increased secretion or high tissue concentrations. In case of a long-lasting normalization, ghrelin may provide an additional mechanism negatively influencing energy intake and growth hormone secretion in HD patients.

Conflict of interest statement. None declared.

Combination of intermittent haemodialysis and high-volume continuous haemofiltration for the treatment of severe metformin-induced lactic acidosis

Sir,

Metformin has been used for many decades as an effective glucose-lowering medication in the treatment of type 2 diabetes mellitus. Recent studies clearly demonstrated that metformin reduced secondary complications of diabetes mellitus type 2 without promoting weight gain, which is in contrast to treatment with insulin and/or sulphonylurea [1]. Lactic acidosis is a serious side effect observed with metformin treatment and an incidence rate of 9 lactic acidoses per 100 000 person-years of metformin treatment, as has been calculated [2]. This side effect is usually found in patients receiving metformin despite major contraindications, such as renal insufficiency and/or cardiopulmonary instability. The mortality in metformin-induced lactic acidosis is very high and has been estimated to be >50% [3]. Only a small number of cases of metformin overdoses with lactic acidosis have been described in the literature [4].

We report the case of a patient with severe lactic acidosis and cardiocirculatory arrest caused by metformin intoxication. Despite a plasma metformin concentration of 191 mg/l (to our knowledge the highest reported value in the literature), the patient recovered totally after treatment with a combination of intermittent haemodialysis and high-volume continuous haemofiltration.

A 42-year-old man was admitted with nausea and vomiting. The patient declared that he wanted to kill himself, but denied that he had taken any medications or drugs. His past medical history included type 2 diabetes that was treated with initial unknown types of oral hypoglycaemics. On admission, the patient was in a stable condition and initial routine laboratory workup was normal.

Four hours later, the patient complained of severe dyspnoea. Laboratory studies revealed a metabolic acidosis (pH 7.20, pCO2 37 mmHg, bicarbonate 15.8 mmol/l, anion gap 18) and a lactate concentration of 8.9 mmol/l. The patient was transferred to the intensive care unit (ICU), where he developed respiratory insufficiency and severe hypotension, resulting in intubation, mechanical ventilation and administration of dopamine and noradrenaline infusion. Laboratory workup showed further progression of the lactic acidosis (pH 6.89, pCO2 30 mmHg, bicarbonate 6.7 mmol/l, lactate 21.6 mmol/l) and a serum creatinine of 1.8 mg/dl. Urine analysis was negative for ketones.

In the meantime, a relative reported that metformin is part of the patient’s medication. This information in combination with the patient’s initial declaration of intending to harm himself led to the assumption of a metformin-induced lactic acidosis.

We started intermittent haemodialysis for 11 h (with 1 h interruption) in order to remove metformin and lactate as fast as possible and to correct acidosis. However, blood lactate levels remained very high and progressive haemodynamic instability occurred. Haemodialysis treatment was stopped and continuous veno-venous haemofiltration (CVVH) with bicarbonate substitute was started. Because of a further rise in the lactate level (25.8 mmol/l) and the poor clinical course of the patient, we intensified the extracorporeal elimination treatment using a second CVVH machine with a femoral catheter access. Under this treatment of severe metformin-induced lactic acidosis.

Table 1. Data of patient groups and control groups matched according to BMI and age

