Safety and efficacy of pulse and daily calcitriol in patients on CAPD: a randomized trial

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Abstract

Background. Calcitriol therapy is the mainstay of therapy for the treatment of secondary hyperparathyroidism. Oral administration of calcitriol is necessary in CAPD patients, but no studies have directly compared different routes of administration in this patient population.

Methods. To determine if the peak serum calcitriol level (pulse therapy) is more important than the total delivered dose, we randomized CAPD patients with mild to moderate secondary hyperparathyroidism to receive either pulse (3.0 μg twice a week, n = 10) or daily (0.75 μg a day, n = 8) oral calcitriol in comparable weekly doses. The main comparison was the rate of decline of serum intact parathyroid hormone (PTH) levels to reach the desired end-point of 100 pg/ml. The patients were dialysed with low-calcium dialysate and received only calcium-containing phosphate binders.

Results. Pharmacokinetic analysis after a single dose of 3.0 μg (pulse) vs 0.75 μg (daily) revealed 1,25(OH)2-vitamin D levels to be higher in the pulse group at 3 and 6 h, but equivalent by 12 h. The area under the curve for 1 week of daily and 1 week of pulse therapy was equal. The patients in the 2 arms had equivalent serum levels of PTH (pulse = 562 ± 291 vs daily = 454 ± 113 pg/ml), calcium (pulse = 2.32 ± 0.20 vs daily = 2.32 ± 0.12 mmol/l) and phosphorus (pulse = 1.32 ± 0.52 vs daily = 1.35 ± 0.26 mmol/l). The time required for the PTH to decrease to 100 pg/ml and the rate of decline in PTH were similar (time: pulse = 14.2 ± 6.8 weeks, daily = 12.2 ± 7 weeks; rate: pulse = 7.4 ± 4.2 vs daily = 8.4 ± 4.2% PTH/week; P = NS). The serum calcium increased similarly in both groups. Hypercalcaemia (> 2.9 mmol/l) was rare (pulse = 3, daily = 2 episodes).

Conclusions. This study demonstrates that pulse and daily calcitriol are similarly effective and safe for the treatment of mild to moderate secondary hyperparathyroidism in CAPD patients despite higher peak levels of 1,25(OH)2-vitamin D with pulse therapy.

Key words: calcitriol; calcium balance; CAPD; dialysis; hyperparathyroidism; renal osteodystrophy

Introduction

Bone disease is a common cause of morbidity in patients with chronic renal failure undergoing dialytic therapy. In patients receiving continuous ambulatory peritoneal dialysis (CAPD), osteitis fibrosa cystica due to secondary hyperparathyroidism is the histological finding in 13 to 66% of biopsies [1,2]. One of the most effective and physiological methods of reducing serum parathyroid hormone concentration (PTH) is treatment with calcitriol, which directly inhibits the transcription of pre-pro-PTH [3] and normalizes bone histology [4,5]. Initially, calcitriol administered orally was utilized for the treatment of secondary hyperparathyroidism [6–8]. However, hypercalcaemia was common, presumably because of the direct action of calcitriol on the gastrointestinal absorption of calcium [9]. To overcome this effect, the intravenous administration of calcitriol became widely utilized for the treatment of secondary hyperparathyroidism in haemodialysis patients [11–13]. In addition to the relative decrease in calcium absorption from the gut, the intravenous administration of calcitriol had the theoretical advantage of higher peak serum levels, providing enhanced end-organ effect at the level of the parathyroid gland. However, recent randomized controlled trials have demonstrated that intravenous and oral calcitriol given in thrice weekly ‘pulse’ doses are equally efficacious for the treatment of secondary hyperparathyroidism in haemodialysis patients, despite greater peak serum levels with the intravenous formulation [14–16].

In CAPD patients, the intravenous administration of calcitriol is not practical. Several recent studies have utilized high pulse doses of calcitriol administered...
orally one to three times per week. The pulse calcitriol effectively suppressed PTH, but hypercalcaemia was common [22–25]. However, no direct comparisons of the pulse administration of calcitriol with the daily administration of calcitriol has been performed in CAPD patients. CAPD patients may be at a greater risk for hypercalcaemia than haemodialysis patients because of the greater overall positive calcium balance [26], and therefore alternatives to the pulse regimen are needed. The purpose of the present study was (1) to determine whether pulse calcitriol is superior to daily calcitriol for the treatment of secondary hyperparathyroidism when given in comparable weekly oral doses, and (2) to determine the safety of oral calcitriol in CAPD patients when used in conjunction with low-calcium dialysate. The pharmacokinetics of the pulse and daily regimens were compared to determine the effect of peak serum levels vs total serum levels on the suppression of PTH. In addition the effect of the two regimens on calcium balance was evaluated.

