High-normal calcium (1.35 mmol/l) dialysate in patients on CAPD: efficient and safe long-term control of plasma calcium, phosphate, and parathyroid hormone

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Abstract

Aim. The aim of the present study was to examine the long-term efficacy and safety of treatment with a high-normal calcium dialysate with a calcium concentration of 1.35 mmol/l in patients on CAPD. This dialysate calcium concentration is close to the high-normal plasma ionized calcium level aimed at in dialysis patients in order to suppress the parathyroid hormone secretion. The end-points of the study were (1) plasma ionized calcium (iCa) and phosphate (P) levels, (2) plasma intact parathyroid hormone (PTH) levels, (3) doses of calcium carbonate and alfacalcidol, (4) requirements of Al-containing phosphate binders, and (5) bone mineral density (BMD).

Results. Thirty-seven non-selected patients on CAPD treatment were followed for an average of 10 months after switching from a dialysate Ca of 1.75 to 1.35 mmol/l. After 1 week, a significant decrease of mean iCa from 1.26 ± 0.01 to 1.23 ± 0.01 mmol/l (P < 0.05) and an increase of median PTH from 80 to 135 pg/ml (P < 0.01) were seen. From the 2nd week and onwards, however, basal levels of iCa and PTH were restored and remained stable. Mean plasma iCa was kept within 1.23–1.31 mmol/l; mean plasma P below 1.65 mmol/l and median PTH within 52–135 pg/ml. Episodes of hypercalcaemia were few (1.2 cases of plasma iCa > 1.45 mmol/l per 100 treatment weeks), and the need for Al-containing P binders low with only five patients requiring this treatment for isolated and four patients for repeated episodes of hyperphosphataemia or hypercalcaemia. After switching from a dialysate Ca of 1.75 to 1.35 mmol/l, the doses of calcium carbonate and alfacalcidol could be significantly increased. Furthermore, using the dialysate Ca of 1.35 mmol/l made it possible to induce a controlled increase of PTH levels to 80–100 pg/ml by a temporarily discontinuation of alfacalcidol and/or a reduction of calcium carbonate dosage in the patients where PTH had become suppressed to levels below the upper normal limit. The intention of the treatment was to maintain PTH levels within 1.5–2.5 times the upper normal limit for non-uraemic patients. Pre-study BMD of the vertebral bodies L2-L4 and of the femoral neck were normal and not significantly different from post-study measurements.

Conclusion. The present study demonstrated that when using a high-normal dialysate Ca concentration of 1.35 mmol/l in non-selected patients on CAPD treatment, high-normal plasma iCa and near-normal plasma P levels could be readily achieved with a minimal risk of incidental hypercalcaemia despite use of calcium carbonate as the main P binder. As a consequence of the tight Ca and P regulation, minimal doses of alfacalcidol were required to keep PTH within acceptable limits. We recommend this dialysate Ca concentration as a first-choice therapy for the majority of patients starting on CAPD treatment.

Key words: bone mineral density; CAPD; dialysate calcium; plasma calcium; plasma parathyroid hormone; plasma phosphate

Introduction

Prophylaxis and treatment of secondary hyperparathyroidism in patients on dialysis include lowering plasma phosphate, raising plasma calcium, and administering vitamin D metabolites [1–2]. After the risk of aluminium accumulation became apparent, aluminium-containing phosphate binders have been replaced by calcium carbonate or calcium acetate as first-line therapy for hyperphosphataemia in most renal units. Hypercalcaemia, however, is a serious side-effect of treatment with calcium-containing phosphate binders and vitamin D metabolites in dialysis patients. It often limits their use, especially when conventionally high dialysate calcium concentrations are used. A reduction of the dialysate calcium concentrations have therefore been recommended [3–4]. Until now the dialysate calcium concentrations examined for use in continuous
ambulatory peritoneal dialysis (CAPD) treatment include 0.6, 1.0, 1.15, 1.25 and 1.45 mmol/l [3-16]. Whereas most reports have shown improved tolerance to calcium carbonate and vitamin D metabolites, the effect on the secondary hyperparathyroidism has been more variable with some investigations showing improvement [6-8], some no change [9-11], and others deterioration [12-16]. The optimal dialysate calcium concentrations for patients on CAPD therefore still remain to be clearly defined as it is of great importance that this dialysis treatment can be performed safely by the patients at home without control too often by the treating physician.

