Efficacy of continuous venovenous haemofiltration (CVVH) in the treatment of severe phenformin-induced lactic acidosis

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Key words: acid–base status; biguanides; continuous venovenous haemofiltration; lactic acidosis; phenformin; phenformin removal

Introduction

The biguanide phenformin was withdrawn from the market of several western countries at the end of seventies because of several cases of lethal lactic acidosis [1]. However, phenformin is still sporadically used in some countries and in immigrant diabetic patients who had this drug previously prescribed. Recently interest for oral biguanides has been renewed, as metformin, reported to induce lactic acidosis very rarely, is widely prescribed for the treatment of non-insulin-dependent diabetes (NIDDM) [1].

Biguanide-induced lactic acidosis is a severe disease with an overall mortality rate of about 50% [1]. Therapeutic approaches consist in respiratory and haemodynamic support and in removing the drug from the circulation. A protocol has been proposed comprising administration of volume expanders, sodium bicarbonate, insulin, dialysis and/or dichloroacetate [1]. In particular, the role of haemodialysis in biguanide-induced lactic acidosis remains controversial. Its effectiveness is a function of the type of drug used, of the amount of drug ingested and of the number of treatments. Whereas metformin and buformin are dialysable, phenformin is poorly eliminated from the body compartments with conventional haemodialysis [2–4].

Continuous venovenous haemofiltration (CVVH) is a well-defined modality of extracorporeal treatment in critical ill patients with unstable haemodynamic conditions [5]. Previous reports described the treatment of lactic acidosis using haemofiltration [6,7], but to our knowledge data on the use of CVVH in biguanide-induced lactic acidosis are not available.

We report here a case of severe phenformin-induced lactic acidosis complicated by acute renal failure treated in the Intensive Care Unit (ICU) with supportive medical therapy and with CVVH. In particular we studied the efficacy of CVVH in controlling severe acidosis, in reversing metabolic alterations and in removing phenformin from the circulation.

Case report

A 68-year-old woman, with hypertension and NIDDM (weight 72 kg, height 171 cm) was admitted to the Emergency Department because of severe tachypnea, nausea, and vomiting. She presented with a 2-day history of urinary-tract infection with fever (38.5°C), stranguria, pyuria, and oliguria. Her medications for hypertension and for NIDDM included amlodipine 10 mg/day, enalapril 20 mg/day and phenformin 90 mg/day + glibenclamide 6 mg/day. Physical examination revealed an obese elderly woman with marked respiratory distress; vital signs included a rectal temperature of 36.5°C, a blood pressure of 75/41 mmHg, a heart rate of 124 b.p.m., and a respiratory rate of 32 breaths/min. She also presented mental confusion, with no focal neurological deficits. ECG showed sinus tachycardia, and the remainder of the examination was unremarkable.

Admission laboratory data included Hb 12.7 g/dl, WBC 14.8x10^9/l, platelets 426x10^9/l, urea 31.4 mmol/l (88 mg/dl), creatinine 186 µmol/l (2.1 mg/dl), Na+ 140 mmol/l, K+ 6.5 mmol/l, Cl− 100 mmol/l, Ca2+ 4.7 mmol/l, phosphate 1.29 mmol/l (4.0 mg/dl), glucose 10.38 mmol/l (187 mg/dl), serum ketone bodies not detectable, bilirubin 10.26 umol/l (0.6 mg/dl), AST 57 (normal <45 mU/ml), ALT 30 (normal <43 mU/ml), LDH 373 (normal <460 mU/ml), CPK 211 (normal <220 mU/ml), amylase 150 (normal <220 mU/ml), and INR 1.1. The patient’s arterial blood gases while breathing room air were...
pH 6.84, $pO_2$ 112 mmHg, $pCO_2$ 12.8 mmHg, $HCO_3^-$ 2 mmol/l, BE $-29$ mmol/l, with lactate serum level of 27.9 mmol/l (normal range 0.5–2.2). The anion gap was 38 mmol/l (normal 12±2).

Phenformin-associated lactic acidosis was diagnosed in this NIDDM patient, urine and blood cultures were drawn, and the patient immediately started intravenous infusion of sodium bicarbonate fluid, dopamine+dobutamine and glucose+insulin. She was transferred to the ICU for further management (APACHE II score 25).

