The synthesis of art and science is lived by the nurse in the nursing act

JOSEPHINE G PATERN

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SEVERAL PHYSIOLOGICAL systems, including the blood buffers, kidneys and respiratory system, are involved in regulating acid-base balance. Normally, blood pH is maintained between 7.35 and 7.45, and is measured using a negative logarithmic scale on which small fluctuations represent large in vivo changes in acid-base balance. For example, a pH change of one represents a tenfold change in hydrogen ion concentration in the blood (Hennessey and Japp 2007). Consequently, even small changes in pH are important.

Proteins and enzymes require a consistent pH to function normally and, if pH deviates from the normal range, the effect on the body is profound and widespread (Hennessey and Japp 2007). On being admitted to an intensive care unit (ICU), the patient in the case study shown on page 20 had a pH of 7.00, which indicates that she had acidosis of life-threatening severity and that her swift transfer to ICU was warranted. It was important that the underlying cause of the acid-base derangement was established quickly so that she could receive targeted treatment.

Acid-base balance disorders can result in acidosis, which is indicated by a fall in pH, or alkalosis, which is indicated by a rise in pH. Disturbances are categorised as respiratory or metabolic depending on primary cause (Patel et al 2008). An acid-base disorder is termed metabolic if its primary cause is unrelated to the patient’s respiratory function. On blood-gas reports, metabolic disturbances are indicated by the values given for base excess/standard base excess and for bicarbonate/standard bicarbonate levels. Metabolic acidosis typically occurs when the body cannot eliminate fixed metabolic acids, for example after renal failure, or when there is an increase in metabolic acid production, for example during diabetic ketoacidosis or following shock.

Accumulation of lactate creates a specific type of metabolic acidosis called lactic acidosis. Under normal conditions, the liver metabolises lactic acid, but is impaired from doing so in patients who are in shock. Patients who have poor tissue perfusion and oxygenation have increased anaerobic
metabolism, and produce high quantities of lactate, and this hyperlactaemia leads to metabolic acidosis (Cooper et al 2014).

The case study below concerns a 68-year-old woman with hypoglycaemia, hypotension, unconsciousness and a severe metabolic acidosis. On her presentation at an emergency department (ED) it transpired that she had type 2 diabetes mellitus, which she managed with metformin. The severity of the patient’s metabolic acidosis was noteworthy and she was initially thought to be experiencing rhabdomyolysis, but was eventually diagnosed with metformin-associated lactic acidosis (MALA).

In a widely cited system devised by Cohen and Woods (1976), lactic acidosis is categorised as type A or type B. In type A lactic acidosis there is clinical evidence of tissue hypoxia or hypoperfusion; in type B lactic acidosis there is not. It was determined that the patient in the case study had type B lactic acidosis.

Types of metabolic acidosis are also differentiated by the ‘anion gap’, which is the difference between the concentration of cations, or positively charged ions, and anions, or negatively charged ions, in a solution. In the blood, the main cations are sodium and potassium, and the normal anion gap is between 10 and 18mmol/L (Hennessey and Japp 2007). A type of metabolic acidosis, such as MALA and rhabdomyolysis, that increases the anion gap is referred to as a high anion-gap metabolic acidosis. The patient in the case study had high anion-gap metabolic acidosis.

Respiratory and metabolic disturbances of acid-base balance should not be considered separate phenomena because one usually produces a response in the other. For example, the patient in the case study had a profound metabolic disturbance, as demonstrated by her severely reduced bicarbonate and base-excess levels, but she also had an extremely low partial pressure of carbon dioxide in her arterial blood (PCO2). A normal pH is important for homeostasis and, when disturbances occur, the body attempts to restore pH to the normal range. Thus, the patient’s initial metabolic disturbance prompted a respiratory response known as compensation, in which her ventilation rate increased to eliminate carbon dioxide (Patel et al 2008). The patient’s low PCO2 signalled an attempt by her body to compensate for severe metabolic acidosis and restore the pH to normal.

Case study

A 68-year-old woman was brought by paramedics to the emergency department (ED). She had failed to report to work that afternoon and a colleague had visited her but had been unable to rouse her. Police had forced entry into her property and discovered she was unconscious.