The aim of the present study, therefore, was to examine the long-term efficacy and safety of treatment with a dialysate with a calcium concentration of 1.35 mmol/l in a group of non-selected patients on CAPD. This dialysate calcium concentration is close to the high-normal plasma ionized calcium level aimed at in dialysis patients in order to suppress the PTH secretion [2]. The end points of the study were (1) plasma ionized calcium (iCa) and phosphate (P) levels, (2) plasma intact parathyroid hormone (PTH) levels, (3) doses of calcium carbonate and alfacalcidol (1-alpha-OH-cholecalciferol), (4) requirements of aluminium-containing P binders, and (5) bone mineral density (BMD). The follow-up period was 48 weeks.

Subjects and methods

Study group

All eligible CAPD patients dialysed with a dialysis solution with a Ca concentration of 1.75 mmol/l (glucose 1.5, 2.5, 4.0%, Mg 0.25 mmol/l; lactate 40 mmol/l; sodium 132 mmol/l; CI 95 mmol/l; Gambro, Lund, Sweden) were invited to join the study. All patients were exchanging 1.5-2.0 l dialysate four to five times a day. The dialysate dose was controlled by regular urea kinetics assessment. A Kt/V > 1.70 per week and a creatinine clearance > 50 l/week/1.73 m2 was the goal. The exclusion criteria were malignancy, tertiary hyperparathyroidism, and prior parathyroidectomy. Patients were withdrawn from the study when one of the following occurred: transplantation, change of dialysis modality or severe intercurrent illness. The study was approved by The Ethical Committee of Copenhagen and The Danish National Board of Health. All patients gave their informed written consent.

From a total of 45 patients who entered the study, 19 dropped out before 48 weeks of study. The reasons for premature termination were kidney transplantation (n=8), change of dialysis modality (n=8) and severe intercurrent illness or death (n=3). Only withdrawals before 12 weeks of study (n=8) were excluded from the study population. The remaining 37 patients, 19 men and 18 women, aged 23-75 years (median, 61 years) who had been on CAPD treatment before the study for 1-47 months (median, 6 months) were followed up for a period of 3-12 months (median, 10 months). The primary renal disease was glomerulovascular (glomerulonephritis, hypertension or diabetes) in 20 patients, tubulointerstitial (polycystic kidneys, interstitial nephropathy, obstructive nephropathy) in nine patients, and unknown (contracted kidneys) in eight patients.

A phosphate-restricted diet was recommended, when plasma P > 1.70 mmol/l before or at the time P-binding medicine was prescribed. All patients received supplements of a vitamin B complex; vitamin C, and folic acid. Antihypertensive treatment with beta-adrenoceptor blockers, calcium entry blockers, vasodilators, or angiotensin-converting enzyme inhibitors was prescribed for 24 patients; treatment with omeprazol or cimetidin for 20 patients, and erythropoietin injections for 25 patients. One patient suffering from polymyalgia rheumatica was on a small maintenance dose (2.5 mg/day) of corticosteroid. Except for this patient, none complained about symptoms relating to the bones and/or muscles.

