High serum d-lactate in patients on continuous ambulatory peritoneal dialysis


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Abstract

Background. As abnormally high serum d-lactate levels may cause neurological impairment, we determined whether patients undergoing continuous ambulatory peritoneal dialysis (CAPD) with lactate-containing fluids have increased serum d-lactate concentrations.

Methods. d- and l-lactate concentrations were determined in peritoneal dialysis fluids and in serum from control subjects (n = 10), haemodialysis patients (n = 10), and CAPD patients (n = 30) before and after 1 h of dialysis.

Results. We found the median d-lactate concentration in Dianeal CAPD fluid to be 26 mM (range 19–27), whereas it was less than 0.5 mM in DPCA2 fluid. Control, haemodialysis, and CAPD (DPCA2) patient median serum d-lactate concentrations were below 0.07 mM. However, CAPD (Dianeal) patient serum d-lactate concentrations were 4-fold higher than controls (P < 0.0001), at 0.28 mM, an hour after instillation of d-lactate-containing fluid. Three patients, whose serum d-lactate averaged 0.59 mM, were found to have d-lactate concentrations at 0.22 mM after overnight cessation of dialysis.

Conclusion. We conclude that CAPD with d-lactate-containing fluids raises serum d-lactate to abnormal levels.

Key words: Continuous ambulatory peritoneal dialysis (CAPD); d-lactate; haemodialysis; l-lactate; renal failure

Introduction

Around 40 mM lactate anion is used in peritoneal dialysis fluid as a substitute for the natural anions, bicarbonate and albumin, that are present in normal plasma, thereby maintaining the ionic balance of plasma. Use of lactate also allows maintenance of plasma levels of chloride and prevents calcium precipitation that would occur were bicarbonate alone, with pH > 8.6, used. In some peritoneal dialysis fluids two lactate stereoisomers, l(+)-lactate and d(−)-lactate, are present and, as there is no racemase in dialysis fluid or the human body, the two stereoisomers cannot be interconverted [1]. Serum l(+)-lactate, a product of glycolysis, normally varies between 0.5 and 6 mM, depending on food intake and exercise level. d(−)-lactate, produced by micro-organisms or from ketone bodies [2], is normally constant at approximately 1.5% of the l-lactate concentration [3,4]. l-lactate is metabolized to pyruvate and the extent and direction of the lactate dehydrogenase (LDH) reaction is determined by the free [NAD+]/[NADH][H+] ratio in the cytosol, with which lactate and pyruvate are in near equilibrium [1]. By contrast, d-lactate is metabolized by a mitochondrial flavoprotein, d-α-hydroxy acid dehydrogenase [5], which appears to be functionally irreversible. Consequently, the metabolism of d-lactate has different metabolic effects to that of l-lactate. High serum d-lactate is known to cause neurological disturbances in adults and children with short bowel syndrome [6–8]. Serum d-lactate levels of 0.7–11.5 mM have been associated with the syndrome d-lactate encephalopathy, which is characterized by ataxia, dysarthria, and dizziness [9]. In 1994, Chan and co-workers [4] reported serum d-lactate concentrations of 3–4 mM in two patients undergoing peritoneal dialysis, both patients having neurological impairment that cleared when placed on haemodialysis with non-lactate-containing solutions. Consequently, we have determined the incidence and severity of elevated serum d-lactate levels in patients on CAPD.

Subjects and methods

Subjects

Twenty-six patients with end-stage renal disease (median age 59 years, range 27–82 years) were recruited consecutively,
having had CAPD treatment for 1–69 months with a median of 14 months. Blood samples were taken in the morning, before and 1 h after exchange of Dianaeal CAPD fluid (Baxter, Berkshire, UK) that contained 1.36, 2.27, or 3.86% glucose, and from four patients on DPCA2 CAPD fluid (Fresenius, Cheshire, UK) (median age 65 years, range 62–73). Results were compared to those from 10 healthy age and sex-matched controls (median age 49 years, range 27–71 years) and from 10 haemodialysis patients (median age 67 years, range 28–79). The haemodialyse (Renacarb B25, Renacare, Notts, UK) contained bicarbonate and no lactate. Three of the patients with high serum ω-lactate participated in an additional time course study in which no dialysis fluid was used overnight, and blood samples were taken before and at 1, 2, 3 and 4 h after the start of dialysis.

The clinical parameters recorded were: haemoglobin and plasma levels of creatinine, urea, Na⁺, K⁺, Ca²⁺, alkaline phosphatase, bilirubin, aspartate transaminase, glucose, albumin, and phosphate. The aetiology of chronic renal failure, length of time on dialysis, number of peritoneal infections, and dialysis prescription were also noted.

Methods

ω- and t-lactate concentrations were determined in both Dianaeal and DPCA2 CAPD fluids as described below for the neutralized blood extracts, except that 0.03 ml of appropriate dilutions were used. Blood samples (~2 ml) were taken from the patients and mixed into 0.025 ml of 11.6 N perchloric acid (HClO₄) and kept at 4°C until centrifuged at 3000 r.p.m. for 10 min. A measured aliquot of the supernatant was removed, neutralized to pH 7.0 with KOH and allowed to sit on ice for 20 min before centrifugation to remove KClO₄.