Her colleague described the patient as a ‘heavy drinker’ and paramedics established that she had consumed half a litre of vodka. They also established that the patient had a long-standing history of type 2 diabetes mellitus, for which she was prescribed metformin, and that she had severe hypoglycaemia. They treated her at the scene with intravenous (IV) glucose before transferring her to the ED, where she was managed in the resuscitation area.

Initial assessment established the patient’s hypoglycaemia required further IV glucose administration. When she regained consciousness following restoration of her blood-glucose level, she was confused and agitated, and had a Glasgow Coma Scale score of 6.

Throughout her time in the ED she maintained a clear airway, and her breathing and oxygenation were good. Assessment of her circulation revealed hypotension and a poor urinary output, which was managed with IV crystalloid administration. Blood-gas analysis demonstrated a profound metabolic acidosis with evidence of respiratory compensation.

The patient was given a provisional diagnosis of hypoglycaemia, alcohol intoxication and rhabdomyolysis. Given the severity of her metabolic acidosis, she was transferred to an intensive care unit. Blood tests undertaken on her admission produced the following results (normal ranges appear in parentheses).

### Arterial blood gas tests:
- **Blood pH:** 7.00 (between 7.35 and 7.45)
- **Partial pressure of carbon dioxide:** 1.6kPa (between 4.7 and 6.0kPa).
- **Partial pressure of oxygen measured on room air:** 13.3kPa (between 11.0 and 13.0kPa).
- **Standard bicarbonate:** 5.7mmol/L (between 22.0 and 28.0mmol/L).
- **Base excess:** 26.7mmol/L (between -2 and +2mmol/L).
- **Lactate concentration:** 20mmol/L (<2 mmol/L).

### Other blood tests:
- **Creatine kinase concentration:** 79U/L (between 25 and 200U/L).
- **Urea concentration:** 15.3mmol/L (between 2.5 and 7.8mmol/L).
- **Creatinine concentration:** 649μmol/L (between 50 and 98μmol/L).**

The patient was treated in the intensive care unit overnight with crystalloid fluid resuscitation, sodium bicarbonate and a sliding-scale insulin infusion. After further assessment, her initial diagnosis of rhabdomyolysis was reconsidered and it was decided that she had metformin-associated lactic acidosis (MALA).

The morning after her admission, the patient was fully conscious and cardiovascularly stable. Her metabolic acidosis had resolved and she was well enough to be transferred to a ward.
Lactic acidosis is acknowledged to be a serious condition, with a mortality rate of 50% or more (Scott et al 2010, Scale and Harvey 2011, Cooper et al 2014). However, the underlying aetiology of the lactic acidosis is important. If the cause is shock and the lactate level is slow to normalise, the outlook is poor (Cooper et al 2014). But, in a review of MALA case reports, Stades et al (2004) calculate a survival rate of 68% so it was important to ascertain what had caused the patient’s lactic acidosis.

Due to the patient’s raised urea and creatinine concentrations, and her high lactate level and consequent metabolic acidosis, she was originally thought to have had rhabdomyolysis. This condition can lead to renal failure and tissue hypoperfusion, particularly if it is accompanied by compartment syndrome. It is often associated with crush injuries in which there is widespread and severe skeletal muscle damage (Cridge 2003). Prolonged periods of unconsciousness are recognised causes of rhabdomyolysis (Lane and Phillips 2003) because lying in one position for a long period, as the patient had, can compress skeletal muscles and cause ischaemia, which in turn leads to anaerobic metabolism, lactic acid formation and metabolic acidosis. In some cases, compartment syndrome can ensue and, unless promptly recognised and treated, can lead to limb ischaemia and even a need for limb amputation (Sivaloganathan et al 2012).

Crushed and damaged muscles release substances, such as phosphate, lactic acid, uric acid, creatine kinase (CK) and potassium, into the circulation (Warren et al 2002, Cridge 2003). In some cases, enough potassium can be released to cause life-threatening hyperkalaemia (Cridge 2003, Lane and Phillips 2003). Muscle trauma can also lead to disruption of myocyte cell membrane function, resulting in substantial fluid and electrolyte shifts, which can cause hypovolaemia and hyper- or hypocalaemia (Cridge 2003).