<table>
<thead>
<tr>
<th>Number of patients (n)</th>
<th>HD patients</th>
<th>HD controls</th>
<th>APD patients</th>
<th>APD controls</th>
<th>CRF patients</th>
<th>CRF controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1 m/7 f</td>
<td>6 m/1 f</td>
<td>5 m/1 f</td>
<td>8 m/2 f</td>
<td>6 m/8 f</td>
<td>7 m/8 f</td>
</tr>
<tr>
<td>Gender [male (m)/female (f)]</td>
<td>15.7±0.6</td>
<td>15.2±0.5</td>
<td>13.3±1.8</td>
<td>13.2±1.2</td>
<td>11.4±1.3</td>
<td>11.3±1.2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>19.9±1.3</td>
<td>18.9±0.7</td>
<td>17.9±1.0</td>
<td>17.8±0.8</td>
<td>17.9±0.9</td>
<td>17.5±0.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>&lt;10</td>
<td>176.3±7.6</td>
<td>&lt;10</td>
<td>179.6±8.7</td>
<td>34.6±6.0</td>
<td>172.5±5.9</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>&gt;10</td>
<td>681.2±119</td>
<td>&gt;10</td>
<td>60.1±1.8</td>
<td>461±74.3</td>
<td>47.1±4.4</td>
</tr>
<tr>
<td>Urea i.s. (mmol/l) (before HD)</td>
<td>&gt;10</td>
<td>1285±308*</td>
<td>&gt;10</td>
<td>542±140</td>
<td>2076±226***</td>
<td>603±113</td>
</tr>
<tr>
<td>Ghrelin i.s. (pg/ml) (after HD)</td>
<td>&gt;10</td>
<td>703±122 (NS)</td>
<td>&gt;10</td>
<td>542±140</td>
<td>1740±152*</td>
<td>1181±203</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; i.s., in serum; (NS), not significant; *P<0.05; ***P<0.001. Values are expressed as the mean±standard error of the mean (SEM).
high-volume CVVH (blood flow 300 ml/min, ultrafiltration 5 l/h) for 16 h (Figure 1), lactic acidosis improved, the haemodynamic situation of the patient stabilized and he was discharged from the ICU.

In conclusion, metformin intoxication should be considered in the differential diagnosis for patients with lactic acidosis in the absence of obvious tissue hypoxia [5]. Only early treatment, even in a suspicious case of metformin intoxication, is able to reduce the high mortality rates in these patients. This case report demonstrates the usefulness of the combination of intermittent haemodialysis with high-volume CVVH using two vascular access sites in the treatment of a patient with severe metformin-induced lactic acidosis and extremely high serum metformin concentrations.

Conflict of interest statement. None declared.

1Medizinische Klinik IV Ulf Panzer
2Medizinische Klinik I Stefan Kluge
Universitätsklinikum Hamburg Georg Kreymann
Eppendorf Gunter Wolf
Germany
Email: panzer@uke.uni-hamburg.de

The authors wish to be known that, in their opinion, the first two authors contributed equally to this work.


DOI: 10.1093/ndt/gfh337

Neutropenia associated with the use of low-dose methotrexate in a peritoneal dialysis patient

Sir,

We describe a case of neutropenia associated with the use of low-dose methotrexate in a patient undergoing continuous ambulatory peritoneal dialysis, who subsequently developed invasive pulmonary aspergillosis.

Case. A 64-year-old man was admitted with fever 23 days after starting methotrexate for the treatment of psoriasis, receiving a cumulative dose of 35 mg. Mouth ulceration developed at day 13 and the full blood count was normal at days 5 and 13. He had end-stage renal failure treated with continuous ambulatory peritoneal dialysis. On admission, examination revealed only oropharyngeal ulceration. The patient had a haemoglobin level of 11.9 g/dl, white cell count of 0.3 × 10⁹/l, zero neutrophils and a normal platelet count. Imipenem, teicoplanin, fluconazole, lenograstim and folinic acid were started as per local neutropenic protocol. A chest radiograph showed no signs of infection and blood cultures were subsequently sterile. The patient’s condition improved, with neutropenia resolving within 10 days, leading to discontinuation of antibiotics and lenograstim.

The patient developed dyspnoea and fever 15 days later with a neutrophilic leukocytosis of 49 × 10⁹/l. The chest radiograph (Figure 1) showed infiltrates at the bottom right and throughout the left field, with suggestion of a cavity formation in the left upper zone. Sputum cultures yielded Aspergillus versicolor. Computerized tomography of the thorax (Figure 2) showed consolidation in both upper lobes and the left lower lobe, with adjacent thick walled dilated bronchi, consistent with bronchopulmonary aspergillosis. Treatment was commenced with amphotericin, but despite respiratory support the patient died 3 weeks later.

Discussion. The kidney is the main route of excretion of methotrexate and the British National Formulary recommends reducing the dose for mild renal impairment and avoiding in moderate–severe impairment [1]. The renal drug handbook advises it is contraindicated in peritoneal dialysis and haemodialysis [2].

In a pharmacokinetic study of one patient undergoing peritoneal dialysis, a 15 mg intravenous dose had a 120 h elimination half-life, compared with 8 h in normal renal function [2]. This patient developed an unspecified drop in leukocyte and platelet count between days 3 and 7.

Fig. 1. Chest radiograph taken at onset of dyspnoea, and fever 15 days after resolution of neutropenia.