Subjects and methods

Patient selection

All patients undergoing CAPD at Indiana University Hospital or Richard L. Roudebush Veterans Administration Hospital between January 1993 and January 1995 and willing to give informed consent were eligible. The study was approved by the Institutional Review Board at each hospital. Inclusion criteria were age greater than 18 years, on CAPD for at least 3 months, and secondary hyperparathyroidism. The latter was defined by an intact PTH of at least 200 pg/ml (normal up to 65 pg/ml) that was stable or rising since the initiation of CAPD, together with an elevated serum total alkaline phosphatase concentration and/or radiographic evidence of subperiosteal bone resorption. Aluminum-associated bone disease was excluded by a desferrioxamine (DFO) stimulation test with a delta serum aluminium of less than 3700 mmol/l in any patient with a history of ingestion of aluminium-containing medications. Patients were also excluded if they had a serum calcium concentration persistently greater than 2.5 mmol/l or serum phosphorus concentration persistently greater than 2.3 mmol/l, were currently receiving medications known to interfere with vitamin D metabolism or bone turnover such as steroids or anticonvulsants, or were non-compliant with dialysis prescription.

Of the 120 CAPD patients screened for enrollment, 42 patients had an elevated serum PTH concentration. Of these, 25 met all the inclusion/exclusion criteria. Four patients refused the study, the other 21 were enrolled. One of these patients decided not to complete the study after only 2 weeks for personal reasons and her position was re-randomized. All calcitriol supplements were stopped at least 1 month prior to the start of the study.

Study design

Patients were randomized by random number generation to receive oral calcitriol administered in a once daily (0.75 μg/day) dose vs a twice weekly pulse (3.0 μg) dose, taken approximately 3 h after the evening meal. The dose of the daily oral therapy was chosen to be comparable to the dose received by CAPD patients in previous studies [8,25]. The pulse dose was chosen to provide a similar total weekly dose as the daily therapy. Given the limitation of available tablet sizes, the weekly dose was 5.25 μg for the daily arm and 6 μg for the pulse arm. Patients in the daily arm were started on 0.25 μg daily with the dose increased by 0.25 μg per day every 2 weeks, until the maximum dose of 0.75 μg was achieved. Patients in the pulse arm were started on 1.0 μg administered twice weekly, with the dose increased by 1.0 μg per dose every 2 weeks, until the maximum dose of 3.0 μg twice weekly was achieved. Thus the maximum dose in each arm was begun on week 4 for all patients. All patients received the same lot number of Rocaltrol® (provided by Roche Laboratories, Nutley, NJ). The dose was continued until the study end-point of an intact PTH of 100 pg/ml was achieved. Compliance was monitored by tablet counts at each clinic visit, with a count discrepancy of >10% on two visits criteria for removal from the study. Upon completion of the study, the patients answered a questionnaire as to their preference of the frequency of administration.

Beginning at least 4 weeks prior to the administration of calcitriol, each patient was switched to a low-calcium (1.25 mmol/l) dialysate and calcium acetate as a phosphate binder. The dose of calcium acetate was adjusted as needed to keep the serum phosphorus below 1.94 mmol/l. If patients could not tolerate calcium acetate, they were switched to calcium carbonate. The mean elemental calcium content of the calcium-containing phosphate binders were calculated at each clinic visit. To confirm a steady state, at least two subsequent serum determinations for calcium, phosphorus and PTH concentration were done after these changes and before enrollment. Patients were counselled on a standard renal diet of 800 mg phosphorus, 2 g sodium, 3 g potassium, 1.2 g/kg protein diet by renal dietitians. The patients completed a 3-day food diary at baseline and at 3 months, and a monthly food frequency survey.

