Abstract. Oral pulse therapy with vitamin D is effective in suppressing parathyroid hormone (PTH) secretion in continuous ambulatory peritoneal dialysis patients with secondary hyperparathyroidism (2'hpt). However, this treatment often leads to hypercalcemia. The goals of the study were: (1) to examine whether the incidence of hypercalcemia decreases when dialysate calcium is reduced from 1.25 to 1.0 mmol/L; (2) to determine the relative role of the factors involved in the pathogenesis of hypercalcemia; and (3) to study the efficacy of a low oral pulse dose of alfacalcidol in preventing the recurrence of 2'hpt. Fourteen continuous ambulatory peritoneal dialysis patients with 2'hpt were treated with pulse oral alfacalcidol and calcium carbonate and dialyzed with a 1.0-mmol dialysate calcium. The decrease in serum PTH, which was associated with an additional increase in iCa from 1.28 ± 0.02 to 1.47 ± 0.04 (P < 0.005). Multivariate analysis showed that the early increase in iCa was positively correlated with alfacalcidol dosage (r = 0.69). In contrast, the late increase in iCa was mostly accounted for by the decrease in serum PTH (r = -0.93). This occurred while calcium carbonate, alfacalcidol dosage, and serum 1,25-hydroxy D3 remained unchanged compared with the early response stage. Finally, an alfacalcidol dose of 1 µg twice weekly was unable to maintain serum PTH at an adequate level in the long term. These data show that a reduction in dialysate calcium from 1.25 to 1.0 mmol does not reduce the occurrence of hypercalcemia and suggest that lowering serum PTH reduces the ability of the bone to handle a calcium load within a few weeks, thus causing hypercalcemia. (J Am Soc Nephrol 8: 1579–1586, 1997)
However, this might not be adequate for patients who reach this range after receiving pulse vitamin D therapy (21). Thus, the third aim of the study was to determine whether a low dose of alfacalcidol administered as pulse therapy could keep PTH at required levels, after the initial reduction has been achieved.

Materials and Methods

Patients

Fourteen nondiabetic CAPD patients participated in the study. They had been on CAPD for 1 to 5 yr. There were 13 men and 1 woman, aged 22 to 84. Their serum intact PTH was above 165 pg/ml, which is more than 3 times the upper normal limit. All of them had been dialyzed with a 1.25-mmol dialysate calcium and had received 0 to 0.5 μg of alfacalcidol daily and calcium carbonate as a phosphate binder. Two had also been given sucralfate at a dose of 2 g/d before enrollment and were maintained on the same dose throughout the study. Aluminum intoxication was ruled out in these two patients by a standard desferrioxamine test (22). These 14 patients were randomized into two groups after matching for serum PTH. Seven patients were started on a 1.0-mmol dialysate Ca (1.0-mmol group), and seven were maintained on a 1.25-mmol dialysate Ca (1.25-mmol group). The characteristics of the two groups before the start of the study are summarized in Table 1.

Study Design

The patients were started on oral pulse therapy with alfacalcidol at a dosage of 2 μg twice weekly. The dose was increased every 2 wk to 3, 4, and 5 μg twice weekly, unless hypercalcemia occurred. Serum phosphorus was maintained below 5.5 mg/dl by increasing the calcium carbonate dose when necessary. Serum was sampled every 2 wk for biochemical assessment. The maximal alfacalcidol dose not causing hypercalcemia was maintained at least for the first 12 wk of the study. However, when mild hypercalcemia (serum ionized calcium [iCa] above 1.3 and below 1.35 mmol/L) occurred while the patient was on the 2-μg dose, pulse therapy was continued at this dose despite hypercalcemia. A response was defined as a decrease in serum PTH below 165 pg/ml, i.e., below 3 times the upper limit of normal. Patients who responded (referred to as responders) had the alfacalcidol dose decreased to 1 μg twice weekly. In patients in whom serum PTH decreased below 110 pg/ml, i.e., twice the upper normal limit, alfacalcidol therapy was discontinued until PTH reached a value 2 to 3 times the upper normal limit. Alfacalcidol was then resumed at a dose of 1 μg twice weekly. Nonresponders at 12 wk were maintained on the maximum tolerated dose. Treatment was discontinued at 12 wk in nonresponders if the maximum tolerated alfacalcidol dose was the 2-μg, twice weekly dose given initially.