For the assay of ω-lactate, between 0.1 and 0.4 ml of neutralized extract was added to 1 ml of reaction mixture comprising 0.2 M 2-amino-2-methylpropanol, pH 9.9, 1.0 M sodium l-glutamate, 8 mM NAD⁺ and 5.6 U glutamate pyruvate transaminase [10], and water added to give a final volume of 1.8 ml. Baseline readings were then taken, whereupon 30 U ω-lactate dehydrogenase (EC 1.1.2.4) was added to the mixture. The increase in optical density was monitored at 340 nm for 60 min, at which time the reaction was finished.

For the assay of t-lactate the above procedure was repeated using between 0.05 and 0.1 ml of neutralized extract and 15.5 U t-lactate dehydrogenase (EC 1.1.2.7) according to previously published methods [10]. The reaction was complete in about 8~12 min. A specificity check gave 103% recovery of ω-lactate in the presence of an equal amount of t-lactate and 95% recovery of t-lactate in the presence of ω-lactate.

Results are presented as either median and ranges or means ±SEM, as indicated. Statistical significance was tested using the Mann–Whitney U test (non-parametric) or analysis of variance followed by a t test [11]. Differences were considered significant at P<0.05.

Results

The total lactate concentration in different batches of Dianaeal fluid varied between 39 and 48 mM (Table 1), most of the variation arising from the 9 mM difference in ω-lactate concentrations. DPCA2 fluid had a total lactate between 30 and 37 mM to which the ω-lactate contributed approximately 1%.

Both before and 1 h after the Dianaeal peritoneal dialysate exchange, patient median serum ω-lactate concentrations were elevated four to nine fold (P<0.0001) compared to those of undialysed controls, haemodialysis patients, and DPCA2 dialysed patients (Figure 1). There was no overlap between control values and those for the Dianaeal CAPD group 1 h post-dialysate instillation. The median serum t-lactate concentrations were the same for the four groups, between 0.4 and 1.4 mM, and were not significantly increased during peritoneal dialysis (Figure 2).

Three patients, found to have a mean serum ω-lactate concentration of 0.59 mM after 1 h Dianaeal CAPD, also had elevated serum ω-lactate concentrations after cessation of peritoneal dialysis for the previous night (Figure 3), concentrations threefold higher than control. After 1 h Dianaeal CAPD, the levels had risen significantly to 0.68 mM and returned to predialysis values by 2 h, but never to control values. No significant change was found in the serum t-lactate concentrations, which remained at 0.17±0.14 mM over the 4-h dialysate dwell time.

No correlation was found between serum ω-lactate levels and any of the clinical parameters recorded for each patient (see Methods). There was also no correlation between the level of ω-lactate in the serum after

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Total lactate (mM)</th>
<th>ω-Lactate (mM)</th>
<th>t-Lactate (mM)</th>
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<tbody>
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<td>Dianaeal</td>
<td>Median</td>
<td>Range</td>
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<tr>
<td></td>
<td>46.3</td>
<td>39.2–47.8</td>
<td>20.6</td>
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<tr>
<td>DPCA2</td>
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<td>Range</td>
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<td></td>
<td>30.7</td>
<td>29.9–37.4</td>
<td>29.9</td>
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Data are based on assays of seven different batches of Dianaeal (Baxter) PD fluid and three different batches of DPCA2 (Fresenius) PD fluid.

Fig. 1. Serum ω-lactate concentrations in control subjects (n=10), haemodialysis patients (n=10), DPCA2 (n=4) and Dianaeal (n=26) CAPD patients before dialysate exchange, and 1 h after exchange of CAPD fluids. *P<0.0001 compared to the other three groups.
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1 h CAPD and the concentrations of glucose or D-lactate in the dialysis fluid.

Discussion

All patients dialysed with the D-lactate-containing CAPD fluid had abnormal serum D-lactate levels, the median concentration 1 h after instillation being 0.28 mM or four times control levels. Three of our 26 peritoneal dialysis patients were found to have serum levels above 0.6 mM, close to the level of 0.7 mM reported by Thurn et al. [9] to be associated with D-lactate encephalopathy, although lower than the 3 to 4 mM levels reported to be associated with coma and semi-coma in two patients undergoing peritoneal dialysis [4]. These concentrations were also lower than those reported for neurologically symptomatic patients with short bowel syndrome [6–8]. Although serum D-lactate levels increased up to nine fold during peritoneal dialysis, the levels of L-lactate remained constant, showing that the two isomers were metabolized differently. Haemodialysis-dialysed patients and DPCA2-dialysed patients had serum D-lactate levels that were similar to controls, indicating that renal failure per se does not cause an increase in D-lactate levels.

The level of D-lactate in Dianeal CAPD fluid was over 50% of the total lactate, whereas the D-lactate in DPCA2 fluid was around 1%. Total lactate concentrations in the different batches of CAPD fluid varied by approximately 9 mM or 23% of the stated value of 40 mM. However, this variation did not influence the patient serum D-lactate concentrations reached during dialysis; probably any effect was masked by variability in patient absorption and clearance rates for the D-lactate. There was no correlation between the elevated serum D-lactate concentrations and any of the clinical parameters, making it difficult to predict those disposed to develop high D-lactate levels. Further studies will be required to confirm that there are no neurological sequelae for these CAPD patients.

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References


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