All values for calcium were corrected to a normal serum albumin of 35 g/l (lower limit of normal for our hospital) based on the patient’s albumin. If hypercalcaemia (defined as serum calcium >2.9 mmol/l[6,7]) developed, the dose of calcitriol was withheld for 3 days. The serum calcium was repeated, and if ≤2.9 mmol/l, and the calcium × phosphorus product <70, the calcitriol was restarted at the previous dose and the dose of calcium containing phosphate binder was reduced. If hypercalcaemia >2.9 mmol/l occurred on two consecutive determinations, the calcitriol was withheld until the calcium concentration normalized and the calcitriol was restarted at a dosage 0.25 μg less per day for the daily dose or 1.0 μg less per dose for the pulse arm. If hyperphosphataemia (defined as serum phosphorus greater than 2.3 mmol/l) or a calcium × phosphorus product >70 developed, 30 cc of aluminium hydroxide was given with each meal for 3 days. The serum calcium and phosphorus was repeated and if the phosphorus was ≤2.3 mmol/l and the product <70, the aluminium was discontinued and the calcium binder restarted at a higher dose.

Serum samples were taken at baseline, 2, 4, 6, 8, 12, 16, 20, and 24 weeks, drawn 12–18 h after the last dose of either daily or pulse calcitriol. The serum was collected and frozen at −70°C until assayed. Serum was analysed for chem-17 and CBC at baseline, 1.25(OH)2-vitamin D, PTH, calcium, phosphorus, albumin, and alkaline phosphatase at each time point, and tartrate-resistant alkaline phosphatase and osteocalcin every 4 weeks. The chem-17, calcium, albumin, phosphorus, and total alkaline phosphatase were measured on a Roche MIRA autoanalyser. The intact PTH was assayed utilizing an immunoradiometric assay (Nichols Institute, Los
Six patients did not complete the study: one received a transplant at 8 weeks (pulse), one underwent surgery and could not take oral medications for a prolonged period at 10 weeks (daily), and a third patient was non-compliant with erroneous pill counts and no rise in calcitriol levels and was dropped from the study at 16 weeks (daily). Eighteen patients completed the study, 10 in the pulse group and 8 in the daily group. The patient characteristics are described in Table 1 and the baseline biochemical values in Table 2. There was no difference between the two groups in baseline demographic or biochemical parameters. Inclusion of the three patients who were randomized but did not complete the study did not alter these characteristics. Eight patients were changed from a 1.75-mmol/l calcium dialysate 78±94 days (range = 21–284) prior to beginning the study. Eight patients had previously received calcitriol therapy, with the maximum dose of 0.25 μg/day. The medication was stopped 96±112 days (range = 31–372) prior to initiation of the protocol. Four patients were changed from calcium carbonate to calcium acetate. The serum calcium, phosphorus, and PTH concentrations (at least two determinations of each) remained stable in the 60 days prior to initiation of the study in all patients, regardless of whether or not any medication or dialysate changes were made.

All patients had serum concentrations of PTH of at least four times the upper limits of normal (65 pg/ml) indicative of mild to moderate secondary hyperparathyroidism. The seven patients who underwent bone biopsy at the start of the study had an elevated bone formation rate (mean 37.5±9.9%/year, range 14.8–69.9%/year, compared to normals 7.6±3.2%/year for blacks [29]). The eroded surface was also increased (mean = 7.8±2.7, range 4.2–11.3%/year, compared to markers of bone metabolism. Patient preferences in the exit survey were compared using Fisher's Exact test. All analysis were done with SPSS (SPSS 6.1 for Windows, SPSS, Inc., Chicago, IL 1994) and results are expressed as mean±SD.

Results

Twenty-one patients were enrolled in the study. Three patients did not complete the study: one received a transplant at 8 weeks (pulse), one underwent surgery and could not take oral medications for a prolonged period at 10 weeks (daily), and a third patient was non-compliant with erroneous pill counts and no rise in calcitriol levels and was dropped from the study at 16 weeks (daily). Eighteen patients completed the study, 10 in the pulse group and 8 in the daily group. The patient characteristics are described in Table 1 and the baseline biochemical values in Table 2. There was no difference between the two groups in baseline demographic or biochemical parameters. Inclusion of the three patients who were randomized but did not complete the study did not alter these characteristics.