The response data were analyzed at two different periods. The early response phase was defined as the time when serum PTH decreased for the first time below 165 pg/ml. After this initial decrease, the data of those responders who had a further reduction in serum PTH were also analyzed at the time of lowest PTH; this period was referred to as the late response phase.

Biochemistry

iCa, phosphorus, and alkaline phosphatase were measured by standard laboratory techniques (normal values: 1.1 to 1.3 mmol/L, 2.7 to 4.5 mg/dl, and 39 to 117 U/L, respectively). Serum levels of PTH were determined by the immunoradiometric assay for intact human PTH, using the N-tact PTH SP kit (Incstar, Stillwater, MN) (normal values: 13 to 54 pg/ml). Serum levels of 1,25-dihydroxyvitamin D3 were determined using a microassay (23) (normal values: 20 to 50 pg/ml).

Statistical Analyses

Results

Table 1 shows the characteristics of the patients in the two groups. They were comparable for age, sex distribution, time on dialysis, baseline iCa, serum phosphorus, and PTH. After 12 wk, 11 patients had responded: five of seven (71%) in the 1.0-mmol group and six of seven (87%) in the 1.25-mmol group (P, NS). They were then placed on low-dose alfacalcidol maintenance therapy. A twelfth patient, who belonged to the 1.0 group, responded at week 18 and was then placed on low-dose alfacalcidol. Two patients, one in each group, did not respond at 12 wk while they were on 2 μg of alfacalcidol twice weekly. The mean iCa, phosphorus, and PTH of the two nonresponders during the treatment period (weeks 2 to 12) were 1.33 ± 0.01 mmol/L, 5.6 ± 0.6 mg/dl, and 524 ± 80 pg/ml, respectively. Because the alfacalcidol dose could not be increased because of hypercalcemia, they were considered nonresponders.

The maximal alfacalcidol dose administered to the responders was 4.7 ± 0.2 μg in the 1.0 group and 3.8 ± 0.4 μg in the 1.25 group (P, NS). The time lapse to response was 7.0 ± 2.7 wk in the 1.0 group and 5.0 ± 1.1 wk in the 1.25 group (P, NS). PTH decreased by 70% in both groups, from 357 ± 51 to 108 ± 9 pg/ml in the 1.0 group (P < 0.01) and from 342 ± 64 to 101 ± 17 pg/ml in the 1.25 group (P < 0.02) (Figure 1). In the early response phase, iCa increased similarly in the two groups, from 1.18 ± 0.02 to 1.27 ± 0.04 mmol/L in the 1.0 group (P < 0.005) and from 1.19 ± 0.02 to 1.29 ± 0.02 mmol/L in the 1.25 group (P < 0.001).

Table 1: Patient's characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1.0 Group</th>
<th>1.25 Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>60 ± 7</td>
<td>73 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7/0</td>
<td>6/1</td>
<td></td>
</tr>
<tr>
<td>Time on CAPD (mo)</td>
<td>21 ± 5</td>
<td>26 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Serum PTH (pg/ml)</td>
<td>420 ± 76</td>
<td>349 ± 55</td>
<td>NS</td>
</tr>
<tr>
<td>Serum iCa (mmol/L)</td>
<td>1.21 ± 0.03</td>
<td>1.21 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Serum P (mg/dl)</td>
<td>4.6 ± 0.3</td>
<td>4.9 ± 0.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

