Reduced calcium dialysate in CAPD patients: efficacy and limitations

A. Armstrong¹, J. Beer¹, K. Noonan² and J. Cunningham¹

Departments of ¹Nephrology and ²Clinical Biochemistry, The Royal London Hospital and Medical College, London, UK

Abstract

Background. The increasing use of ‘reduced calcium’ dialysate in CAPD patients treated with calcium-based phosphate binders has raised concerns that this could lead to negative calcium balance, worsening hyperparathyroidism, and osteopenia.

Methods. The present study was conducted to examine the possibilities (a) that 1.25 mM calcium dialysate leads to negative calcium balance and worsening hyperparathyroidism, and (b) that conversely 1.25 mM calcium dialysate is still too high for some patients. We studied 22 patients who, after a 2-month run in using 1.75 mM calcium dialysate and aluminium hydroxide binders, entered a 3-month phase of 1.25 mM calcium dialysate with continuation of aluminium hydroxide as the sole phosphate binder. The patients then entered a final 9-month phase in which dialysate calcium remained at 1.25 mM and calcium carbonate was substituted for aluminium hydroxide and progressively titrated to achieve optimum phosphate control.

Results. During the initial 3-month period, parathyroid hormone increased from 259, range 11–1149 to 405, range 16–1318 pg/ml (P = 0.0001) and ionized calcium decreased from 1.17 ± 0.06 to 1.11 ± 0.08 mM (P = 0.0004). The subsequent 9-month phase was associated with return of parathyroid hormone to baseline levels. Further dialysate calcium reduction to 0.6 mM was implemented in the four patients who became hypercalcaemic.

Conclusion. This study has clearly shown that reduction of dialysate calcium to 1.25 mM can be harmful to CAPD patients if oral calcium availability is inadequate. It has also shown that dialysate calcium at 1.25 mM is a compromise, with increased risk of hyperparathyroidism if calcium intake is too low and, conversely, risk of hypercalcaemia and unacceptable increases of the Ca × Pi product in a minority of patients. At these extremes there is a need for a high-calcium dialysate (1.75 mM) and a very low-calcium dialysate (0.6 mM or less), to optimize management.

Key words: CAPD; calcium; PTH; dialysis

Introduction

The shift away from phosphate-binding aluminium salts as the mainstay of phosphate control in haemodialysis and continuous ambulatory peritoneal dialysis (CAPD) patients has led to a marked increase in the use of calcium carbonate and calcium acetate [1]. Calcium salts have been in use for nearly quarter of a century in dialysis patients, initially to achieve positive calcium balance in the era before 1α hydroxylated vitamin D metabolites were available [2], and more recently to reduce the bioavailability of dietary phosphorus [3]. Achievement of this latter objective has been hampered by the relatively low phosphate-binding capacity of calcium salts with attendant need for large oral doses of the phosphate binder, and also by the difficulty of restricting dietary phosphate while allowing sufficient protein intake. Despite their shortcomings these therapies can, however, now be regarded as standard in end-stage renal disease patients.

The requirement for large doses of calcium salts has led to frequent and troublesome hypercalcaemia, and this has often limited the dose that can be given without unacceptable increases of the calcium × phosphate product [3,4]. We and others have achieved some success by combining calcium salts with the reduction of dialysate calcium from the ‘normal’ level of 1.75 mM to as low as 0.6 mM [5–7]. This approach has generally allowed patients to use calcium salts effectively and in many countries dialysate calcium at 1.25 mM is now used routinely in CAPD patients taking calcium-based phosphate binders.

The present study addresses itself to two concerns arising from these new strategies. The first is the possibility that reduced calcium dialysate, if inadequately compensated by high oral calcium intake, could lead to negative calcium balance, worsening hyperparathyroidism, and osteopenia [4,5,8,9]. The second is that at 1.25 mM the dialysate calcium may still be too high for some patients in whom effective phosphate control without hypercalcaemia could only be achieved by using even lower dialysate calcium.

We therefore examined sequentially the effect in the short term of deliberately using 1.25 mM calcium dialysate without supplementary oral calcium in the form of a calcium-containing phosphate binder.
Aluminium hydroxide was used to control phosphate as necessary. This initial period was followed by withdrawal of aluminium hydroxide and reversion to an orthodox regimen comprising provision of sufficient calcium carbonate to control serum phosphate and dialysate calcium at 1.25 mM, with the option to reduce to 0.6 mM in those patients becoming hypercalcaemic.

**Subjects and methods**

**Patients and protocol**

Thirty consecutive patients entering the CAPD programme were enrolled. After a 2-month run in using 1.75 mM calcium dialysate and aluminium hydroxide, the subjects entered a 3-month phase of 1.25 mM dialysate with continuation of aluminium hydroxide as the sole phosphate binder. Subsequently the patients entered a final 9-month phase in which dialysate calcium remained at 1.25 mM and calcium carbonate was substituted for aluminium hydroxide progressively, and titrated to achieve optimum phosphate control with a target range of 1.00–1.75 mM. During this phase, patients becoming hypercalcaemic had their dialysate calcium reduced further to 0.6 mM with the aim of allowing continuation of effective doses of calcium carbonate. No patient received vitamin D therapy for 12 weeks prior to or during the protocol. Of the 30 patients enrolled, drop outs comprised six because of transplantation, one following failure of CAPD, and one death. Amongst those completing the protocol were 13 males and nine females with an average age of 52 (ranging from 23 to 73 years). Measurement times were at entry, +3 and +9 months.

