**CASE REPORT**

**Use of two continuous venovenous haemofiltration devices in metformin-associated lactic acidosis**

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**Abstract**

A male patient was admitted to the intensive care unit with severe shock and lactic acidosis following an intentional metformin overdose and possible co-ingestion of nifedipine. Despite supportive care and prompt initiation of continuous venovenous haemofiltration (CVVH) with a replacement rate of 35 ml/kg/h, the patient’s medical condition, including shock and lactic acidosis, rapidly deteriorated. In order to further increase metformin and lactate clearance the patient was connected to a second CVVH device resulting in a total effluent rate of 7 l/h. In the following hours the patient stabilised, and plasma lactate levels steadily decreased. Within a few days, haemofiltration was stopped and the patient was discharged from the ICU. This case report highlights the feasibility of high-volume CVVH using a second CVVH machine as a rescue therapy in patients with severe lactic acidosis.

**Introduction**

Metformin-associated lactic acidosis (MALA) refers to a blood lactate concentration > 5 mmol/l and arterial pH < 7.35 in association with metformin exposure.¹ Metformin is a biguanide antihyperglycaemic agent widely used for the treatment of type 2 diabetes mellitus. MALA is a rare and potentially fatal complication of metformin therapy and can be seen in both therapeutic use and after intentional or accidental overdose of metformin.¹² Risk factors are renal impairment, liver disease, alcoholism, cardiopulmonary disease and advanced age.¹³ There is no specific antidote available to reverse the toxic effects of metformin. The mainstay of initial therapy for MALA, regardless of chronicity or cause, is resuscitation and supportive care. Extracorporeal treatment is often initiated in case of kidney failure, significant electrolyte disturbances, metabolic acidosis, and failure of supportive care. Intermittent haemodialysis with bicarbonate buffer is the preferred extracorporeal treatment because it is superior in terms of its correction of acidaemia and removal of metformin and lactate.¹⁵ Continuous renal replacement therapy is an acceptable alternative if haemodialysis cannot be performed; however, clearance is much lower because of the technical limitations of low blood and effluent flow rates.¹⁶ This report demonstrates the possibility of increasing the effluent rate with continuous venovenous haemofiltration (CVVH) by using two devices.

**Case history**

A 66-year-old obese black male was admitted to the emergency department after a suicide attempt with an overdose of metformin and possible co-ingestion of glimepiride and nifedipine. The approximate time of ingestion was estimated between 19:45 and 21:45 on the evening before presentation at the emergency department. He reported taking 60 tablets containing 1000 mg metformin (60 gram). His past medical history consisted of type 2 diabetes mellitus, mental retardation, substance use (cocaine and heroin), hypertension and chronic hepatitis C infection. His normal therapeutic regimen was glimepiride, metformin, nifedipine and hydrochlorothiazide. At admission he had a total Glasgow Coma Scale score of 14 out of 15, a tympanic temperature of 35.2°C, pulse rate of 92 beats/min, blood pressure of 114/72 mmHg and respiratory rate of 25 breaths/min with 99% oxygen saturation on room air. He rapidly became hypotensive and required intubation for airway protection. After intubation his venous blood gas analysis revealed a high anion gap (26 mmol/l; normal, 12 to 20 mmol/l) metabolic and respiratory acidosis with pH 6.98 (normal 7.35-7.45), pCO₂ 6.7 kPa (normal 4.4-6.3 kPa), PO₂ 6.7 kPa, and bicarbonate 11.5 mmol/l (normal 23-29 mmol/l). The plasma lactate was found to be 20.1 mmol/l (normal 0.2-4 mmol/l). The patient’s serum glucose was 1.6 mmol/l, which had been 6 mmol/l earlier in the ambulance. He received immediate intravenous treatment with 100 ml glucose 20% and the patient was admitted to the intensive care unit. At admission, his creatinine level was 161 μmol/l (previously 92 μmol/l) and he had normal liver function tests. Toxicology screening was not performed. Because of severe
hypotension, norepinephrine was started to a maximum of 3.7 μg/kg/min and epinephrine to a maximum of 0.074 μg/kg/min. Sodium bicarbonate 8.4% was infused in a dose of 300 ml/h until the bicarbonate level was > 15 mmol/l in an attempt to correct his severe metabolic acidosis. He received 100 mg thiamine, calcium gluconate and glucagon intravenously, and a continuous infusion with insulin was started for the possible intoxication with nifedipine. The patient was oliguric. Post dilution CVVH (NxStage System One, NxStage Medical Inc) with a bicarbonate buffer solution (Duosol, B. Braun, Melsungen, Germany) was started (blood flow 200 ml/min, effluent flow 3.5 l/h). Despite this high flow, the plasma lactate level rose to 26 mmol/l and the shock state remained refractory. Due to concomitant infusion of sodium bicarbonate, in an attempt to correct the severe acidosis, hypernatraemia up to 162 mmol/l occurred. Extracorporeal clearance was then intensified using a second CVVH machine with a bicarbonate buffer solution.