*CAPD, continuous ambulatory peritoneal dialysis; iCa, serum ionized calcium; P, phosphorus.
mmol/L in the 1.25 group ($P < 0.005$) (Figure 2). Serum phosphorus was similar at baseline and at early response in both groups (4.7 ± 0.3 and 4.8 ± 0.3 mg/dl, respectively, in the 1.0 group and 4.9 ± 0.1 and 4.7 ± 0.9 mg/dl, respectively, in the 1.25 group). Among the responders, hypercalcemia occurred in two-thirds of the patients (4 of 6) in the 1.0 group.
and in all of the patients (6 of 6) in the 1.25 group (P, NS). All episodes of hypercalcemia in the responders occurred after they had responded (1.5 ± 1 wk after response in the 1.0 group and 2.0 ± 0.5 wk after response in the 1.25 group; P, NS). Mean iCa at the time of first occurrence of hypercalcemia was 1.45 ± 0.06 mmol/L in the 1.0 group and 1.37 ± 0.01 mmol/L in the 1.25 group (P, NS). Mean serum PTH at this time was 57 ± 26 pg/ml in the 1.0 group and 47 ± 6 pg/ml in the 1.25 group (P, NS).

After the initial decrease in PTH (early response phase), nine of the 12 responders had a further decrease in serum PTH while they were maintained on pulse alfacalcidol until week 12 (late response phase). Table 2 shows values for iCa, PTH, and doses of alfacalcidol and calcium carbonate at early and late response phases for these nine patients. Despite the fact that alfacalcidol and calcium carbonate doses, as well as serum 1,25-dihydroxyvitamin D3, were similar during these two periods, the decrease in serum PTH from 114 ± 10 to 31 ± 6 pg/ml was associated with an increase in iCa from 1.28 ± 0.02 to 1.47 ± 0.04 mmol/L (P < 0.005). Table 3 shows the changes in iCa and alkaline phosphatase for these nine patients at baseline, early, and late phases, depicting the concomitant changes in these variables. These findings show that the decrease in serum PTH was associated with an increase in iCa to the high-normal range in the early response phase, and with a further increase in the late response phase. To investigate the respective role of the factors that could be involved in the regulation of iCa, we performed a regression analysis of four variables (serum PTH, dialysate calcium, alfacalcidol, and calcium carbonate dose) over iCa. Figure 3 shows the regression of serum PTH over iCa at baseline and early and late response phases, revealing that changes in PTH accounted for 79% of the changes in iCa. A separate analysis was performed for the first period (baseline and early response phases, 12 patients, n = 24) and the second period (early and late response phases, nine patients who had a further decrease in PTH after initial response, n = 18). Results for univariate regression analysis are shown in Table 4. During the first period, alfacalcidol dosage and serum PTH accounted each for 47 to 48% of the variation in iCa, with serum PTH negatively correlated. Calcium carbonate dose accounted for only 22% of the variation. The multivariate analysis showed that addition of other variables did not increase the predictive value of alfacalcidol dosage for calcemia: iCa = 0.03 alfacalcidol dose + 1.19, r = 0.69, r² = 8%, P < 0.001. During the second period, univariate analysis revealed that serum PTH was negatively correlated with iCa, accounting for 86% of its variation. Alfacalcidol dosage had a much weaker correlation, accounting for only 30% of the iCa variation. Multivariate analysis showed that serum PTH and alfacalcidol dosage were independently correlated with iCa, together accounting for 94% of its variation: iCa = 0.04 alfacalcidol dose − 0.29 Log PTH + 1.75, r = 0.97, r² = 94%, P < 0.001.

Eleven of the 12 responders were maintained on 1 μg of alfacalcidol twice weekly, after they had responded. As shown in Figure 4, serum PTH had increased to more than 3 times the upper limit of normal in 55% of the patients at 6 wk of maintenance therapy and in all of the patients at 46 wk.