Treatment schedule

After a basal period of 1 month using a dialysis fluid with a calcium concentration of 1.75 mmol/l, all patients were switched to a dialysate with a Ca concentration of 1.35 mmol/l (Gambro, Lund, Sweden). The electrolyte composition of this dialysis fluid was the same as the original dialysate, except that the calcium concentration was reduced. Calcium carbonate (0.5 g/tablet) was used as the main P binder, and the dose adjusted to maintain plasma P:<1.70 mmol/l. When plasma P was >1.70 mmol/l and iCa <1.35 mmol/l, treatment with oral intermittent alfacalcidol (Leo Pharmaceuticals, Copenhagen, Denmark) was undertaken, starting with 1 µg twice weekly. A lower maintenance dose of alfacalcidol was given if plasma iCa was >1.35 mmol/l or plasma P>1.70 mmol/l. Alfacalcidol was not started, however, or was temporarily discontinued, when PTH <53 pg/ml as determined by the third monthly routine control. Only in the case of combined hyperphosphataemia and hypercalcaemia (P>2.0 mmol/l and iCa >1.35 mmol/l) the calcium carbonate was temporarily replaced by aluminium aminoacetate. The patients were seen weekly during the 1st month and every 2nd week during the 2nd and 3rd months of the study. Thereafter the control was scheduled at every 4 weeks until week 48.

Study parameters

Plasma iCa and P were assessed on every visit, and plasma samples obtained and frozen for later serial analysis of intact PTH (‘study samples’). In addition, intact PTH was determined every 3rd month as part of the routine control. Plasma alkaline phosphatase and standard bicarbonate; serum aluminium and magnesium were measured every 3rd month. Bone mineral density of the vertebral bodies L2-L4 and the femoral neck was evaluated at the start and at the end of the study.

Laboratory methods

Intact PTH was measured by a two-site immunoradiometric assay (Allegro, Nichols Institute, USA). The normal level in our laboratory is less than 53 pg/ml. The intra-assay variation was 3%, and the interassay 6%. Plasma iCa was measured by a calcium ion electrode (Radiometer, Copenhagen, Denmark) and plasma P by an enzymatic calorimetric method (Sera-pak inorganic phosphorus kit, Ames Division, Miles Ltd., England). Serum aluminium was determined by electrothermal atomic absorption spectrometry and serum magnesium by flameless photometry. All other parameters were analysed by standard laboratory techniques.

Bone mineral density was assessed by dual-energy X-ray...
Table 1. Number of intercurrent hypercalcaemia episodes per 100 treatment weeks

<table>
<thead>
<tr>
<th>Calcium Level</th>
<th>Episodes per 100 Treatment Weeks</th>
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<tr>
<td>iCa &lt;1.55 mmol/l</td>
<td>0.93</td>
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<tr>
<td>1.55 &lt;iCa &lt;1.65 mmol/l</td>
<td>0.07</td>
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<tr>
<td>iCa ≥1.65 mmol/l</td>
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absorptiometry (DEXA) using a Norland 2600 scanner at the levels of lumbar spine L2-L4 and femoral neck. The mineral concentration of the examined bone regions was determined by comparison of the scans with a standardized model of a defined mineral concentration. Calibration was performed daily. The results are expressed in absolute values (g/cm²) and in deviation in percent from the mean of age- and sex-matched normal subjects. Coefficients of variation were 1.0 and 1.2% for lumbar spine and femoral neck measurements respectively.

Statistical analysis

All descriptive data are expressed as mean ± SEM or median/range. Comparison to baseline values were performed using Student’s t-test for paired samples or Wilcoxon’s matched-pairs test (Statistica for Windows, Statsoft Inc. 1993).

Results

Plasma ionized calcium and phosphate

One week after switching from dialysate calcium 1.75 mmol/l to 1.35 mmol/l, mean plasma iCa decreased slightly, but significantly from 1.26 ± 0.01 to 1.23 ± 0.01 mmol/l (P<0.05). From the second week and onwards, however, basal levels were restored and maintained stable (Figure 1). The number of hypercalcaemic events were few and are displayed in Table 1. The elevated iCa levels normalized in all affected subjects within a few days, when the doses of calcium carbonate and/or alfalcaldol were reduced.

Mean plasma P was significantly reduced from 1.65 ± 0.06 mmol/l at baseline to 1.37 ± 0.06 mmol/l after 10 weeks of treatment with the dialysate calcium concentration of 1.35 mmol/l (P<0.01). Thereafter mean plasma P increased gradually to a level not significantly different from baseline (Figure 1).