**Discussion**

We present the case of a male patient with severe lactic acidosis due to metformin intoxication with suspected concomitant nifedipine intoxication that was successfully treated by high-volume CVVH using two devices.

Metformin-associated lactic acidosis (MALA) has a high mortality rate which is estimated to be between 8% and 50%.[4] Metformin has direct effects on the metabolism, including inhibition of pyruvate carboxylase, which impairs the conversion of lactate to pyruvate, and impaired cellular respiration.[8] This results in both increased production and decreased metabolism of lactate. Because the elimination of metformin is predominantly by the kidneys, the most common factor contributing to metformin toxicity is impaired kidney function,[4,14] The risk of lactate acidosis is augmented by factors that increase the production of lactate, or impair its clearance. The patient in the current case report presented with an oliguric acute kidney injury and severe shock possibly exacerbated by co-ingestion of nifedipine. The mainstay of the initial therapy for MALA is resuscitation and supportive care. Bicarbonate has been used to correct acidemia. However, there are concerns that it may exacerbate intracellular acidosis, thereby causing a leftward shift of the oxyhaemoglobin dissociation curve and electrolyte abnormalities,[5] including hypernatraemia.[15] Extracorporeal treatment is strongly recommended for severe refractory lactic acidosis (lactate concentration > 20 mmol/l, blood pH ≤ 7.0) or in patients with severe comorbid conditions (shock, impaired kidney function, liver failure, decreased level of consciousness).[5] In patients with MALA and renal insufficiency the endogenous clearance of metformin and lactate are severely diminished. Lactate and metformin are small molecules with no protein binding that easily pass through haemofilters.[11,12] The limiting factor for the extracorporeal elimination of metformin is the relatively large volume of distribution (1-5 l/kg) as a result of binding to the intracellular microsomes, although it has been suggested that in the context of acute kidney injury and poisoning the volume of distribution is reduced.[13,14] Sirtori et al. showed that after administration of intravenous metformin the volume of distribution was significantly reduced in patients with different

**Figure 1.** Plasma concentration of metformin (blue line) and lactate (red line). A indicates start of CVVH; B indicates start CVVH high flux (second machine)

**Figure 2.** Plasma concentration of electrolytes: calcium (blue line), magnesium (green line), phosphate (pink line), potassium (grey line) and sodium (orange line). Underneath the graph the correction of electrolytes is shown: infusion of magnesium sulphate 8 mmol (green arrow), phosphate 40 mmol, potassium 30 mmol, sodium 30 mmol (pink arrow), calcium gluconate 2.25 mmol (blue arrow), calcium gluconate continuous infusion 0.7 mmol/h (blue thick line) and potassium chloride continuous infusion 3.6 mmol/h (grey thick line). A indicates start of CVVH; B indicates start CVVH high flux (second machine)
degrees of renal impairment when compared with subjects with normal renal function: mean (SEM) 34.4 (1.9) vs. 62.7 (7.7) litres. The creatinine clearance rate of patients with altered renal function varied between 20 to 48 ml/min and creatinine clearance rate of those with normal renal excretory function varied between 92 to 108 ml/min. Possible mechanisms for the reduction in volume of distribution of metformin in patients with impaired renal function are increased protein binding, decreased tissue binding or alterations in body composition. A limiting factor for extracorporeal elimination of lactate is ongoing increased production of lactate secondary to ischaemia and inhibition of pyruvate carboxylase by remaining metformin activity.

Conventional intermittent haemodialysis is superior to continuous techniques in terms of elimination rate; however, due to haemodynamic instability in the critically ill, intermittent haemodialysis may be impossible. In the present case lactate and metformin levels remained high despite CVVH (3.5 l/h). In addition the patient developed severe hypernatraemia secondary to bicarbonate infusion and remained hypotensive despite extremely high levels of vasopressors. In order to further increase extracorporeal clearance a second dialysis catheter was introduced and the patient was treated with two CVVH machines achieving a total effluent rate of 7 l/h.

High-volume CVVH by a second CVVH machine has been previously reported by Panzer and colleagues in a patient with severe MALA.[14] Elimination with two devices may have contributed to the clearance of lactate and correction of the acidosis with subsequent resolution of shock. However, high-volume CVVH did not alter metformin clearance in this case, since the half-life stays approximately the same, as illustrated in figure 1. The use of two CVVH devices was associated with hypokalaemia, hypomagnesaemia, hypophosphataemia and hypocalcæmia in this case, requiring substitution of electrolytes. Therefore, careful monitoring of electrolytes is essential. We recommend measuring the plasma concentration of glimepiride was undetectable. Therefore, in this case, hypoglycaemia due to high metformin activity is probable. A potential mechanism is diminished hepatic glucose production in combination with fasting or decreased intestinal glucose absorption.

In conclusion, high-volume CVVH using a second CVVH machine as a tool to increase the effluent rate in patients with metformin intoxication and severe lactic acidosis is feasible.

Disclosure
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REFERENCES