Although the patient had hypovolaemia and hypotension, which required treatment with fluid resuscitation, she showed no other signs of rhabdomyolysis, such as hyperphosphataemia or hyperkalaemia. CK is considered to be the most sensitive indicator of muscle injury and patients who experience rhabdomyolysis demonstrate massively elevated CK levels (Warren et al 2002, Cridge 2003). At 79U/L, the patient’s CK level was not deemed to be consistent with severe muscle damage.

In patients with rhabdomyolysis, myoglobin, an oxygen-carrying protein in muscle that is highly nephrotoxic, is released into the circulation by injured muscles. Thus, rhabdomyolysis often precipitates acute renal failure (De Wolff 2012) and patients with rhabdomyolysis typically present with anuria. Any urine they produce is the colour of dark tea or cola due to the presence of myoglobin (De Wolff 2012). The raised urea and creatinine levels seen in patients with rhabdomyolysis are usually due to renal failure (Cridge 2003). In the patient in the case study, however, raised creatinine levels were not due to muscle damage and subsequent myoglobin-induced renal failure, and once her blood pressure had been restored to normal her urinary output was noted to be of good volume and the urine of normal colour. Urine dipstick testing for haemoglobin, in which the reagent reacts in the presence of myoglobin and haemoglobin, was also negative. Such a test offers a quick way to rule out the presence of myoglobinuria (Cridge 2003).

The patient’s profound lactic acidosis and history of prolonged unconsciousness lent support to the initial assumption that she had rhabdomyolysis. However, on physical examination, no signs or symptoms of muscle injury or associated compartment syndrome were found. Because overt muscle injury, myoglobinuria and hyperkalaemia were absent, and urine output and CK levels were normal, the patient’s initial diagnosis was reappraised and it was decided that she probably had MALA.

Metformin
A long-established biguanide treatment for type 2 diabetes, metformin is particularly recommended for obese or overweight patients (Souto et al 2011). The drug is considered to be effective and safe, and can reduce diabetes-related complications and mortality (UK Prospective Diabetes Study Group 1998). Metformin’s most commonly reported side effect is gastrointestinal upset, but cases of MALA have also been reported regularly in the literature (Assan et al 1977, Krentz and Bailey 2005, Silvestre et al 2007, Runge et al 2008).

Metformin has numerous actions that reduce blood glucose levels, some of which also increase the production and reduce the metabolism of lactate (Holt et al 2010, Rang et al 2012). In most people, metformin’s effect on lactate is not problematic and the risk of developing lactic acidosis is considered to be low unless other co-morbidities, such as poor tissue perfusion, and renal or hepatic failure, are present. Such conditions can also increase lactate production or reduce its metabolism and elimination (Scott et al 2010, Keller et al 2011, Scale and Harvey 2011). Patients who have such problems, or are at high risk of developing them during periods of acute illness, should not be given metformin (Senior 2012), yet many are with little apparent increased risk of metabolic acidosis.
In a study of adherence to prescribing guidelines, Emslie-Smith et al (2001) found that metformin was contraindicated in 25% of the surveyed patients who had been prescribed it. The drug was rarely discontinued but there was no marked increase in the incidence of MALA in the cohort because lactic acidosis remained rare.

The safety of metformin is also illustrated by Salpeter et al (2002), who examined the incidence of fatal and non-fatal lactic acidosis in patients taking metformin compared to placebo or non-metformin therapies. They found no case of lactic acidosis, fatal or otherwise, in more than 70,000 patient years of metformin use, and conclude there is no evidence that metformin is associated with a higher risk of lactic acidosis than other anti-hyperglycaemic treatments. These studies suggest that the risk of developing MALA is low for most individuals when they are well, even if there are contraindications. During periods of acute severe illness, however, risks associated with the drug can increase, as was the case with the patient in the case study.

Because metformin is not metabolised and is eliminated in the urine unchanged, it has been suggested that the drug can accumulate when renal function is poor, and that its actions can lead to hypoglycaemia and elevated lactate levels (Krentz and Bailey 2005). In addition, although most lactate metabolism occurs in the liver, the kidneys play a role in the removal of lactate and this renal mechanism becomes increasingly important during periods of hyperlactataemia (Phypers and Pierce 2006).