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Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pulse (n = 10)</th>
<th>Daily (n = 8)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>50.6±15.9</td>
<td>41.2±17.8</td>
</tr>
<tr>
<td>Male/female</td>
<td>5/5</td>
<td>4/4</td>
</tr>
<tr>
<td>Black/White</td>
<td>9/1</td>
<td>5/3</td>
</tr>
<tr>
<td>Months on dialysis</td>
<td>12.8±8.9</td>
<td>21.0±11.5</td>
</tr>
<tr>
<td>Diabetic patients</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Previous calcitriol</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Previous transplant</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Taking oestrogen</td>
<td>2/5</td>
<td>1/4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.4±15.5</td>
<td>70.6±10.0</td>
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</table>

Values are expressed as mean±standard deviation. There were no significant differences in any of the variables between the two groups.
During the course of the study and similar in both hyperphosphataemia (>0.12 mmol/l) and 0.037 to 2.65 ± 0.027 mmol/l in the pulse group and 0.037 ± 0.027 mmol/l/weeks in the daily group (P = NS). The serum phosphorus was not altered during the course of the study and similar in both groups (pulse = 1.74 ± 0.48 to 1.68 ± 0.58 mmol/l; daily = 1.74 ± 0.48 to 1.52 ± 0.29 mmol/l, P = NS). Hypercalcaemia (>2.9 mmol/l), requiring holding the calcitriol for 3 days, occurred three times in the pulse group (three different patients, or 3/65 (4.6%) determinations) and twice in the daily group (1 patient, or 2/47 (4.2%) determinations). All of these episodes of hypercalcaemia >2.9 mmol/l occurred at the end-point or the visit before the end-point, and all were associated with a PTH concentration of <150 pg/ml. Twelve other episodes of mild hypercalcaemia (>2.6 mmol/l, the upper limit of normal for assay) occurred seven times in the pulse group (four different patients) and six times in the daily group (four different patients). One of these patients was given aluminium hydroxide for 3 days for an elevated calcium × phosphorus product, but all the other episodes of mild hypercalcaemia occurred in the presence of a calcium × phosphorus product <70. No other patients required aluminium-containing phosphate binders, and no episodes of hyperphosphataemia (>2.3 mmol/l) were observed.

### Table 2. Baseline serum laboratory values, dietary and phosphate binder use

<table>
<thead>
<tr>
<th></th>
<th>Pulse (n=10)</th>
<th>Daily (n=80)</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>562 ±291</td>
<td>454±113</td>
<td>&lt;65</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.32 ±0.20</td>
<td>2.32±0.12</td>
<td>2.10–2.64</td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>1.71 ±0.52</td>
<td>1.74±0.26</td>
<td>0.81–1.58</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU)</td>
<td>102 ±51</td>
<td>81±19</td>
<td>25–125</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>34 ±5</td>
<td>35±3</td>
<td>35–50</td>
</tr>
<tr>
<td>Total CO₂ (mM/l)</td>
<td>26.4 ±2.0</td>
<td>26.6±3.2</td>
<td>22–26</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>30.1 ±4.8</td>
<td>30.6±3.4</td>
<td>40–54</td>
</tr>
<tr>
<td>Blood urea nitrogen (mM/l)</td>
<td>21 ±6</td>
<td>18±5</td>
<td>1.8–7.1</td>
</tr>
<tr>
<td>Creatinine (mM/l)</td>
<td>1078 ±415</td>
<td>1132±327</td>
<td>71–123</td>
</tr>
<tr>
<td>1,25(OH)₂-vitamin D (pg/ml)</td>
<td>17.5 ±9.2</td>
<td>19.7±14.6</td>
<td>9.6–56</td>
</tr>
<tr>
<td>Dietary calcium intake (mg/day)</td>
<td>476 ±129</td>
<td>328±92</td>
<td>50–200</td>
</tr>
<tr>
<td>Dietary phosphorus intake (mg/day)</td>
<td>768 ±367</td>
<td>785±77</td>
<td>60–200</td>
</tr>
<tr>
<td>Phosphate binder elemental</td>
<td>1285 ±667</td>
<td>951±534</td>
<td></td>
</tr>
<tr>
<td>calcium content (mg/day)</td>
<td></td>
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</table>

Values are expressed as mean ± standard deviation. There were no significant differences in any of the variables between the two groups.

Because of the variable initial PTH concentrations and differing time to the stated end-point PTH concentration of 100 pg/ml, the decline in PTH was expressed as % change PTH/time, as described in the methods. The % change PTH/time was 7.4 ± 4.2%/week in the pulse group and 8.4 ± 4.2%/week in the daily group (P = NS). The weeks of calcitriol therapy required to reach the PTH end-point of 100 pg/ml was not different between the two groups (pulse = 14.2 ± 6.8 weeks, daily = 12.2 ± 7.0 weeks), and both groups had similar PTH value at end-point (pulse = 86.9 ± 24.7 pg/ml, daily = 90.2 ± 32.3 pg/ml). The response of each patient is shown in Figure 1. Analysis of these results indicates that it would require 275 subjects per group to have 80% power to find a difference of this magnitude at the 0.05 significance level, suggesting that our inability to find a difference reflects a true lack of difference in therapy.

