient was admitted to the intensive care unit for organ support, being ultimately discharged home after one month in hospital. At discharge, she had full neurologic recovery, improvement of renal dysfunction and was under glycaemic control with insulin therapy.

Metformin-associated lactic acidosis’ mortality rate is about half that of the mortality rate seen in individuals with lactic acidosis of other cause. Despite current therapies being effective, preventive measures should always be primal. It is important to educate patients to discontinue this medication when appropriate and keep hydrated. Both upper and lower endoscopies should not be undertaken during the same day, as this further worsens dehydration. Other medications capable of impairing renal function should also be reviewed.

Key words
acute kidney injury; colonoscopy; lactic acidosis; metformin; mortality; type 2 diabetes

Introduction
Metformin is the preferred initial drug treatment for adults with pre-diabetes and type 2 diabetes mellitus. Metformin is effective, inexpensive and may reduce risk of cardiovascular events and death. Although safe, it may cause several adverse effects. The most common are of gastrointestinal nature, with an incidence of 20–30%. Other adverse effects include headache, agitation and dizziness. However, a serious potential side effect is metformin-associated lactic acidosis (MALA).

MALA’s physiopathology is not fully understood. It is probably a consequence of metformin inhibition of the mitochondrial respiratory chain, blocking the conversion of gluconeogenic precursors such as lactate and alanine to pyruvate, promoting anaerobic metabolism and lactate accumulation. Acidemia itself impairs catecholamine binding to its receptors, leading to loss of vascular tone, hypotension, organ hypoperfusion, shock and, eventually, death.

MALA is believed to occur at a rate of about 1/23 000–30 000 person-years of metformin use. A Cochrane meta-analysis found a similar incidence of lactic acidosis in patients treated with metformin (4/100 000 person-years) when compared to other anti-hyperglycaemic drugs (5/100 000 person-years). However, the safety of metformin in the presence of renal insufficiency was not assessed, raising the important question of precipitating factors. MALA is more likely to occur in individuals with dehydration and acute kidney injury, especially in elderly people who have a reduced glomerular filtration rate. Acute kidney injury reduces metformin clearance raising plasma metformin levels, especially if...
its administration is continued. The current recommendation is that metformin should be omitted during illness that may predispose to acute kidney injury, such as diarrhoea and vomiting.

MALA has a mortality of between 30–50% per episode. However, the outcome of severe MALA is much better than lactic acidosis of other cause with similarly severe acid-base imbalance, even at mean acidemia levels deemed to be fatal. In this article, we describe the case of a person presenting with severe MALA due to pre-renal acute kidney injury following a colonoscopy preparation who, despite initial severe acidemia (arterial pH of 6.6), survived.

Case history
A 72-year-old woman with type 2 diabetes mellitus and dyslipidaemia (Table 1) presented to the emergency department with worsening abdominal pain, vomiting and diarrhoea. Later, she was found to be less reactive and hypothermic (32°C). An arterial blood gas analysis revealed a severe metabolic acidosis, with a pH of 6.64, pCO2 3.57kPa, HCO3 2.88mmol/L, lactate 17mmol/L and glucose 3.55mmol/L. She was promptly admitted to the emergency room.

In the emergency room she was in peri-arrest. Supportive measures were undertaken. Further discussion with the woman’s husband revealed that she, due to complaints of dyspepsia, underwent an upper endoscopy and a colonoscopy the day before. Her daily medications were metformin/vildagliptin 1000/50mg twice-daily, metformin 850mg once-daily (daily dose of metformin of 2850mg), clopidogrel 75mg once-daily, rosuvastatin 10mg once-daily, pantoprazole 20mg once-daily, and ibandronic acid 150mg once a month. With this information, the diagnosis of MALA was made. Further testing also revealed a stage 3 acute kidney injury (serum creatinine 661.23µmol/L, urea 43.91mmol/L) and mild elevation of transaminases. A repeat blood gas analysis showed pH 6.88, HCO3 5.99mmol/L and lactate 19.02mmol/L. She was subsequently admitted to the intensive care unit, intubated, ventilated and on vasopressor support with norepinephrine at 0.33µg/kg/min. Thereafter, continuous veno-venous haemofiltration was started.

During the first 24 hours of intensive care unit admission, the patient’s clinical condition worsened, needing high-dose norepinephrine (up to 3.5µg/kg/min). She also had persistent hyperlactataemia (maximum of 20mmol/L) and hypoglycaemia. A bedside echocardiogram showed preserved biventricular ejection fraction, apical hypokinesia, and a non-dilated inferior vena cava without respiratory variability. Besides fluid optimisation, adjustment of ventilatory parameters and renal replacement therapy, neuromuscular blockade and low-dose steroids were started. This allowed the reduction of vasopressor dose and an improvement in metabolic acidosis (arterial pH 7.58, pCO2 3.33kPa, HCO3 27.22mmol/L, lactate 12.66mmol/L).

