Submitted July 2016; Accepted November 2016

CASE REPORT

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

J.E. Schopman[1], C.S. Bouman[2], C.M. Canté[1], S. Kouwen[3], F. Holleman[1], N.P. Juffermans[2]

[1]Department of Internal Medicine, [2]Intensive Care Medicine, [3]Hospital Pharmacy, Academic Medical Center, Amsterdam, the Netherlands

Correspondence

C. Canté - c.m.cante@amc.uva.nl

Keywords - **metformin, lactic acidosis, continuous veno-venous hemofiltration, intoxication, case report**

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.[2] Risk factors are renal impairment, liver disease, alcoholism, cardiopulmonary disease and advanced age.[3,4] 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.[5] 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.[6,7]

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), pCO_2 6.7 kPa (normal 4.4-6.3 kPa), PO_2 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

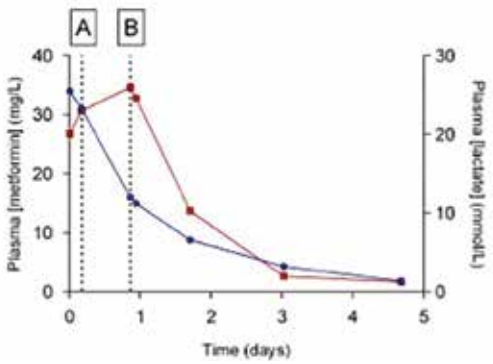

Figure 1. Plasma concentration of metformin (blue line) and lactate (red line). A indicates start of CVVH; B indicates start CVVH high flux (second machine)

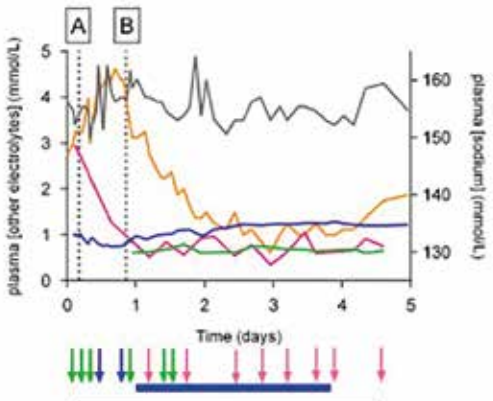

Figure 2. Plasma concentration of electrolytes: calcium (blue line), magnesium (green line), phosphate (pink line), potassium (grey line) and sodium (orange line). Underneath the graph the correction of electrolytes is shown: infusion of magnesium sulphate 8 mmol (green arrow), phosphate 40 mmol, potassium 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 3-8 mmol/h (grey thick line). A indicates start of CVVH; B indicates start CVVH high flux (second machine)

resulting in a total effluent rate of 7 l/h. Under this high-volume CVVH regime the patient's clinical status gradually improved and the plasma lactate started to decline *(figure 1)*. A continuous infusion with calcium gluconate and potassium chloride was started due to rebounding hypocalcaemia and hypokalaemia, respectively. He received multiple doses of magnesium sulphate for hypomagnesaemia and intermittent potassium phosphate infusion to correct hypophosphataemia *(figure 2)*. In the following days the patient could be weaned from inotropic support and the diuresis returned. Five days after admission CVVH was stopped, and he was extubated on day six. Eight days after admission he was transferred to a general medical ward where he needed no further renal replacement therapy. At discharge his creatinine concentration was 98 μmol/l. His metformin plasma concentration at admission was 34 mg/l (normal therapeutic range 0.1-4 mg/l). Glimepiride plasma levels were undetectable. Levels of nifedipine were unfortunately not measured.

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.[3,4] 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 acidaemia. However, there are concerns that it may exacerbate intracellular acidosis, thereby causing a leftward shift of the oxyhaemoglobin dissociation curve and electrolyte abnormalities,[9] including hypernatraemia.[10] 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

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.[13] 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.[15] 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 hypocalcaemia in this case, requiring substitution of electrolytes. Therefore, careful monitoring of electrolytes is essential. We recommend measuring electrolytes at least every six hours and more often when this is necessary.

Notably, our patient may have co-ingested nifedipine, but unfortunately we could not measure the nifedipine levels. There is no standardised approach for the management of intoxications with calcium channel blockers and reported first-line treatment includes supportive care, calcium salts, glucagon and hyperinsulinaemia-euglycaemia therapy.[16] Although nifedipine is a small molecule its elimination by haemofiltration is negligible due to its high protein binding and large volume of distribution (mean (SD) 1.47 (0.24) l/kg in patients with impaired renal function).[17]

The patient in our case had a hypoglycaemic episode at admission to the emergency department. Metformin generally does not cause hypoglycaemia when administered as monotherapy. However, hypoglycaemia has been previously observed in the setting of metformin-associated lactic acidosis[18,19] and in metformin overdose.[20,21] In the current case report, simultaneous ingestion of glimepiride was ruled out because 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

All authors declare no conflicts of interest. No funding or financial support was received.