**Laboratory methods**

Plasma calcium, inorganic phosphate, albumin and total alkaline phosphatase were measured in serum using a DAX autoanlyser (Bayer Diagnostics, Basingstoke, UK). Measured total calcium was adjusted for concomitant serum albumin concentration using the formula [10]:

\[
\text{Ca (adjusted)} = \text{Ca (total)} + 0.02 (46\text{–albumin})
\]

Ionized calcium was measured in fresh whole blood using a Ciba Corning 634 ISE Ca²⁺/pH Analyser (Ciba Corning Diagnostics Ltd, Halstead, Essex, UK). The normal range (defined as mean±2 SD) in 42 healthy subjects was 1.16–1.28 mM. Samples for PTH and osteocalcin assays were cooled and separated immediately, and then stored at −20°C pending assay. Intact parathyroid hormone (PTH) was measured in plasma using a 2-site immunnoassay (Allegro, Nichols Institute, San Cupistrano, Ca). The normal range is 11–55 pg/ml with intra-assay CV of <7% and interassay CV <5% over the range 10–1000 pg/ml. Osteocalcin was measured in plasma using a human osteocalcin immunoradiometric assay (Nicholls Institute, San Cupistrano, Ca). Between batch precision was 6% at 12 ng/ml.

**Data presentation and analysis**

Data are given as mean±SD, mean (range), or as 10, 25, 50, 75, 90 centile box plots. Paired comparisons were made using Student’s t test, or the Wilcoxon signed rank sum test as appropriate and multiple group comparisons using Fisher’s least significant difference test. A value of \( P<0.05 \) (2-tailed) was regarded as significant.

**Results**

The conversion from dialysate calcium at 1.75 mM to 1.25 mM (Table 1, Figures 1 and 2) led to an initial slight deterioration of phosphate control by aluminium hydroxide evident at 3 months (1.59±0.47 vs 1.80±0.42 mM, \( P<0.002 \)). This change was transient, and by 9 months mean plasma phosphate (now controlled using calcium carbonate) did not differ significantly from that at entry (1.66±0.44 vs 1.59±0.47 mM, NS).

Ionized calcium showed a small but highly significant decrease from 1.17±0.06 to 1.11±0.08 mM (\( P=0.0004 \)) following conversion from 1.75 to 1.25 mM calcium dialysate (Figure 1). This change was seen in nearly all the patients (20 of 22), and was not related to changes in inorganic phosphate (\( r=0.27, P=0.22 \)) or to PTH at entry (\( r=0.34, P=0.12 \)). Parallel changes in serum total calcium were found (2.48±0.15 vs 2.38±0.14 mM, \( P<0.01 \)).

Changes in PTH are shown in Table 1. PTH rose significantly as calcium fell (259, range 11–1149 vs 405, range 16–1318 pg/ml, \( P=0.0001 \)). This increase was seen in nearly all patients (21 of 22), but was not predicted by the accompanying change in ionized calcium (\( r=0.34, P=0.12 \)), or that in inorganic phosphate (\( r=0.08, P=0.73 \)). Total alkaline phosphatase increased slightly but significantly (105, range 36–368; to 130, range 39–544 113 IU/l, \( P<0.003 \)). Osteocalcin remained unchanged throughout (Table 1).

Following substitution of calcium carbonate for aluminium hydroxide, four patients became hypercalcaemic and required further reduction of dialysate calcium to 0.6 mM. Of those three were able to continue using calcium carbonate as their sole phosphate binder but in one patient partial reversion to aluminium hydroxide was necessary (Table 1).

Ionized calcium increased following introduction of calcium carbonate, reaching levels that were slightly above those at entry (1.21±0.09 vs 1.17±0.06 mM, \( P=0.047 \)). Total calcium did not change significantly (2.52±0.16 vs 2.48±0.15 mM, NS). These increases took ionized and total calcium to concentrations significantly above the 3-month nadir (1.21±0.09 vs 1.11±0.08 mM, \( P=0.0001 \) for ionized calcium and 2.52±0.16 vs 2.38±0.14 mM, \( P=0.0003 \) for total calcium).