Plasma PTH levels

One week after lowering the dialysate calcium from 1.75 to 1.35 mmol/l, the median PTH increased significantly from 80 to 135 pg/ml (P<0.01), as shown in Figure 1. After the second week, however, median
High-normal calcium (1.35 mmol/l) dialysate in patients on CAPD

PTH was again suppressed to 101 pg/ml and after another 8 weeks to 80 pg/ml. From the second week and until the end of the study, the PTH levels were not significantly different from baseline. Before switching to the dialysate calcium of 1.35 mmol/l, 10 patients had PTH levels greater than 200 pg/ml (PTH range 205–1050) and 12 patients had PTH levels less than 53 pg/ml; at the end of the study the number of patients with iPTH > 200 pg/ml was reduced to five (PTH range 225–390), whereas the number of patients with iPTH levels less than 53 pg/ml was nine. Only in two patients with intermittent severe hyperphosphataemia did initial PTH levels increase by a factor > 2 during the study period.

Phosphate binders and alfacalcidol

After switching from a dialysate calcium concentration of 1.75 to 1.35 mmol/l, the median dosage of calcium carbonate was increased significantly from 3 g/day (range 0–12) to 4 g/day after 1 week (range 0–15) and to 4.5 g/day after 2 weeks (range 1.5–15) (P<0.01). From week 24 and onwards, however, the doses were again reduced to levels not significantly different from baseline (Figure 1).

Five patients required treatment with aluminium aminocacetate for isolated episodes and four patients for repeated episodes of hyperphosphataemia and/or hypercalcaemia.

The median dosage of alfacalcidol was increased significantly from the pre-study levels of 0 μg/week (range 0–6) to 1–2 μg/week (range 0–12) from the 3rd week of the study (P<0.01) and until weeks 28–32, at which time median dosage was temporarily reduced to the pre-study level. From week 36 and throughout the rest of the study, however, the dosage was again significantly increased to 1–2 μg/week (range 0–8) (Figure 1). Before switching from dialysate Ca 1.75 to 1.35 mmol/l, alfacalcidol treatment was received by 38% of the patients as compared to 58% after 1 year of treatment with dialysate Ca 1.35 mmol/l.

Alkaline phosphatase, hydrogen bicarbonate, magnesium, and aluminium

The pre-study median activity of alkaline phosphatases and mean levels of hydrogen bicarbonate and magnesium were normal and remained unchanged during the study period. The basal median serum concentration of aluminium was not elevated and remained unchanged. The pre- and post-study levels are shown in Table 2.

Bone mineral density

The mean values of bone mineral density (expressed in g/cm² and in deviation in percentage from the mean of age- and sex-matched normal subjects) at the level of L2–L4 and at the femoral neck before and after the 48-week study period are shown in Table 3. Only patients who completed the study were re-scanned. Pre-study bone mineral density did not differ from that of age- and sex-matched controls, nor were there any significant differences between pre- and post-study levels.

Discussion

The current study showed that when dialysing with a high-normal Ca concentration (1.35 mmol/l) in patients on CAPD treatment, high-normal plasma iCa and near-normal plasma P levels could be readily achieved. The initial increase of PTH observed after switching from dialysate calcium 1.75–1.35 mmol/l seemed to be related to the initial decrease of plasma iCa. Accordingly, as soon as iCa was stabilized at high-normal levels due to increased dosage of calcium carbonate and alfacalcidol, PTH was again suppressed to baseline. The median dosage of alfacalcidol needed to keep PTH within acceptable limits was surprisingly low, only 1–2 μg/week (range 0–12). A possible explanation for this, however, might well be that plasma P and iCa levels were well-controlled by the calcium carbonate treatment. As compared to treatment with a dialysate calcium of 1.75 mmol/l, the tolerance to calcium carbonate and alfacalcidol was significantly improved. Furthermore, using a dialysate Ca of 1.35 mmol/l made it possible to induce a controlled rise of iPTH levels to 80–100 pg/ml by a temporary discontinuation of alfacalcidol treatment and/or a reduction of Ca carbonate dosage, when PTH

| Table 2. Pre- and post-study levels of plasma alkaline phosphatase, plasma hydrogen bicarbonate, serum magnesium, and serum aluminium |
|---------------------------------|-----------------|-----------------|
|                                  | Pre-study       | Post-study      |
| Alkaline phosphatase (U/l)       | 163 (89–667)    | 165 (103–415)   |
| Hydrogen bicarbonate (mmol/l)    | 23.8±0.9        | 25.6±0.6        |
| Magnesium (mmol/l)               | 0.95±0.03       | 0.89±0.02       |
| Aluminium (μmol/l)               | 0.4 (0.2–2.5)   | 0.5 (0.19–1.41) |