The corrected serum calcium increased similarly in both groups from baseline to end-point. The corrected serum calcium increased from 2.32 ±0.20 to 2.59±0.25 mmol/l in the pulse group and 2.32 ±0.12 to 2.65±0.30 mmol/l in the daily group (P<0.01, baseline vs end-point). The mean change in corrected calcium ([calcium at end-point-calcium at start]/weeks to endpoint) was 0.025 ±0.022 in the pulse group and 0.037 ±0.027 mmol/l/weeks in the daily group (P = NS).
Thus, no calcitriol dose reduction was required in any patient.

There was no difference in the monthly dietary calcium or phosphorus intake, or the elemental calcium content of phosphorus binders between the two groups (Table 2), nor was there a change during the study (data not shown). No patient showed evidence of protein-calorie malnutrition by food diaries. There was no correlation between the serum calcium, phosphorus, alkaline phosphatase, and 1,25(OH)\_2-vitamin D serum levels and % change PTH/time. However, there was a correlation between the calcium and simultaneous PTH values (\(P < 0.001, r = -0.30\)). There was no change in the serum osteocalcin or tartrate acid phosphatase during the course of the study and no correlation with the % change PTH/time (data not shown).

The initial pharmacokinetic studies performed in the General Clinical Research Center utilizing the maximum administered dose of 3.0 \(\mu\)g for the pulse group (\(n = 4\)) and 0.75 \(\mu\)g in the daily group (\(n = 5\)) demonstrated equivalent basal 1,25(OH)\_2-vitamin D levels (pulse = 14.5 ± 1.4 pg/ml, daily = 11.5 ± 6.3 pg/ml), but significantly elevated 1,25(OH)\_2-vitamin D levels at 3 and 6 h in the pulse group compared to the daily group (3 h, pulse = 72.9 ± 24.7 pg/ml, daily 31.7 ± 12.9 pg/ml; 6 h, pulse = 63.8 ± 20.2 pg/ml, daily = 37.9 ± 8.5 pg/ml; both \(P < 0.05\), Figure 2). There was no statistical difference in the calcitriol levels at 24 h, but the level was still above baseline in both groups, indicating a nadir had not yet been reached. Thus the true area under the curve could not be determined. However, in pharmacokinetic studies of 1 week duration in a single patient, the area under the curve was equivalent in the pulse vs daily route of administration (36 vs 35 ng/ml/week; Figure 3). The serum 1,25(OH)\_2-vitamin D level increased significantly in both groups from baseline to end-point with a greater rise observed in the pulse group (18.0 ± 9.6 to 85.1 ± 49.9 pg/ml in the pulse group and 19.7 ± 14.6 to 42.5 ± 13.7 pg/ml, \(P < 0.05\) for comparison between pulse and daily, \(P < 0.02\) for comparison between baseline and end-point). The maximum 1,25(OH)\_2-vitamin D level achieved by each patient was also greater in the pulse group (76.9 ± 49.2 pg/ml) compared to the daily group (48.3 ± 16.3 pg/ml, \(P < 0.05\)). Therefore, despite greater peak serum levels in the pulse group compared to the daily group, PTH was equally suppressed. An exit interview indicated patients had no preference of pulse vs daily routes of administration.

The total body calcium measured by DEXA increased similarly in both groups (pulse = 2956 ± 791 to 3060 ± 788 g, \(n = 7\); daily = 2868 ± 518 to 2913 ± 550 g, \(n = 5\); \(P < 0.04\), baseline compared to end-point for each group). Unfortunately these studies do not differentiate soft-tissue from bone calcium. However, bone densitometry of hips, spine, and radius were unchanged in both groups.

