Oral calcitriol and calcium: Efficient therapy for uremic hyperparathyroidism

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Oral calcitriol and calcium: An efficient therapy for uremic hyperparathyroidism. Therapy with orally administered calcitriol often does not adequately control the biochemical manifestations of secondary hyperparathyroidism in uremic patients. This may be due to inadequate serum concentrations of 1,25(OH)₂ vitamin D and/or to insufficient dietary calcium supplementation. In the present study, therefore, we examined the effect on parathyroid function of calcitriol and calcium carbonate, administered orally, in doses sufficient to normalize the serum 1,25(OH)₂ vitamin D and calcium concentrations. After nine months of combined therapy, marked suppression of immunoreactive PTH occurred in the absence of hypercalcemia. Furthermore, prolonged therapy resulted in additional suppression of the PTH concentrations comparable in magnitude to that reported following intravenous calcitriol therapy and was associated with a mild degree of hypercalcemia similar to that which occurs with intravenous therapy. Euparathyroidism was achieved in 25% of the patients by 15 months of treatment. In conclusion, secondary hyperparathyroidism can be effectively controlled with combined oral therapy without significant hypercalcemia in selected patients with end-stage renal failure. This salutary effect may result from direct actions of 1,25(OH)₂ D on the parathyroid gland and/or gastrointestinal tract, or from an overall action of combined treatment to restore calcium homeostasis.

The optimal therapy for secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) has not been established. Therapeutic strategies, using either high-dose oral calcium carbonate [1, 2] or vitamin D analogues, alone or in combination with phosphate binders [3–5], have not universally resulted in adequate suppression of PTH secretion and often have been associated with significant hypercalcemia [6, 7]. More recently, intravenous calcitriol therapy has been advocated as more effective than conventional oral therapies [8, 9].

The absence of an efficient oral therapy may be due to the incomplete restoration of all factors necessary for the maintenance of calcium homeostasis; particularly, the provision of adequate calcium intake and the normalization of serum calcitriol concentrations. In this regard, calcitriol is necessary for normal gastrointestinal absorption of calcium and may be important in suppression of PTH synthesis [10, 11]. Therefore, we investigated whether secondary hyperparathyroidism in patients with ESRD could be effectively treated with a combination of orally administered calcitriol, in doses sufficient to normalize the serum calcitriol concentration, and dietary supplementation of calcium, as calcium carbonate, administered in an amount adequate to normalize the serum calcium concentration. Our results show that combined therapy with calcitriol and calcium results in marked suppression of PTH secretion, comparable to that reported with intravenous therapy. Euparathyroidism was achieved in several subjects. Moreover, the decrement in PTH occurred without the development of significant hypercalcemia.

Methods

Patients

We selected eight, chronic maintenance hemodialysis patients who were being treated with four hours of dialysis thrice weekly at Duke University. Criteria for inclusion were: serum calcium less than 10 mg/dl, serum phosphorus less than 7.0 mg/dl, and serum immunoreactive PTH greater than 65 pg/ml. Five patients were female and three were male. The average age of the patients was 53 ± 5 years (range 30 to 69). No patient had significant residual renal function. The average duration of end-stage renal disease as estimated by the onset of hemodialysis was approximately five years. The underlying causes of renal failure were primary glomerulonephritis in 2, hypertension in 3, and unknown in 3. No patients had diabetes mellitus or were receiving steroids.

Treatment protocol

For at least four months prior to beginning this study, all patients had been receiving variable amounts of calcium carbonate between meals and aluminum-containing phosphate binders with meals to control serum phosphorus concentrations. Prior to the initiation of this study, four patients were receiving low dose calcitriol (0.25 µg/day) and four were taking no vitamin D or its analogues. During this period serum calcium, phosphorus and alkaline phosphatase were measured at monthly intervals. In addition, at the outset of the study intact PTH, ionized calcium and calcitriol concentrations were measured in each patient on the existing therapeutic regimen. These served as baseline measurements for subsequent comparisons. In one patient the baseline intact PTH was estimated from results obtained from a mid-region assay. The mid region
assay correlates linearly with the intact assay ($r^2 = 0.51; P = 0.0001$).

The protocol began with the administration of calcitriol (Rocaltrol, Hoffman La Roche, Nutley, New Jersey, USA) in increasing doses until the serum calcitriol concentrations exceeded 15 pg/ml (normal range 15 to 50). Rocaltrol was taken orally in divided doses twice or thrice daily. Concomitantly, calcium carbonate was administered with each meal and adjusted to titrate the serum calcium to between 10.0 and 10.5 mg/dl. All between meal supplements of calcium were discontinued. Further adjustments in the dose of Rocaltrol and calcium carbonate were made to maintain the serum calcium and calcitriol concentrations within the normal range. Therapy was temporarily interrupted if calcium levels exceeded 11.5 mg/dl. The calcium concentration of the dialysate was maintained at 1.75 mmol/liter (3.5 mEq/liter) throughout the study. The amount of aluminum containing phosphate binders was adjusted to maintain the serum phosphorus concentration between 3.0 and 6.0 mg/dl. Patients were instructed in a diet consisting of an estimated 900 mg phosphorus and 800 mg calcium. Thereafter, serum calcium, phosphorus and alkaline phosphatase determinations were repeated monthly. Reported values represent the concentration averaged over the entire period of study. Serum intact PTH and ionized calcium measurements were repeated at approximately 9 and 15 months after initiating therapy.

