Severe lactic acidosis and rhabdomyolysis following metformin and ramipril overdose

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We report the case of a 46-yr-old male who developed severe lactic acidosis, cardiorespiratory arrest, and rhabdomyolysis following an overdose of metformin and ramipril. The lactic acidosis was successfully treated with early high-volume continuous veno-venous haemofiltration. Rhabdomyolysis and lower limb compartment syndrome developed later. The patient otherwise made a good recovery. We discuss the management of severe lactic acidosis secondary to metformin overdose and the association with rhabdomyolysis.


Keywords: blood, haemofiltration; complications, acidosis, lactic; complications, rhabdomyolysis; compartment syndrome; metformin

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Severe lactic acidosis is a recognized and often fatal complication of metformin overdose. Early recognition, the correction of metabolic acidosis, intensive support of the cardiovascular system, and the maintenance of body temperature are essential aspects of management. Patients who are treated with high-volume continuous veno-venous haemofiltration (CVVHF) have a better outcome. Rhabdomyolysis has not been reported in association with either metformin or ramipril overdose, although it has been reported with phenformin.

Case report
A 46-yr-old male was admitted to the Accident and Emergency Department after taking 56 g of metformin, 35 mg of ramipril, and 500 ml of alcohol over a period of 4 h. The patient had a Glasgow Coma Scale Score of 15. He was vomiting, complaining of colicky lower abdominal pain, and had diarrhoea. His past medical history included hypertension, type 2 diabetes, and a previously reported codeine overdose. There was no history of chronic alcohol abuse. On examination, he was pale, dehydrated, tachypnoeic and his peripheral oxygen saturation was 98% on room air. Arterial pressure was 91/54 mm Hg, heart rate 84 beats min⁻¹, respiratory rate 25 bpm, and blood glucose 8.2 mmol litre⁻¹. He complained of abdominal pain but there was no evidence of abdominal pathology, and there was no clinical evidence of abdominal compartment syndrome. The first arterial blood gas showed a marked metabolic acidosis with a high lactate level (Table 1). Liver function tests were within normal limits. Renal function was deranged (Na⁺ 139 mmol litre⁻¹, K⁺ 4.4 mmol litre⁻¹, urea 18.8 mmol litre⁻¹, creatinine 368 μmol litre⁻¹, estimated glomerular filtration rate 16 ml min⁻¹). ECG and CXR were normal. An i.v. infusion of 1.26% sodium bicarbonate was started at 250 ml h⁻¹. However, a venous blood gas 4 h later revealed worsening metabolic acidosis and rising lactate levels (Table 1). The patient was thus transferred to the intensive care unit (ICU) for high-volume CVVHF.

In ICU, the patient became hypotensive and arterial pressure dropped to 60/40 mm Hg and epinephrine was started at 0.14 μg kg⁻¹ min⁻¹. Arterial blood pressure remained low, and epinephrine dose was increased incrementally up to 0.64 μg kg⁻¹ min⁻¹. About 90 min after admission to ICU, the patient became apnoeic and had an asystolic cardiac arrest, resulting in intubation of the trachea and mechanical ventilation of the lungs. Sinus rhythm was restored following four cycles of cardiopulmonary resuscitation, epinephrine 2 mg, atropine 3 mg, and sodium bicarbonate 8.4%, 50 ml. An arterial blood gas analysis showed further progression of the lactic acidosis (Table 1).
The patient then had a focal seizure, which was terminated with 5 mg of midazolam. The seizure was thought to be secondary to severe lactic acidosis. The arterial pressure was 60/30 mm Hg and body temperature 33.9°C. Forced air warming therapy and infusion of norepinephrine was started. The PiCCO® monitor (Pulsion Medical, Munich, Germany) was used to monitor the patient’s haemodynamic status. His cardiac index was 5.26 litre min\(^{-1}\) m\(^{-2}\) and extrathoracic blood volume index (an indicator of volume status; normal value 850–1000 ml m\(^{-2}\)) 718 ml m\(^{-2}\) and extravascular lung water index (an indicator of water content of the lungs, i.e. a measure of pulmonary oedema; normal value 3–10 ml kg\(^{-1}\)) 10 ml kg\(^{-1}\).

Fifteen hours after the overdose, CVVHF with bicarbonate buffer, via a double-lumen femoral dialysis line, was commenced at 3.5 litre h\(^{-1}\) (50 ml kg\(^{-1}\) h\(^{-1}\)) and blood flow 250 ml min\(^{-1}\). There was no improvement of the severe lactic acidosis after 6 h (Table 1), therefore the extracorporeal treatment was intensified by using high-volume CVVHF [blood flow 300 ml min\(^{-1}\) with a filtrate flow rate of 5 litre h\(^{-1}\) (72 ml kg\(^{-1}\) h\(^{-1}\))] after 16 h of haemofiltration, the arterial pH steadily increased back to normal levels, and lactic acidosis improved (Table 1) and was transferred to a renal unit for intermittent haemodialysis 10 days after admission to ICU. He was discharged after a few days with normal renal function.