REFERENCES

1. Luft D, Deichsel G, Schmulling RM, Stein W, Eggstein M. Definition of clinically relevant lactic acidosis in patients with internal diseases. Am J Clin Pathol. 1983;80:484-9.
2. Graham GG, Punt J, Arora M, et al. Clinical pharmacokinetics of metformin. Clin Pharmacokinet. 2011;50:81-98.
3. Stades AM, Heikens JT, Erkelens DW, Holleman F, Hoekstra JB. Metformin and lactic acidosis: cause or coincidence? A review of case reports. J Intern Med. 2004;255:179-87.
4. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010(4):CD002967.
5. Calello DP, Liu KD, Wiegand TJ, et al. Extracorporeal Treatment for Metformin Poisoning: Systematic Review and Recommendations From the Extracorporeal Treatments in Poisoning Workgroup. Crit Care Med. 2015;43:1716-30.
6. Barrueto F, Meggs WJ, Barchman MJ. Clearance of metformin by hemofiltration in overdose. J Toxicol Clin Toxicol. 2002;40:177-80.
7. Mujtaba M, Geara AS, Madhrira M, et al. Toxicokinetics of metformin-associated lactic acidosis with continuous renal replacement therapy. Eur J Drug Metab Pharmacokinet. 2012;37:249-53.
8. Donnino M, Montissol S, Andersen LW, Chase M, Liu X. Metformin inhibits pyruvate dehydrogenase at high dosages: A potential mechanism for lactic acidosis. 25th Annual Meeting of the Society for Academic Emergency Medicine; May 2014; Dallas, Texas.2014. p. S181.
9. Heaney D, Majid A, Junor B. Bicarbonate haemodialysis as a treatment of metformin overdose. Nephrol Dial Transplant. 1997;12(5):1046-7.
10. Radej J, Matejovic M, Krouzecky A, Sykora R, Chvojka J, Novak I. How Severe Acidosis Can a Human Survive? Successful Hemofiltration Use. Dial Transplant. 2007;36:608–10.
11. Akoglu H, Akan B, Piskinpasa S, Karaca O, Dede F, Erdem D, et al. Metformin-associated lactic acidosis treated with prolonged hemodialysis. Am J Emerg Med. 2011;29:575 e3-5.
12. Cheungpasitporn W, Zand L, Dillon JJ, Qian Q, Leung N. Lactate clearance and metabolic aspects of continuous high-volume hemofiltration. Clin Kidney J. 2015;8:374-7.
13. Sirtori CR, Franceschini G, Galli-Kienle M, et al. Disposition of metformin (N,N-dimethylbiguanide) in man. Clin Pharmacol Ther. 1978;24:683-93.
14. Lalau JD, Lacroix C. Measurement of metformin concentration in erythrocytes: clinical implications. Diabetes Obes Metab. 2003;5:93-8.
15. Panzer U, Kluge S, Kreymann G, Wolf G. Combination of intermittent haemodialysis and high-volume continuous haemofiltration for the treatment of severe metformin-induced lactic acidosis. Nephrol Dial Transplant. 2004;19:2157-8.
16. Mokhlesi B, Leikin JB, Murray P, Corbridge TC. Adult toxicology in critical care: Part II: specific poisonings. Chest. 2003;123:897-922.
17. Kleinbloesem CH, van Brummelen P, van Harten J, Danhof M, Breimer DD. Nifedipine: influence of renal function on pharmacokinetic/hemodynamic relationship. Clin Pharmacol Ther. 1985;37:563-74.
18. Lacher M, Hermanns-Clausen M, Haeffner K, Brandis M, Pohl M. Severe metformin intoxication with lactic acidosis in an adolescent. Eur J Pediatr. 2005;164:362-5.
19. Yang PW, Lin KH, Lo SH, Wang LM, Lin HD. Successful treatment of severe lactic acidosis caused by a suicide attempt with a metformin overdose. Kaohsiung J Med Sci. 2009;25:93-7.
20. Al-Abri SA, Hayashi S, Thoren KL, Olson KR. Metformin overdose-induced hypoglycemia in the absence of other antidiabetic drugs. Clin Toxicol (Phila). 2013;51:444-7.
21. Forrester MB. Adult metformin ingestions reported to Texas poison control centers, 2000-2006. Hum Exp Toxicol. 2008;27:575-83.