**Analytical methods**

Parathyroid hormone was measured by radioimmunoassay; the Allegro PTH assay (Nichols Institute, San Juan Capistrano, California, USA) is specific for the intact, secreted, biologically-active 84 amino-acid PTH molecule [12]. The concentration of intact PTH is a more accurate measure of PTH secretion since biologically inactive circulating fragments of PTH which accumulate because of impaired renal clearances are not detected by this system. Intra- and interassay coefficients of variation are 5.7 and 14.9%, respectively. A concentration below 165 pg/ml is associated with mild bone disease in patients with renal failure, while 65 pg/ml is the upper limit in apparently healthy subjects [13]. Total calcium, phosphorus and alkaline phosphatase were measured by automated methods (Beckman auto analyzer, Beckman Institution Co, Somerset, New Jersey, USA). Ionized calcium was determined by an ICAI analyzer (Radiometer Company, Copenhagen, Denmark). Serum 1,25 dihydroxyvitamin D (calcitriol) concentrations were measured by the calf thymus receptor assay described by Reinhardt et al [14], purchased from Instar Corp. (Stillwater, Minnesota, USA). Established intra- and interassay coefficients of variation are 5.4 and 16%, respectively.

**Statistics**

The effect of therapy was analyzed by the Friedman analysis of variance technique, a non-parametric procedure for repeated measures data. Differences in response at the three sampling intervals (0, 9, and 15 months of therapy) were detected using the Wilcoxin signed ranks test with a Bonferonni correction for multiple comparisons [15]. Differences in selected biochemistries measured monthly in individual patients were analyzed by Kendall Tau [16]. Multiple regression was performed using INT-PTH expressed in ranks as the dependent variable and ionized calcium, phosphorus, alkaline phosphatase, and calcitriol concentrations as predictors in order to explore possible functional relationships among the variables that could account for any decrement in PTH concentration associated with therapy. All analyses were performed using the Statistical Analysis System Version 6 software (SAS Institute, Cary, North Carolina, USA).

**Results**

During the period of treatment, the requisite dose of calcitriol necessary to establish and maintain a normal serum calcitriol concentration averaged approximately 0.6 micrograms per day (Table 1). During the first nine months of the study, the daily calcitriol dose was distributed as follows: 0.5 micrograms in six patients; 0.75 micrograms in one; and 1.0 microgram in one. During the latter period of therapy three patients received 0.5 micrograms per day, four patients received 0.75 micrograms per day, and one continued to receive 1.0 microgram per day. Increasing amounts of calcium carbonate were administered during the study period compared to baseline doses; moreover, during the period of investigation, calcium was administered exclusively with meals and titrated to achieve a serum calcium concentration near the upper limit of normal (Table 1). In concert with the administration of dietary calcium carbonate, the dose of aluminum containing antacids was reduced during the last period of study (Table 1). All aluminum-containing phosphate binders were discontinued in one patient.

At the outset of the study, the serum calcitriol concentration was below normal in all patients (Table 2). After intensified treatment with calcitriol, the serum calcitriol concentration increased from a baseline concentration of 6.7 to 21.8 pg/ml and was maintained at this concentration during the study period (Table 2). The concentration of ionized calcium increased from a baseline value of 1.10 to 1.20 and 1.27 mmol/liter at 9 and 15 months of therapy, respectively (Table 2). In addition, the total serum calcium concentration, measured monthly, increased progressively and significantly ($P < 0.05$) in each patient throughout the period of observation (Fig. 1). The average concentration of this cation, however, was maintained within the normal range. Transient hypercalcemia developed in several patients during the second period of observation and resolved with temporary cessation of therapy (Fig. 1). The serum phosphorus concentration was not different from baseline values in spite of a reduction in the dose of aluminum-containing antacids (Table 2).

At the outset of therapy, severe hyperparathyroidism, evidenced by the grossly-supranormal intact PTH levels, prevailed (Table 2). Significant reductions in the serum PTH concentra-

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Calcitriol μg/day</th>
<th>Calcium carbonate g/day</th>
<th>Aluminum hydroxide g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.13 ± 0.05</td>
<td>1.3 ± 0.6</td>
<td>3.5 ± 0.8</td>
</tr>
<tr>
<td>9.0</td>
<td>0.60 ± 0.07</td>
<td>1.9 ± 0.5</td>
<td>3.2 ± 1.0</td>
</tr>
<tr>
<td>15.0</td>
<td>0.64 ± 0.06</td>
<td>2.6 ± 0.6</td>
<td>2.2 ± 0.7</td>
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</tbody>
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* Administered exclusively with meals during period of therapy.
Table 2. Serum biochemistries in chronic maintenance hemodialysis patients before, 9 and 15 months after combined therapy with calcitriol and calcium carbonate