### Discussion

Metformin is a biguanide oral hypoglycaemic agent used to treat type 2 diabetes mellitus. It is the only biguanide available in the UK. Phenformin, another biguanide, was withdrawn due to the association with a high risk of lactic acidosis. The mechanism of metformin-associated lactic acidosis is not fully understood. It accumulates in the intestine, leading to an increased production of lactate, which lowers the pH within the liver and decreases lactate metabolism by suppressing pyruvate carboxylase. It also decreases glucose utilization and increases lactate production by the hepatocytes. It is excreted largely unchanged by the kidneys. Metformin can cause lactic acidosis even in patients taking therapeutic doses. This occurs most commonly in patients with significant underlying medical problems especially renal insufficiency, and is associated with more than 50% mortality. Mortality does not correlate well with either lactate levels or metformin levels. Case reports of metformin overdose are rare and have in most cases been associated with a fatal outcome. The minimum lethal dose which has been reported was in a 42 yr old who had a blood metformin level of 188 μg ml\(^{-1}\) (therapeutic range level 0.5–2.5 μg ml\(^{-1}\)). The maximum tolerated exposure reported was in a 70 yr old who ingested 63 g of metformin. He developed severe metabolic acidosis but recovered completely.

Severe nausea, vomiting, and diarrhoea may be the principal effects after acute overdose. Further significant clinical features of metformin overdose include pancreatitis, hypoglycaemia, hypothermia, hypotension, tachyphoea, tachycardia, severe lactic acidosis, cardiac arrest, coma, and acute renal failure. Our patient developed all of these features, except pancreatitis.

Lactic acidosis is defined as a metabolic acidosis with a blood pH less than 7.35 and a serum lactate more than 2 mmol litre\(^{-1}\). It is subdivided into type A, which is associated with tissue hypoxia, as occurs in sepsis, and type B, which occurs in the absence of hypoxia, and is the type associated with metformin overdose. Mortality secondary to lactic acidosis in intensive care patients is

### Table 1  
Arterial blood gas results showing progression of acidosis. Cardiac arrest occurred 9 h post-admission. CVVHF was started 15 h after admission. The acidosis started to improve after about 30 h of high-volume CVVHF

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>4 h</th>
<th>8 h</th>
<th>12 h</th>
<th>16 h</th>
<th>24 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.24</td>
<td>6.95</td>
<td>6.89</td>
<td>6.80</td>
<td>6.99</td>
<td>7.15</td>
<td>7.38</td>
</tr>
<tr>
<td>Base excess (mmol litre(^{-1}))</td>
<td>−11.1</td>
<td>−24.1</td>
<td>−28.3</td>
<td>−27.4</td>
<td>−26.0</td>
<td>−13.7</td>
<td>−3.4</td>
</tr>
<tr>
<td>Lactate (mmol litre(^{-1}))</td>
<td>11.6</td>
<td>&gt;15</td>
<td>&gt;15</td>
<td>&gt;15</td>
<td>&gt;15</td>
<td>&gt;15</td>
<td>5.5</td>
</tr>
<tr>
<td>Bicarbonate (mmol litre(^{-1}))</td>
<td>15.4</td>
<td>9.1</td>
<td>3.9</td>
<td>6.5</td>
<td>5.2</td>
<td>14.6</td>
<td>29.2</td>
</tr>
</tbody>
</table>
reported to be as high as 80%.

Treatment options for metformin-associated lactic acidosis include i.v. sodium bicarbonate, intermittent haemodialysis, and CVVHF with a bicarbonate substitute. There is no consensus as to the best management. Sodium bicarbonate alone frequently fails to correct the acidosis. Survival appears to be better in patients treated with early high volume CVVHF or haemodialysis. This treats the metabolic acidosis and removes the metformin from the circulation, preventing further acidosis. The patients may be too haemodynamically unstable to tolerate haemodialysis. Thus, haemofiltration seems to be the better option. In our patient, blood flow rates of 300 ml min\(^{-1}\) and ultrafiltration flow rates of 5 litre h\(^{-1}\) (72 ml kg\(^{-1}\) h\(^{-1}\)) were used successfully to restore serum pH and lower the serum lactate level. This is higher than flow rates used in previously reported cases. However, in a case reported by Panzer and colleagues, a patient with a serum lactate level of 25.8 mmol litre\(^{-1}\) and a metformin level of 191 mg litre\(^{-1}\) was treated successfully with concomitant haemodialysis and then two high-volume CVVHF when serum lactate continued to increase with one, achieving a total blood flow of 300 ml min\(^{-1}\) and ultrafiltration rate of 5 litre h\(^{-1}\). Cardiovascular support and maintenance of body temperature are also important in patients with severe lactic acidosis secondary to metformin. Our patient was hypothermic on admission to intensive care. This was probably related to the lactic acidosis and compounded by the infusion of high volume of fluids.

The aetiology of rhabdomyolysis in our patient is likely to be multifactorial. Potential contributory causes included hypotension, hypothermia, lactic acidosis, cardiac arrest, inotropic infusions, diabetic myonecrosis, the focal seizure and toxic levels of metformin and ramipril. The seizure was short lasting and focal and therefore unlikely to be the sole cause for the increase in enzyme levels and the rhabdomyolysis. Also, it affected the contralateral leg from the compartment syndrome. Spontaneous compartment syndrome in type 2 diabetes has been reported as a rare occurrence. We did not find any reports of a causal link between metformin or ramipril with rhabdomyolysis, but it has previously been reported with phenformin.

Toxic levels of metformin potentially could also have contributed to the development of rhabdomyolysis.

**Conclusion**

This case report emphasizes the importance of early treatment with high-volume haemofiltration in severe lactic acidosis secondary to metformin overdose, together with concomitant cardiovascular support, maintenance of blood glucose, and core body temperature. The possibility of an association of compartment syndrome and rhabdomyolysis with severe lactic acidosis and metformin overdose is raised.

**Reference**