**Discussion**

The present study shows, in accordance with previous reports, that oral pulse therapy with an active vitamin D3 sterol is an efficient treatment for secondary hyperparathyroidism in CAPD patients, decreasing PTH secretion in approximately 80% of the patients. Decreasing calcium dialysate from 1.25 to 1.0 mmol did not reduce the incidence and severity of hypercalcemia. The pathogenesis of hypercalcemia during the early response phase differed from that seen in the late response phase

### Table 2. Serum PTH, iCa, alfacalcidol, and calcium carbonate doses at early and late response phases in nine patients whose serum PTH decreased into the low to normal range during alfacalcidol pulse therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early Response Phase</th>
<th>Late Response Phase</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from start of pulse therapy (wk)</td>
<td>3.6 ± 0.6</td>
<td>8.7 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Serum PTH (pg/ml)</td>
<td>114 ± 10</td>
<td>31 ± 6</td>
<td></td>
</tr>
<tr>
<td>Serum iCa (mmol/L)</td>
<td>1.28 ± 0.02</td>
<td>1.47 ± 0.04</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Serum P (mg/dl)</td>
<td>4.5 ± 0.3</td>
<td>5.2 ± 0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum 1,25-dihydroxy D3 (pg/ml)</td>
<td>58 ± 16</td>
<td>57 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Alfacalcidol dose (μg/twice/wk)</td>
<td>2.8 ± 0.3</td>
<td>3.0 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium carbonate dose (mg/d)</td>
<td>2760 ± 460</td>
<td>2200 ± 320</td>
<td>NS</td>
</tr>
</tbody>
</table>

*a* Abbreviations as in Table 1.

*b* *c*, different by definition.

### Table 3. iCa and alkaline phosphatase at baseline and early and late response phases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Early Response Phase</th>
<th>Late Response Phase</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iCa (mmol/L)</td>
<td>1.18 ± 0.02</td>
<td>1.28 ± 0.02*a</td>
<td>1.47 ± 0.04*b</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>93 ± 6</td>
<td>89 ± 9</td>
<td>76 ± 7</td>
<td></td>
</tr>
</tbody>
</table>

*a* P < 0.001 versus baseline.

*b* P = 0.001 versus early response.

*c* P = 0.001 versus baseline.
Pulse D3 and Hypercalcemia: The Role of PTH

Figure 3. Correlation between serum PTH (log units) and iCa in 12 responders at three time periods: baseline (n = 12, circles), early response (n = 12, squares), and late response (n = 9, triangles). Open symbols, 1.0-mmol group; closed symbols, 1.25-mmol group.

Table 4. Univariate regression analysis of four variables over serum iCa

<table>
<thead>
<tr>
<th>Variable</th>
<th>First Period (n = 24)</th>
<th>Second Period (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>r²</td>
</tr>
<tr>
<td>Serum PTH</td>
<td>-0.68</td>
<td>0.47</td>
</tr>
<tr>
<td>Alfacalcidol dose</td>
<td>0.69</td>
<td>0.48</td>
</tr>
<tr>
<td>Calcium carbonate dose</td>
<td>0.47</td>
<td>0.22</td>
</tr>
<tr>
<td>Dialysate calcium</td>
<td>0.08</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* The first period includes baseline and early response phases (12 patients, 24 measurements). The second period includes early and late response phases (nine patients, 18 measurements).

period. After a response had been obtained, administration of a low-maintenance dose of 1 μg of alfacalcidol twice weekly was not effective in keeping PTH serum levels in the desired range.