By the end of the second day of intensive care unit admission, weaning was started, and norepinephrine perfusion was stopped. Blood lactate was 2.96mmol/L and she recovered some diuresis (0.02ml/kg/hour).

She was successfully extubated on day seven of intensive care unit admission. By then, her lactate was normal (1.16mmol/L) and renal replacement therapy had been stopped the day before. Serum creatinine was now 269.62µmol/L with preserved diuresis under diuretic stimulation. During intensive care unit admission, she also complicated with a type 2 myocardial infarction (maximum troponin I 1147µg/L) and rhabdomyolysis. Three days after extubation, she was transferred to the internal medicine ward.

The patient’s stay at the internal medicine ward was complicated with a bilateral pulmonary embolism, a left leg deep venous thrombosis, an acute cystitis and iron deficiency anaemia. She also had critical illness myocardopathy. Twenty-three days after the ward admission, she was discharged home. At time of discharge, she had full neurologic recovery and her renal dysfunction improved (serum creatinine 203.32µmol/L). She was also under insulin therapy for glycaemia control, as it was decided not to re-introduce oral hypoglycaemic agents given her renal dysfunction and the episode of MALA.

Discussion
Metformin-treated individuals are more than twice as likely to develop lactic acidosis when compared with non-metformin-treated individuals with or without diabetes. In the GoDarts study, a clear association was found between metformin, lactate accumulation and the development of lactic acidosis, but this relationship was strongest in those with acute kidney injury.

In this article, we report the successful revival of a patient with severe lactic acidosis following endoscopic procedures. MALA’s mortality is lower than in lactic acidosis.
in general, where rates up to 83% have been reported. Different explanations have been put forward to help understand this striking difference. One is the presence of less severe acidosis triggering comorbidities in MALA patients: lactic acidosis in MALA is not due primarily to shock or ischaemia; besides, patients have no underlying condition serious enough to cause severe lactic acidosis in the absence of metformin accumulation. Another possible explanation is the protective effect of metformin, due to its beneficial effects on vaso-motility and its action on the respiratory-chain complex.

We should nevertheless bear in mind that most MALA cases are related to an inappropriate use of metformin in individuals with risk factors. Here, the patient continued her usual medications during the preparation for the procedures, which were undertaken at the same time. An important detail should be noted: while colonoscopy requires a high fluid intake to avoid dehydration, upper gastrointestinal endoscopy requires fluid restriction, and patients may find it hard to meet their fluid intake needs. While this patient was advised to keep hydrated, she was also advised to stop fluid intake before the procedures. In fact, previous case reports have advised against the use of metformin prior to endoscopies, including stopping other medications that can impair renal function, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers and diuretics. Another paper reported a case where an 86-year-old patient, while not having a formal contraindication for metformin, developed dehydration, renal failure and ultimately MALA after a colonoscopy.

Older patients are prone to iatrogenesis, and clinicians should pay attention to this population when ordering investigations. Any investigation or procedure causing, or aggravating, fluid restriction should be carefully planned in patients taking metformin or any other potentially harmful drugs in the face of impaired renal function.

In the absence of absolute contraindications, there is no compelling evidence to deny individuals the benefits of metformin, which is in line with the findings of the Cochrane review. Nevertheless, MALA has a very poor prognosis if not promptly diagnosed and treated. Although renal replacement therapies have been successfully employed, preventive measures are always better.

Clinicians who start metformin should assess renal function periodically and instruct patients to discontinue the medication and consult their physician in case of events that might prompt dehydration or hypovolaemia, including medical procedures like colonoscopy. To the best of our knowledge, there is only one guideline for individuals with diabetes undergoing colonoscopy preparation, advising to stop metformin the night before the procedure and resuming the evening dose after the procedure. However, due to the long half-life of metformin, it would probably be reasonable to stop metformin for a longer interval and advise individuals to drink plenty of fluids meanwhile.

Conclusion

Metformin is a relatively safe first-line diabetes drug. Nevertheless, one must be aware of its most dangerous side effect – MALA.

Although treatment options available nowadays seem to allow for better outcomes, prognostic factors are still not completely understood. Therefore, prevention is, as always, the key, and we as clinicians have a duty to inform our patients about metformin risks.

In this particular scenario, patients should stop metformin for at least a day before endoscopic procedures, which should not be performed at the same time. They should also be advised to drink plenty of fluids and have other medications capable of impairing renal function reviewed. Unnecessary risks should be avoided.

Declaration of interests

There are no conflicts of interest declared.

References


Key points

- Metformin is a valued drug for the treatment of diabetes, but has a potentially life-threatening risk – metformin-associated lactic acidosis
- Although treatment options available nowadays seem to allow for better outcomes, prevention is key:
  - Patients should stop metformin for at least a day before endoscopic procedures
  - Upper and lower endoscopy should not be performed at the same time
  - Patients should be advised to drink plenty of fluids
  - Other medications capable of impairing renal function should be reviewed prior to these procedures