PTH, which at 3 months was significantly above baseline, decreased after the introduction of calcium carbonate, finally at 9 months reaching values indistinguishable from those at entry (entry value 259, range 11–1149 and 9 months value 305, range 7–1030 pg/ml, NS). Neither alkaline phosphatase nor osteocalcin changed following the introduction of calcium carbonate.
Fig. 1. Parathyroid hormone (top panel) and ionized calcium (bottom panel) at entry, 3 months, and 9 months. Dialysate calcium was 1.75 mM at entry, and 1.25 mM at 3 months and 9 months. Data are shown as 10, 25, 50, 75, 90 centile box plots. Statistical comparison using the Wilcoxon signed rank sum test (PTH) or Student t test (Ca$^{2+}$).
Calcium (Ca) × phosphate (Pi) product (top panel) and inorganic phosphate (bottom panel) at entry, 3 months, and 9 months. Dialysate calcium was 1.75 mM at entry, and 1.25 mM at 3 months and 9 months. Data are shown as mean in the top panel and 10, 25, 50, 75, 90 centile box plots in the bottom panel. Statistical comparison using Student t test.
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Table 1. Therapy and biochemical details of entry, 3 months and 9 months

<table>
<thead>
<tr>
<th></th>
<th>Entry</th>
<th>3 Months</th>
<th>9 Months</th>
</tr>
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<tbody>
<tr>
<td>Ca(^{2+}) (mM)</td>
<td>1.17 ± 0.06</td>
<td>1.11 ± 0.08*</td>
<td>1.21 ± 0.09**</td>
</tr>
<tr>
<td>Ca(^{2+}) (mM)</td>
<td>2.48 ± 0.15</td>
<td>2.38 ± 0.14*</td>
<td>2.52 ± 0.16**</td>
</tr>
<tr>
<td>Pi (mM)</td>
<td>1.59 ± 0.47</td>
<td>1.80 ± 0.42*</td>
<td>1.66 ± 0.44</td>
</tr>
<tr>
<td>Alk Phos (IU/l)</td>
<td>105 (36–368)</td>
<td>130 (39–544)*</td>
<td>124 (39–479)*</td>
</tr>
<tr>
<td>PTH 1–84 (pg/ml)</td>
<td>259 (11–1149)</td>
<td>405 (16–1318)*</td>
<td>305 (7–1030)</td>
</tr>
<tr>
<td>Osteocalcin (ng/ml)</td>
<td>14.64 ± 9.5</td>
<td>17.07 ± 12.8</td>
<td>17.77 ± 16.6</td>
</tr>
<tr>
<td>1.75 mM dialysate (n pts)</td>
<td>22</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.25 mM dialysate (n pts)</td>
<td>0</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>0.6 mM dialysate (n pts)</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>CaCO(_3) (mM/day)</td>
<td>0</td>
<td>0</td>
<td>81</td>
</tr>
<tr>
<td>Aluminiun (g/day)</td>
<td>2.5</td>
<td>3</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Parentheses indicate range around geometric mean. *P < 0.05 vs entry; **P < 0.05 vs 3 months.

Discussion

This study has clearly shown that reduction of dialysate calcium to 1.25 mM can be harmful to CAPD patients if oral calcium availability is inadequate. As such, the results emphasize the importance of using reduced calcium dialysate only in combination with oral calcium carbonate and/or vitamin D metabolites. Even so, there is some evidence that when giving oral calcium carbonate, there is still a tendency for PTH to increase in some patients [9].

The observation that these patients’ hyperparathyroidism could be improved by the subsequent introduction of calcium carbonate is reassuring, and suggests that the deterioration of hyperparathyroidism during the early part of the protocol was the direct result of reduced calcium dialysate in combination with inadequate oral calcium intake, rather than being merely part of an underlying trend of worsening hyperparathyroidism [11].

As in earlier studies of reduced calcium dialysate in CAPD [5–7], we found that the combination of 1.25 mM calcium dialysate and oral calcium carbonate was effective and well tolerated in most of the patients. In the light of recent studies emphasizing the direct stimulating effect of phosphate on the parathyroids [12], phosphate targets were stringent and were achieved without difficulty in most subjects. As previously reported some CAPD patients (4 of 22 in the present study) became hypercalcaemic even while using 1.25 mM dialysate. This proportion (18%) is less than the 30% that we found in an earlier study [6], but confirms that there exists a subgroup of CAPD patients for whom 1.25 mM calcium dialysate is not low enough. For these either further reduction of dialysate calcium or reversion to aluminium-containing phosphate binders is necessary.

As before, we found striking variability in the propensity of CAPD patients to become hypercalcaemic, and we still do not have an adequate explanation for this observation. We have previously found that vitamin D metabolite concentrations are similarly reduced in both normocalcaemic and hypercalcaemic patients [6] and it is likely, although unproven, that variation in vitamin-D-independent gut calcium absorption is a determinant of this problem.

Our work and that of others suggests that the increasing use of 1.25 mM calcium dialysate and calcium carbonate or calcium acetate combinations in CAPD patients is appropriate, provided that PTH is monitored closely, especially after a change to a patient’s dialysate. It is clear, however, that 1.25 mM calcium represents a compromise, resulting in increased risk of hyperparathyroidism if calcium intake is too low (inadequate prescription or poor compliance) and conversely in a risk of hypercalcaemia and unacceptable increases of the Ca \( \times \) Pi product in a minority of patients. At these extremes there remains a need for a high-calcium dialysate (1.75 mM) and a very low-calcium dialysate (0.6 mM or less), to allow sufficient flexibility for optimum management.

References

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