Values are given as median, range or mean±SEM.

| Table 3. Pre- and post-study bone mineral density (BMD) of the vertebral bodies L2–L4 and the femoral neck expressed in absolute values (g/cm²) and in deviation in percentage from the mean of age- and sex-matched normal subjects |
|---------------------------------|-----------------|-----------------|
|                                  | Pre-study       | Post-study      |
| L2–L4                           |                 |                 |
| BMD                             | 1.051±0.037     | 1.111±0.049     |
| % age-matched                   | 100.4±4.6       | (n=33)           |
| Femoral neck                    |                 |                 |
| BMD                             | 0.816±0.036     | 0.810±0.042     |
| % age-matched                   | 99.2±5.8        | (n=20)           |

Values are given as mean±SEM. Pre- and post-study levels are compared by a paired t-test. Only patients who completed the study were re-scanned.
became suppressed to levels below the upper normal limit. The intention of treatment was to maintain PTH within a range of 1.5–2.5 times the upper normal limit for non-uraemic subjects, which according to previous studies comparing bone histology with PTH measurements is the level required to maintain normal bone remodelling in uraemic patients [17,18]. Since no bone histology was available in the present study, it is not possible to prove that the PTH levels obtained in this study actually were optimal. The data on bone mineral density and alkaline phosphatase activity, however, indicate that bone remodelling in general was not accelerated. Neither did adynamic bone disease seem to be highly prevalent, as the incidence of hypercalcaemia was low [18]. Low bone turnover, though, is likely to be present in at least two subjects with repeated episodes of hypercalcaemia, since these two also showed suppressed PTH levels in spite of no alfalcaldol treatment.

The relatively high number of patients (n=9) with PTH values <53 pg/ml at the end of the study reflects the fact that PTH levels were regulated in retrospect according to the routine PTH measurements, which were only performed every 3rd month. As overshuppression of PTH is reversible, however, we do not consider this delay to be of clinical significance.

With a single exception [11], most other reports on peritoneal dialysis fluids with a lower Ca concentration have shown improved tolerance to calcium-containing P binders and/or vitamin D metabolites without an increased incidence of hypercalcaemia, as well as a reduced need for Al-containing P binders. However, there is no consensus on what dialysate Ca concentration is the optimal for the majority of patients on CAPD. Although several studies on a dialysate Ca of 1.25 mmol/l have shown that it is safe as regards control of PTH in compliant, well-monitored patients [6–9,11], other studies have clearly demonstrated a deterioration of the secondary hyperparathyroidism when using a dialysate Ca concentration of 1.25 mmol/l [3,12–13,15–16]. In two of the latter studies, hypocalcaemia developed after switching to low-Ca dialysate because of a delay in dosage adjustments [3,13]. Further, in the paper by Honkanen et al. [13] very high plasma P levels were described during the initial 8 weeks of study. In the study by Rotellar et al. [12] PTH increased after 1 year, and in the study of Piraino et al. [16] PTH increased after 10 months of dialysis with a dialysate Ca of 1.25 mmol/l. In both studies there was a tendency for plasma P levels to increase, but the changes were not statistically significant. No information, however, was available on the variations of plasma concentrations of Ca and P during the study periods. The short-term study by Pagliari [15] found an initial increase of PTH secondary to a decrease in serum iCa levels, which also was found in the present and other studies [8]. As demonstrated in our study, however, this stimulatory effect on PTH secretion could rapidly be reversed, when the doses of calcium carbonate and alfalcaldol were adjusted. The importance of close monitoring of the patients is clearly demonstrated by a multicentre randomized study comparing a dialysate Ca concentration of 1.00 mmol/l with that of 1.75 mmol/l in non-selected CAPD patients [9]. The authors showed that this very low dialysate Ca concentration was completely safe when the patients were followed closely and the doses of calcium carbonate adjusted according to blood levels. Utilization of solutions with such low Ca concentrations, however, put the patient into a permanent negative calcium balance [19], and therefore very close attention must be given to the plasma Ca and P levels and to the compliance with oral calcium carbonate and vitamin D therapy. As in the present study, Carozzi et al. [8] and Hercz et al. [20] took advantage of the lower calcium (1.25 and 1.00 mmol/l respectively) dialysates to induce a controlled rise of PTH in patients with suppressed PTH levels.