**Discussion**

The results of this randomized study demonstrate that the pulse and daily routes of administration of calcitriol, when administered in comparable total weekly doses are similarly efficacious in suppressing PTH in patients on CAPD. There was no difference in dietary calcium or phosphorus intake or phosphate binder use in the two treatment arms, and no dose reductions in calcitriol were required. Pharmacological evaluation confirmed that the two dosing regimens gave similar AUC, despite higher peak serum concentrations of calcitriol in the pulse regimen. To minimize the incid-
ence of hypercalcaemia, the calcitriol was administered at night and low-calcium dialysate was utilized. As a result, hypercalcaemia was a rare finding compared to previous studies [22–25]. Positive calcium balance was achieved despite the low-calcium dialysate. These results demonstrate, for the first time in CAPD patients, that the total amount of calcitriol administered is more important than the peak serum levels in suppressing PTH secretion. Furthermore, not only is daily and pulse calcitriol efficacious in CAPD patients for the treatment of secondary hyperparathyroidism, but, when administered at night in conjunction with a low-calcium dialysate, is a safe therapy at doses previously found to cause hypercalcaemia. These results confirm those found by Herrmann et al. in a similar study of haemodialysis patients, but with less frequent hypercalcaemia and hyperphosphataemia [21].

The initial studies evaluating oral calcitriol therapy were in HD patients. These studies found 0.5–1.0 µg/day of oral calcitriol effective in decreasing the serum PTH, but one-third to one-half of patients had at least one episode of hypercalcaemia (>2.9 mmol/l; [6,7]). In paediatric CAPD patients, oral calcitriol (mean dose 0.61 ± 0.37 µg/day) significantly decreased the serum PTH after 12 months of treatment but 18 episodes of hypercalcaemia occurred in 11 patients [8]. The frequent occurrence of hypercalcaemia prompted the study of other administrative routes. Slatapolsky et al. first demonstrated the effectiveness of up to 4.0 µg of calcitriol given intravenously thrice weekly to haemodialysis patients in lowering serum PTH [11], and Andress et al. demonstrated coincident improvement in bone histology [12]. Sprague and Moe demonstrated that even lower doses of intravenous calcitriol are also effective in reducing serum PTH [13]. Theoretically the intravenous route of administration would bypass some of the direct effect of calcitriol on calcium absorption in the gut [9], while increasing the delivered dose of calcitriol to target organs such as the parathyroid glands. Studies in rats supported a greater effect with greater serum levels [30].

Oral calcitriol administered in large, intermittent pulse doses was first evaluated as an alternative to the intravenous formulation in Japan. A study in 29 haemodialysis patients demonstrated a 41% decrease in serum PTH concentration over a 6-month period with pulse therapy of 4.0 µg calcitriol administered orally twice weekly [17,18]. Recent prospective, randomized trials have directly compared pulse intravenous and pulse oral administration of calcitriol in haemodialysis patients and found equal efficacy, despite peak serum levels up to 10 times greater with the intravenous administration [14–16]. In contrast, Mazzafatto found the intravenous formulation to be superior to the pulse oral therapy, but used lower doses of calcitriol and had a rise in serum calcium only in the intravenous group [31]. Thus, in haemodialysis patients, intravenous and pulse oral calcitriol are equally effective in suppressing parathyroid hormone, providing a similar rise in serum calcium is observed.

In CAPD patients the intravenous use of calcitriol is impractical. Martin et al. [19] first utilized pulse oral calcitriol in five CAPD patients, administering 5 µg calcitriol orally, twice weekly. They demonstrated a 60% decline in serum PTH after 6 weeks of therapy, but hypercalcaemia required a dose reduction to 3 µg in one patient. Juergensen et al. [23] found oral calcitriol to be effective in the suppression of PTH in 38 of 43 CAPD patients studied, administering 5 µg calcitriol twice weekly for 1 year. However, hypercalcaemia was a problem in six patients, and several required aluminium-containing phosphate binders [23]. Scanziani et al. [22] followed 19 CAPD patients for 18 months, utilizing 0.5–4.0 µg three times weekly (mean maximum dose 1.21 ± 1.53 µg/dose). In order to control hypercalcaemia, patients required the use of magnesium-containing phosphate binders, and five patients required the use of dialysate containing no calcium [22]. Hypercalcaemia was an even greater problem in a study of 15 CAPD patients given only 0.5 µg twice weekly for 8 weeks [24]. These patients had a significant increase in their serum calcium and calcium × phosphorus product despite a pulse dose of only 0.5 µg twice weekly. The high incidence of hypercalcaemia probably reflected the inclusion of patients with previous hypercalcaemia in response to vitamin D therapy [24].