Biochemical parameters

Lactate levels in serum and in ultrafiltrate were determined by clinical analyser ACA SX (Du Pont, Wilmington, DE, USA).

Phenformin in serum and in ultrafiltrate was determined by reversed-phase high-performance liquid chromatography (HPLC) (Waters Assoc., Milford, MA, USA) after deproteinization with acetonitrile (final ratio 1:5). Isocratic separations were performed at room temperature on a prepacked 300×3.9 mm I.D. C₁₈ Bondapack (10 mm) reversed-phase liquid chromatography column obtained from Waters and monitored by UV detection at 254 nm, modulating the amplification from 0.005 to 0.2. The mobile phase consisted of 0.01 M phosphate buffer-acetonitrile (50:50). The linearity of the method was tested by plotting the peak heights of phenformin chromatographed by HPLC against their concentrations in standard solutions (range 25–5000 ng/ml). The plots were linear ($r=0.99$) and passed through the origin. The within- and between-assay coefficients of variation of the HPLC peak heights were 3 and 4.3% respectively. The limit of detection of phenformin was 12.5 ng/ml. Selectivity of the analysis was tested by chromatographing plasma samples from patients taking widely used drugs including glibenclamide and Ca²⁺ antagonists and no interference was observed between such drugs and phenformin [8].

Clinical course

During the first 12 h of observation, the general condition worsened. The patient underwent assisted ventilation and infusion therapy comprising sodium bicarbonate, dopamine+dobutamine, glucose+insulin, and antibiotics. She developed anuria (Table 1). The abdominal ultrasound showed normal size and shape of kidneys, an increased cortical echogenicity, and no evidence of urinary tract obstruction. At time −6 and time 0 blood bicarbonate increased and pH reached values of 7.01 and 7.04 respectively (Figure 1). Serum lactate also increased to 37.8 and 43.8 mmol/l at time −6 and 0 respectively (Figure 2). Because of hypernatraemia, salt overload and supraventricular arrhythmia (treated with i.v. digoxin), the central venous pressure increased (Table 1). Twelve hours after hospital admission CVVH (blood pump HP 300 with Equaline system, QB 150 ml/min, ultrafiltration rate at about 15–20 ml/min; filter D-20, Amicon Co., Beverly, MA, USA) with bicarbonate-containing replacement fluid (CB30, bicarbonate 30 mmol/l, SIFRA, Isola Della Scala, VR, Italy) was started.

Hypernatraemia peaked at 6 h of CVVH (time 6) and then gradually decreased to normal value after 48 h of treatment (Table 1). Levels of lactate were very high at the admission and changed in parallel in serum and ultrafiltrate. They peaked at 6 h of CVVH (time 6) and progressively decreased subsequently (Figure 2). They returned into the normal range by the 5th day. After 72 h of CVVH diuresis resumed (Table 1).

In the following days the clinical course was uncomplicated, except for transitory thrombocytopenia (days 3 and 4 of CVVH). CVVH was stopped after 96 h of treatment. The patient was switched to insulin treatment and at 18 months follow-up is well.

During CVVH treatment urine, blood, and broncho-aspirate cultures were negative and values of potassium, calcium, and phosphate were maintained within normal limits, with mild hypochloraemia (peak value 84 mEq/l at time 6). AST presented a peak value of 80 mU/ml at 24 h of CVVH and returned normal after 48 h; ALT were normal. Glucose was maintained by glucose+insulin between and 5.51 and 13.87 mmol/l (100 and 250 mg/dl).

Discussion

Treatment with CVVH was remarkably successful in this patient with phenformin-induced lactic acidosis, particularly on view of the high initial levels of serum lactate (40 mmol/l).

As shown in Figure 3, serum level of phenformin reached a value of about 10 times the therapeutic range [8], comparable to that reported in a patient who attempted suicide by ingesting 900 mg of phenformin [3]. Thus, lactic acidosis was primarily related to phenformin accumulation. Indeed, although others factors present on admission, e.g. hypotension (possibly the result of urosepsis), hyperkalaemia or enalapril-induced, and liver injury, could have aggravated lactic acidosis [1], the significant relationship between phenformin blood levels and severity of lactic acidosis (Figure 4) suggests a causal role of phenformin.