Our finding of a normal and unchanged mean bone mineral density of the lumbar spine in CAPD patients after treatment for 1 year with the reduced dialysate Ca concentration is in accordance with the reports of Weinreich et al. [9] using dialysate Ca 1.00 mmol/l and Cheng et al. [7] using dialysate Ca 1.25 mmol/l. According to Johnson et al. [21] DEXA bone densitometry is a reliable indicator of osteopenia in CAPD patients. Its usefulness, however, in detecting renal osteodystrophy is limited because of the heterogeneity of this condition. Biochemical parameters do not reliably predict bone mineral density measurements, but patients with radiographic evidence of hyperparathyroid bone disease may show increased bone mineral density.

The concentrations of magnesium (Mg) and lactate in the dialysis fluid were unchanged (Mg 0.25 mmol/l; lactate 40 mmol/l) after switching to dialysate Ca 1.35 mmol/l, and the mean plasma concentrations of Mg and standard bicarbonate remained unchanged and within reference limits (Mg 0.67–0.93 mmol/l; standard bicarbonate 22.5–26.9 mmol/l) during the study period. Only two patients showed subnormal Mg values at inclusion and throughout the study (minimum value 0.50 mmol/l). Both suffered from protein-malnutrition. Twelve patients occasionally showed marginally elevated plasma standard bicarbonate concentrations (occasional standard bicarbonate levels >29 mmol/l was only seen in three patients). Therefore we cannot confirm the findings by Ejaaz et al. [22] that the majority of CAPD patients (21 of 33) treated with a dialysate Mg concentration of 0.25 mmol/l developed hypomagnesaemia after a mean of 8 months, nor the findings by Tattersall et al. [23], who found that of 43 patients treated for 4 months with a dialysate Mg concentration of 0.25 mmol/l and a lactate concentration of 40 mmol/l, seven patients developed hyponomagnesaemia and 17 patients alkalosis. Five of the alkalotic patients were reported to have bicarbonate levels as high as 35–40 mmol/l. In conclusion, a reduction of the Ca concentration in the dialysate has proved to be useful in CAPD patients, since it allowed larger doses of Ca-containing P binders and reduced the need for aluminium-
High-normal calcium (1.35 mmol/l) dialysate in patients on CAPD containing P binders, allowed higher doses of vitamin D metabolites to be used in order to suppress elevated PTH levels, and induced a controlled increase of PTH levels in patients where it had been suppressed too much. However, the lower the dialysate Ca concentration, the more close follow-up is required. The present study demonstrated that when using a high-normal dialysate Ca concentration of 1.35 mmol/l in non-selected patients on CAPD treatment, high-normal plasma iCa and near-normal plasma P levels could be readily achieved with a minimal risk of incidental hypercalcaemia despite use of calcium carbonate as the main P binder. As a consequence of the tight Ca and P regulation, minimal doses of alfacalcidol were required to keep PTH within acceptable limits. We recommend this dialysate Ca concentration as a first choice therapy for the majority of patients starting on CAPD treatment. For patients with special problems, e.g. hypercalcaemia without elevated PTH, or symtomatic secondary hyperparathyroidism with severely elevated PTH levels, however, lower dialysate calcium concentrations should be considered.

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