In early studies with pulse vitamin D3 in which aluminum hydroxide was the main phosphate binder, hypercalcemia was not reported as a major problem (4,6–8). An adequate control of serum phosphate is necessary during treatment of secondary hyperparathyroidism, because hyperphosphatemia directly stimulates PTH secretion (13,24–26), thus reducing the efficiency of pulse therapy (13), and increases the calcium-phosphate product, causing extraosseous calcifications. Because the dangers of aluminum accumulation have become apparent, calcium salts have replaced aluminum hydroxide as the phosphate binder of choice. However, this substitution often led to episodes of hypercalcemia (11,12,16–20). This complication may be avoided by using one or more of the following options: (1) decreasing the calcium carbonate dosage (however, this would result in increased serum phosphorus concentration); (2) reducing calcium salts dosage and adding aluminum-containing phosphate binders, with the risks associated with an aluminum burden; (3) decreasing dialysate calcium to enable the elimination of the excess calcium absorbed by the gut (27). Cunningham et al. (28) succeeded in avoiding hypercalcemia in most CAPD patients treated with calcium carbonate and no vitamin D by decreasing calcium dialysate from 1.75 to 1.45 mmol, and in some cases to 1.0 mmol. However, the addition of daily low-dose alfacalcidol resulted in hypercalcemia in more than 20% of the patients despite a reduction in calcium dialysate to 1.0 mmol. Only a decrease in calcium dialysate to 0.6 mmol eliminated hypercalcemia in all of the patients treated with calcium carbonate and low-dose daily alfacalcidol.
Hutchison and Gokal (20) also demonstrated a decrease in the incidence of hypercalcemia when they decreased calcium dialysate from 1.75 to 1.25 mmol. However, the effectiveness of these low calcium solutions as a method of decreasing the incidence of hypercalcemia during oral pulse therapy has not been tested previously.

The present study was designed to verify whether 1.0-mmol calcium solutions would decrease the incidence of hypercalcemia during oral pulse therapy. Serum phosphorus was adequately controlled with calcium carbonate, due to a stepwise increase in alfacalcidol and calcium carbonate dose. Hypercalcemia occurred at a similar rate in the 1.0- and 1.25-mmol calcium groups and was equally severe in the two groups. PTH decreased similarly. Two patients, one in each group, could not receive high alfacalcidol dose because of hypercalcemia, and did not respond. These findings suggest that a 20% decrease in dialysate calcium is insufficient to enable oral pulse therapy without the occurrence of hypercalcemia. The use of a dialysate with a calcium concentration lower than 1.0 mmol could allow an increase in vitamin D3 dosage in those patients who had hypercalcemia at the relatively low alfacalcidol dose of 2 µg twice weekly. It could also attenuate the incidence and severity of hypercalcemia in patients treated with higher alfacalcidol doses.

In the two nonresponders, serum PTH did not decrease despite mild hypercalcemia. Because uremic patients need a slightly elevated iCa to achieve inhibition of PTH secretion, the two nonresponders were maintained on alfacalcidol despite the increased iCa. The lack of response in these two patients was in part due to the low alfacalcidol dose administered. To prevent a further rise in iCa, this low dose was not increased. The hypercalcemia occurring at low alfacalcidol dosage in these two nonresponders could either reflect the severity of the secondary hyperparathyroidism, or, on the contrary, be the consequence of an aplastic bone state. Although this is very unlikely considering the serum PTH level, it cannot be entirely ruled out, because bone biopsies were not performed.

The observed decrease in serum PTH in the responders was associated with an increase in iCa. Often, serum PTH decreased below the target level of 2 to 3 times the upper normal limit. This overshooting was usually associated with the occurrence of hypercalcemia. This relationship between serum PTH and calcium has been reported by Slatopolsky et al. (4) in the first study investigating the effects of intermittent 1,25-dihydroxyvitamin D3 therapy in patients with secondary hyperparathyroidism. More recently, Quarles et al. (12) showed that increases in iCa predicts decrements in serum PTH during intermittent calcitriol therapy. However, the pathogenesis of this increase in iCa has not been elucidated. The relative role of the different factors that may be responsible for this increase, such as vitamin D dose, calcium salts dose, serum PTH, dialysate calcium concentration, and bone activity, has not been determined. In the present study, the similar rate and severity of hypercalcemia in the groups with 1.0 and 1.25 mmol of dialysate calcium and the lack of correlation between iCa and dialysate calcium suggest that the variation in dialysate calcium did not account for the changes in iCa. Multivariate analysis revealed that the factors that had been independently correlated with iCa differed during the early and late periods of pulse therapy. During the first period, when serum PTH decreased from baseline to a value of twice the upper normal limit, changes in alfacalcidol dosage accounted for most of the changes in iCa, whereas serum PTH and the calcium carbonate dosage were found not to be independently correlated with calcemia. In contrast, during the late period, when serum PTH further decreased to the normal level, the main factor whose changes accounted for the changes in iCa was serum PTH, which was negatively correlated, explaining 86% of the cal-
cium variation. Alfacalcidol dosage was also independently correlated, although much more weakly, increasing the $r^2$ to 94%.