The link between renal failure, metformin and metabolic acidosis is illustrated by Keller et al (2011), who report that six severely ill patients experienced elevated metformin levels and lactic acidosis. All experienced renal failure and dehydration, and required continuous renal replacement therapy (CRRT). Two had pre-existing chronic renal impairment and all were receiving potentially nephrotoxic drugs. In a larger study of 30 MALA patients, Peters et al (2008) report that 80% of the patients had renal failure. Other case reports support the importance of adequate renal function and the role that chronic or acute renal failure can play in the development of MALA (Assan et al 1977, Silvestre et al 2007, Buruijstens et al 2008, Runge et al 2008, van Berlo-van de Laar et al 2011).

The creatinine levels of the patient in the case study were elevated, indicating impaired renal function. Because her renal function before admission was unknown, the aetiology of her kidney injury was unclear. Due to dehydration, she was hypovolaemic and hypotensive, which could have caused acute kidney injury or worsened pre-existing renal dysfunction. Whatever the mechanism, it was thought that impaired renal function had resulted in accumulation of metformin and was the main cause of the patient’s MALA.

It should be noted that several writers think the role played by metformin in metabolic acidosis has been overstated (Misbin 2004, Stades et al 2004, Scale and Harvey 2011). Stades et al (2004), for example, conducted a review of published case reports and established that many cases of metabolic acidosis attributed to metformin concern individuals with histories of underlying conditions, such as sepsis, cardiovascular events and hepatic failure, that are likely to produce lactic acidosis. They argue these conditions are much more likely than metformin to be the main cause of lactic acidosis. Misbin (2004) also states that metformin is unlikely to be the cause of most cases of metformin-associated metabolic acidosis. Stades et al (2004) and Krentz and Bailey (2005) suggest that metformin has been overly associated with a now-withdrawn biguanide drug called phenformin, which did cause metabolic acidosis.

References
In an investigation of lactic acidosis in a single hospital setting, Scott et al (2010) reviewed all hospital admissions over a three-month period. They identified 28 people with confirmed lactic acidosis, of whom five were known to have type 2 diabetes mellitus but only two were taking metformin. Scott et al (2010) therefore state that factors such as hepatic, renal or cardiac failure are more likely than metformin use to lead to the development of lactic acidosis. Nevertheless, Stades et al (2004) acknowledge that acute renal failure seems to be a common antecedent of MALA and suggest that current recommendations to stop metformin use when acute renal failure is likely should be observed.

There are no good controlled studies of the best way to manage patients with MALA. Evidence consists of case studies, usually involving few patients (Heaney et al 1997, Kruse 2001, Alivanis et al 2006, Keller et al 2011, Perrone et al 2011). Published reports tend to involve critically ill patients with numerous comorbidities who require cardiovascular interventions such as inotropes, vasopressors and intermittent positive-pressure ventilation.

The patient in the case study required low-key interventions because, once her blood pressure had been restored after intravenous fluid administration, she was clinically well, her respiratory function was good and she was cardiovascularly stable. She was also given intravenous sodium bicarbonate even though this practice is controversial because sodium bicarbonate can add to acidosis (Cooper et al 2014).


Although older papers emphasise the use of haemodialysis, recent reports cite the use of CRRT. This suggests that both treatments work but, because CRRT is the readily available, it is more likely to be the first-choice treatment for patients admitted to intensive care.

The patient in the case study was taken to an ICU with an initial plan to insert a temporary dialysis line in preparation for CRRT, although this eventually proved unnecessary. Her treatment was largely supportive. Once her hypovolaemia was corrected and her blood pressure restored, her urine output improved. Given her clinically ‘well’ state, lack of overt comorbidities and increased urine output, it was decided to proceed with dialysis function, increased urine output and subsequent elimination of lactate and metformin. By the morning, her blood gases had normalised and she was well enough to be transferred to a ward.

Conclusion
This article discusses a patient with a severe metabolic acidosis who, immediately after being brought to an ED, was thought to have rhabdomyolysis. It transpired that MALA secondary to renal impairment was a more feasible explanation for the patient’s illness, although factors not explored in this article, such as the patient’s potential for hepatic disease or self-poisoning, could offer alternative explanations. It is clear from the evidence reviewed that the precise role and role that metformin plays in the development of hyperlactataemia and subsequent metabolic acidosis have resulted in debate and disagreement in the literature.

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None declared