In the present study we found a low incidence of hypercalcaemia in both the pulse and daily calcitriol groups even with the exclusive use of calcium-containing phosphate binders. The serum calcium levels were measured within 18 h of administration of calcitriol, excluding unmeasured episodes of hypercalcaemia. This relatively low incidence of hypercalcaemia is probably due to the administration of calcitriol at night in conjunction with low-calcium dialysate. Schaefer et al. [20] directly compared the administration of calcitriol in the morning or late night in CAPD patients in a cross-over study. Eighty per cent of the patients developed hypercalcaemia when the calcitriol was administered in the morning, compared to 50% when it was administered at night [20].

Patients on CAPD may be more prone to the development of hypercalcaemia than patients on haemodialysis because of a net influx of calcium from dialysate to patients using standard (1.75 mmol/l) calcium dialysate concentrations [26]. In contrast, low-calcium dialysate (0.875 mmol/l) results in a net removal of calcium [32] and allows the use of higher quantities of calcium-containing phosphate binders with less incidence of hypercalcaemia. Thus, lower-calcium dialysate should be utilized in CAPD patients receiving calcitriol. Despite the use of low-calcium dialysate we still generated a net positive calcium balance, as demonstrated by the significant increase in total body calcium together with an increase in serum calcium concentration from baseline to end-point. Unfortunately, the measurement of total body calcium does not differentiate between soft-tissue and bone calcium, and no increase in bone density was observed. Therefore it is possible that some of the observed increase in total calcium...
body calcium was due to calcium deposits in soft tissue, reinforcing the need for careful monitoring of serum calcium concentration and calcium × phosphorus product in the administration of calcitriol therapy. It also raises the question of whether the calcium × phosphorus product should be much lower than the goal of 70 utilized in this study. This increase in total body calcium is most probably due to an increase in calcium absorption from the gastrointestinal tract or a decrease in the ability of bone to take up calcium. Kurz et al. [33] demonstrated the latter phenomenon in patients with adynamic or low-turnover bone disease.

Of interest is the finding that all the significant episodes of hypercalcaemia (≥2.9 mmol/l) occurred when the PTH concentration was under 150 pg/ml. At the initiation of the present study [1992], the inclusion criteria of an intact PTH of ≥200 pg/ml was thought to represent significant hyperparathyroidism, and the desired end-point PTH of 100 pg/ml consistent with normal bone turnover. However, recent large prospective studies evaluating bone histomorphometry in patients with end-stage renal disease have found that “normal” bone formation is observed at serum PTH concentrations between 100 and 450 pg/ml, with extreme variability [34,35]. The conclusion of these studies indicate that a PTH concentration of 200 pg/ml for haemodialysis patients and 300 pg/ml for peritoneal dialysis patients is predictive of normal bone turnover in approximately 80% of patients [34,35]. Our additional inclusion criteria of patients with either an elevated alkaline phosphatase and/or radiographic evidence of bone resorption ensured some degree of hyperparathyroidism, corroborated by the initial bone biopsies in seven randomly chosen patients. However, our desired end-point of 100 pg/ml may reflect lower than desired bone turnover, perhaps predisposing to hypercalcaemia. In an individual patient, the development of hypercalcaemia may indicate that the maximum buffering capacity of the patient’s bone has been reached. Given the relative poor predictive value of serum PTH in determining underlying bone histology, perhaps the ‘goal’ PTH should not be a set PTH value, but a PTH slightly higher than the PTH at which level hypercalcaemia persistently develops. What level of hypercalcaemia is optimal remains to be determined, given the coexistence of hyperphosphataemia and risk of metastatic calcifications in patients with ESRD. This poor correlation with PTH and bone turnover in end-stage renal disease indicates that multiple factors are involved in the pathogenesis of renal osteodystrophy, and calcitriol therapy must be individualized while further insight into the pathogenesis is obtained.

In conclusion, the frequency of administration of calcitriol to CAPD patients does not affect the ability of calcitriol to suppress PTH. These results, together with other recent studies [14,16,21], confirm that the route of administration of calcitriol (oral vs intravenous, and pulse vs daily) is not important in the treatment of secondary hyperparathyroidism. In addition, supraphysiological serum levels of 1,25(OH)₂-vitamin D are not necessary to suppress mild to moderate elevations of PTH, providing serum calcium and phosphorus concentrations are optimized. Finally, the present study demonstrates that relatively high daily doses of 1,25(OH)₂-vitamin D can be safely given to CAPD patients when utilized in conjunction with low calcium dialysate and when administered at night.

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