The fact that few cases of hypercalcemia occurred during the first treatment period may be explained by several factors: the population studied had mild to moderately severe hyperparathyroidism, with a mean serum PTH of approximately 7 times the upper normal limit; dialysate calcium was equal to or less than the normal iCa concentration; alfacalcidol dose was increased stepwise, allowing an adjustment of the vitamin D and calcium carbonate dose according to the iCa and phosphorus concentrations. The strong negative correlation between serum PTH and calcium when serum PTH decreased below the target level does not in itself point to a cause-and-effect relationship. However, the finding that iCa was higher during the late response phase compared with the early response phase, whereas alfacalcidol and calcium carbonate dosages were similar, suggests that the decrease in serum PTH to below the level of twice the upper normal limit was the main pathogenic factor that increased iCa. This is in accordance with the known effects of PTH on bone turnover (29–31). Suppressed PTH levels are associated with low bone turnover osteodystrophy and high iCa (29). Goodman et al. (30) demonstrated that adynamic bone develops in 50% of children and adolescents with secondary hyperparathyroidism after 12 mo of intermittent calcitriol therapy. The adynamic bone is characterized by a state of low calcium retention, with low bone capacity to buffer calcium and with an inability to handle an extra calcium load (31).

The decrease in alkaline phosphatase in the late period is in accordance with the decrease in bone turnover associated with the decrease in PTH (31). These data suggest that excessive PTH reduction may lead within a few weeks to a state of adynamic bone, decreasing the tolerability of a calcium load that had been adequately handled when PTH levels were higher. Because intermittent vitamin D therapy reduces serum PTH levels at every iCa concentration (32), increases in iCa result in a self-perpetuating sequence of events: PTH secretion is initially directly reduced by 1,25-dihydroxycholecalciferol (33–35), which also increases intestinal calcium absorption; the resulting increase in iCa further suppresses PTH secretion, leading to a more profound decrease in bone turnover and a higher iCa, thus creating a vicious circle.

Another issue examined in this study was the effect of a low pulse dose of 1 μg of alfacalcidol twice weekly on serum PTH, after response has been obtained. About half of the patients had an increase in PTH at 6 wk to more than 3 times the upper normal limit, and all had such an increase at 46 wk. Until recently, the management of patients after successful medical treatment of secondary hyperparathyroidism was unclear. The recommendation not to administer vitamin D3 to patients with mildly increased serum PTH does not apply to those patients who had responded to pulse therapy. Conventional treatment with daily vitamin D is usually ineffective in controlling PTH secretion after a successful calcitriol pulse therapy (21). Liach et al. have recently reported (36) that PTH is maintained at adequate levels when IV calcitriol is administered at a mean dose of 1.2 μg three times weekly, after an initial response has been obtained. A decrease in the maintenance dosage resulted in a rapid increase in PTH. From the present study, it appears that an oral alfacalcidol pulse dose of 1 μg twice weekly is insufficient in the long term. Because vitamin D3 metabolite serum concentrations are lower after oral than after intravenous administration (4), our findings are in accordance with those reported by Llach et al. (36). A possible solution would be to administer a maintenance dose greater than 1 μg twice weekly, with the potential hazard of decreasing serum PTH to inadequately low values. An alternative approach would be to measure serum PTH frequently and to increase alfacalcidol dosage, as soon as serum PTH increases above target levels.

This study shows that: (1) reducing serum PTH is a major pathogenic factor, causing hypercalcemia within a few weeks during pulse therapy with alfacalcidol; (2) lowering dialysate calcium to 1.0 mmol/L is insufficient in preventing hypercalcemia; and (3) a maintenance treatment with a relatively low dose of alfacalcidol does not prevent increases in serum PTH after successful oral pulse therapy.

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References