In the present case, accumulation of phenformin was presumably due to reduced renal clearance of the drug. On admission the patient presented an anuric renal failure and a 2-day history of urinary-tract infection. Renal cortex and liver utilize lactate. In these organisms phenformin interferes with production and clearance of lactate [1]. Actually most of the reported cases of biguanide-associated lactic acidosis have been...
Table 1. Outcome of urine output, mean arterial pressure, central venous pressure, and serum sodium concentration

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Pre CVVH</th>
<th>CVVH</th>
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<tr>
<td></td>
<td>-12 -6</td>
<td>0</td>
<td>6 12 18 24 36 48 60 72</td>
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<tr>
<td>Na⁺ (mEq/l)</td>
<td>140 152</td>
<td>158 163</td>
<td>155 157</td>
<td>158 151</td>
<td>142  —</td>
<td>134</td>
<td></td>
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<tr>
<td>Urine output (ml)</td>
<td>100  0</td>
<td>0 0 0</td>
<td>0 0 15 0 48 76 288</td>
<td></td>
<td></td>
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<tr>
<td>MAP (mmHg)</td>
<td>52 56</td>
<td>48 57</td>
<td>58 56 56 70 72 72 72</td>
<td>72 87 78</td>
<td></td>
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<tr>
<td>CVP (cmH₂O)</td>
<td>5.5 15</td>
<td>13 8 8 5 7 7 12 14 12</td>
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Time 0, start of CVVH; MAP, mean arterial pressure; CVP, central venous pressure.

described in patients with impaired renal and/or hepatic functions [1].

The therapeutic approach in this patient was directed toward circulatory support, volume expansion, increase of serum pH above 7.0, and removal of the drug.

During the first 12 h of bicarbonate infusion (Figure 1, period —12 to 0), an improvement of blood pH and of BE was accompanied by a paradoxical increase of lactate (Figure 2, period —12 to 0). The increase of serum lactate may be explained by the observation that bicarbonate administration or, in general, relative or absolute alkalinization strongly stimulates peripheral lactate production [1,9]. On the other hand, severe acidemia exerts adverse haemodynamic effects, including impairment of cardiac contractility, reduction of cardiac output, arteriolar dilatation, hypotension with reduction in hepatic and renal blood flow, peripheral venous constriction and increased pulmonary vascular resistances [9]. In severe acidemia changes in liver metabolism of phenformin also occur, with a severely impaired elimination [10]. Moreover in the isolated perfused rat liver lactate
CVVH in phenformin-induced lactic acidosis

uptake decreases when intracellular pH falls below 7.0 and lactate handling shifts from uptake to output [1,9]. Therefore the correction of pH improves hepatic handling of phenformin and lactate, and reversal of circulatory abnormalities [1,9].

After 12 h of bicarbonate administration, anuria persisted and the patient started CVVH using bicarbonate replacement fluid. Treatment with CVVH, suited to the unstable haemodynamic conditions of this patient [4], corrected hypernatraemia (Table 1) and the initially net positive sodium balance (due to infusion of about 1000 moles of bicarbonate during the first 12 h) (Figure 5).

CVVH was found to remove appreciable amounts of phenformin from the circulation (Figure 3). The elimination of the drug continued throughout treatment (mean clearance and total amount removed respectively: 12.09 ml/min and 11.89 mg). These figures suggest that a deep compartment exists in which the drug accumulates. Consequently, for dialytic removal of the drug, a continuous modality of treatment appears superior to conventional intermittent haemodialysis [3]. The further reduction in phenformin blood concentration observed during the follow-up of this anuric patient might be due to hepatic metabolism of the drug. In humans phenformin is largely metabolized by hydroxylation in the liver [1,10]. We cannot exclude a role of CVVH in the removal of potential hepatic metabolites of phenformin.

In conclusion, CVVH appears to be an efficient tool to minimize side-effects of bicarbonate administration and remove phenformin.

Acknowledgements. We thank Pharmacovigilance Service, Guidotti S.p.A., Pisa and in particular Dr Mario Gori. This work was supported for determination of phenformin by a grant of Guidotti Laboratories, Guidotti S.p.A, Pisa, Italy.

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Received for publication: 19.6.97
Accepted in revised form: 2.12.97