

Lactic acidosis in a diabetic patient treated with metformin undergoing hepatic resection

Introduction

This case report provides a reminder of profound lactic acidosis as a potential complication of metformin and its severity. It also highlights factors that place patients at increased risk of developing metformin-associated lactic acidosis – dehydration, sepsis, cardiac, hepatic and/or renal insufficiency. Metformin is very commonly prescribed and this case highlights why clinicians must be aware of the risks of its use. By recognizing patients at risk and instigating appropriate management, the incidence of developing metformin-associated lactic acidosis may be greatly reduced.

Discussion

Metformin has been used for the treatment of diabetes for over 50 years. It has been used more recently to treat polycystic ovary syndrome (where it reduces insulin resistance, facilitates conception and reduces the rate of first trimester spontaneous abortion) and non-alcoholic steatohepatitis.

Biguanide drugs such as metformin act by a number of mechanisms including inhibiting hepatic and renal gluconeogenesis (Salpeter et al, 2003). This process supplies nicotinamide adenine dinucleotide (NAD⁺) required for the conversion of lactate to pyruvate. Inhibition of this process therefore results in a tendency for lactate to accumulate. An earlier biguanide, phenformin, was taken off the market in the United States in 1977 because of the risk of causing lactic acidosis and the associated mortality (approximately 50%). While metformin is not risk free in this respect the incidence of metformin-associated lactic acidosis is low (estimated 3–9 cases per 100 000 patient-years) and it is widely regarded as a very safe drug.

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A number of factors predispose to metformin-associated lactic acidosis, and two groups of metformin-associated lactic acidosis have been described: type A are pathological states associated with processes that generate anaerobic metabolism and lactic acidosis (dehydration, sepsis, cardiac, hepatic, renal insufficiency) without metformin accumulation. Type B is associated with metformin accumulation (overdose or lack of elimination) usually as a result of renal impairment (Vreven and De Kock, 2005).

Liver resection surgery has the potential for massive blood loss, which historically

carried a high morbidity and mortality. A number of changes in practice have resulted in reduced blood loss and blood transfusion rates approximating 5%. One such change is reducing central venous pressure which itself reduces back bleeding from the hepatic veins (Johnson et al, 1998; Jones et al, 1998). There are many methods used to reduce central venous pressure including vasodilators and epidural anaesthesia, but many involve a degree of fluid restriction and the use of diuretics to reduce central venous pressure. The former involves no overnight fluid administration.

Case Report

A 63-year-old man was scheduled for hepatic resection. He had been diagnosed with colonic cancer 5 years previously and undergone a hemicolectomy at that time. Four years later he was diagnosed with liver metastases. Magnetic resonance imaging showed extensive disease, with nodules in segments III, IVa, V, VI and VIII. The treatment plan was to commence a course of chemotherapy followed by hepatic resection.

Having completed the chemotherapy he attended the preoperative assessment clinic. His past medical history included non-insulin dependent diabetes mellitus, hypertension and hypercholesterolaemia. Medications were metformin 500 mg twice a day, bendrofluzide 2.5 mg once a day, doxazocin 4 mg once a day, nifedipine 45 mg once a day and simvastatin 40 mg once a day. There were no known allergies. Examination and investigations were unremarkable, blood pressure 137/82 mmHg, blood glucose 4.2 mmol/litre, serum creatinine 87 µmol/litre, glomerular filtration rate >60 ml/min, glycosolated haemoglobin A 6.9%, electrocardiogram sinus rhythm. He was scheduled for an elective open hepatic resection.

He was admitted to the ward on the evening before surgery and kept nil by mouth from midnight. No intravenous cannula was sited and no fluid given overnight, as per protocol. On the morning of surgery the patient received all his regular medications including his metformin. He arrived in the anaesthetic room at 08.30hrs. A 20G intravenous cannula was sited, anaesthesia was induced with alfentanil 1 mg, propofol 200 mg and cisatracurium 14 mg, and the patient's trachea was intubated with a size 8.0 tracheal tube. An epidural was sited at T8/9, an arterial line inserted and a central line sited in the right internal jugular vein. Anaesthesia was maintained with isoflurane and remifentanyl. While being prepared for surgery the patient was given intravenous fentanyl 80 mg. A glyceryl trinitrate infusion and a phenylephrine infusion were commenced, and 10 ml 0.25% bupivacaine was administered epidurally.

At the start of surgery an arterial blood gas was sent for analysis which showed a metabolic acidosis with pH 7.32, base excess -5.0 mmol/litre and lactate 3.5 mmol/litre. The blood glucose level in that sample was 15.0 mmol/litre. Surgery proceeded but was more complex than anticipated, resulting in the patient undergoing an extended right hepatectomy and a wedge resection of segment III. The total operative time was 6.5 hours with an estimated blood loss of 1500 ml. Despite intraoperative optimization of patient parameters and the use of oesophageal Doppler cardiac output monitoring to guide fluid therapy, the lactic acidosis worsened throughout the course of surgery. An arterial blood gas measurement taken at the finish showed pH 7.14, base excess -11.6 mmol/litre and lactate 9.1 mmol/litre.

The patient was kept anaesthetized and transferred to the intensive care unit for postoperative management where he received renal replacement and inotrope therapy. He remained on the intensive care unit for 15 days while receiving supportive treatment for multi-organ failure, and then continued his recovery on the ward, where he stayed for a further 7 days before he was ready to be discharged home.

The combination of metformin and a degree of fluid restriction appears to have precipitated lactic acidosis at a very early part of the anaesthetic which, in spite of early and aggressive fluid therapy, led to a marked hyperlactaemia. There is an 80% mortality with a serum lactate >5 mmol/litre together with a base excess of >6 mEq/litre (Stacpoole et al, 1994). The metabolic upset in this patient was nearly twice these levels.

Although many would discontinue metformin before surgery, some leave patients on the drug to give a background of glycaemic control. Hyperglycaemia results in an increase in perioperative complications.

The recommendations concerning cessation of metformin before surgery vary: some recommend at least 48 hours (Vreven and De Kock, 2005) whereas the British National Formulary recommends cessation only on the morning of surgery to coincide with the period of fasting. It is interesting that many clinicians appear to have little caution about the use of metformin, often ignoring contraindications to its use. This may be because lactic acidosis with this drug is a rare event (Holstein et al, 1999).

Conclusions

This case is interesting in that the patient not only developed a lactic acidosis relatively early on in surgery, but was also resistant to early and aggressive resuscitation. Although it is a rare complication of this drug, it is likely that stopping the drug 48 hours beforehand would have prevented this problem. In spite of the popularity and apparent safety of this drug for diabetes and other conditions, early cessation and monitoring of blood lactate levels is advocated for patients undergoing major surgery who have been treated with metformin. **BJHM**

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LEARNING POINTS

- Lactic acidosis is a well recognized but often underestimated complication of metformin therapy.
- Metformin is a commonly prescribed drug indicated in diabetics, polycystic ovarian syndrome and non-alcoholic steatohepatitis.
- Risk factors for developing metformin-associated lactic acidosis include sepsis, dehydration and cardiac, hepatic and/or renal insufficiency.
- Recognizing patients at risk and managing them appropriately can dramatically reduce the chances of developing metformin-associated lactic acidosis.
- Cessation of metformin therapy ideally for 48 hours before major surgery is advocated.