<table>
<thead>
<tr>
<th>Months time</th>
<th>Ionized calcium mmol/liter</th>
<th>Phosphorus mg/dl</th>
<th>Alkaline phosphatase U/liter</th>
<th>Calcitriol pg/ml</th>
<th>Intact parathyroid hormone pg/ml</th>
<th>% decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.10 ± 0.27</td>
<td>5.5 ± 0.3</td>
<td>295 ± 65</td>
<td>6.7 ± 1.7</td>
<td>968 ± 176</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>1.20 ± 0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.4 ± 0.2</td>
<td>177 ± 30</td>
<td>21.8 ± 2.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>607 ± 157&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44 ± 7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>15</td>
<td>1.27 ± 0.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.5 ± 0.5</td>
<td>97 ± 20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20.9 ± 1.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>365 ± 149&lt;sup&gt;b&lt;/sup&gt;</td>
<td>71 ± 9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>(Normal range)</td>
<td>(1.19–1.31)</td>
<td>(2.7–4.6)</td>
<td>(20–96)</td>
<td>(15–50)</td>
<td>(13–64)</td>
<td></td>
</tr>
</tbody>
</table>

Values represent the mean ± SEM. Data within each column were compared by Wilcoxon’s signed ranks test with a Bonferonni correction for multiple comparisons.

<sup>a</sup> Significant difference from time 0 at P < 0.05
<sup>b</sup> Significant difference from 9 months at P < 0.05

Fig. 1. The monthly serum total calcium concentration in 8 patients with end-stage renal disease maintained on chronic hemodialysis as a function of time on combined therapy with calcium and oral calcitriol. Each symbol represents the serial measurements in individual patients; all patients demonstrated a significant increase in serum calcium by Kendall Tau at P < 0.05. The normal range is indicated by the shaded area.

Fig. 2. Serum intact PTH concentrations in 8 patients with end-stage renal disease maintained on hemodialysis as a function of time on combined therapy with calcium carbonate and oral calcitriol. Symbols represent serial determinations in individual patients. The upper limit of normal is delineated by the horizontal shaded area.

The factors responsible for genesis of secondary hyperparathyroidism in patients with ESRD are well known, yet in the uremic environment, progressive hyperparathyroidism often occurs in spite of efforts to normalize serum phosphorus and calcium concentrations [17]. This may result from failure to fully restore the milieu necessary for the maintenance of calcium homeostasis. In this regard, most dialysis patients consume a diet deficient in calcium which, along with the absence of calcitriol, results in the inadequate gastrointestinal absorption of calcium [10, 11]. In addition, recent studies illustrate that calcitriol, the most potent vitamin D analogue, directly inhibits the synthesis of PTH and alters the set point for secretion of PTH [18–21]. Thus, restoration of the serum calcitriol concentrations and provision of adequate dietary calcium should together restore normal gastrointestinal calcium absorption, and possibly lead to more effective suppression of synthesis and secretion of parathyroid hormone.

In our investigations we administered doses of calcitriol sufficient to normalize the serum calcitriol concentration, and...
gave calcium carbonate with meals to supplement dietary calcium and to augment phosphate binding. This therapeutic approach resulted in an overall reduction in serum PTH concentrations of 70% after 15 months, even achieving euglycemia in several subjects (Table 2; Fig. 2). Moreover, during the initial nine months of therapy, significant reductions in PTH concentrations were observed in the absence of hypercalcemia. During the last period of observation, however, transient mild hypercalcemia was observed in several patients, but all responded to reductions in the doses of calcium carbonate and calcitriol.

The effectiveness of our therapy to suppress PTH may be due to several factors. The intact assay that we used may be a more direct measure of PTH secretion, since it does not detect circulating inactive fragments of PTH. Others may also have achieved comparable suppression of PTH with oral therapy, but the use of less effective assays may have obscured this outcome [6]. Alternatively, the salutary effect of combined therapy may have resulted from specific actions of calcitriol on the gastrointestinal tract to augment the absorption of calcium alone or in combination with a direct effect on the parathyroid gland to suppress PTH synthesis and release. Indeed, multiple regression analysis indicates that the increase in calcitriol concentrations had a significant effect in suppressing PTH concentrations. While this is consistent with an effect of calcitriol at the level of the parathyroid gland (vide supra), an alternative explanation might be that this therapy provides a more effective and continuous augmentation of the intestinal absorption of calcium. Whether this therapy allows for a more sustained physiologic calcium homeostasis over a 24 hour period requires further study. Marked fluctuations in serum calcium concentration, however, typically occur during hemodialysis and the interdialytic period in patients who do not receive vitamin D [22]. The contribution of these fluctuations in the serum calcium to the maintenance of hyperparathyroidism should be considered. A related issue is whether combined oral therapy would allow for the maintenance of the serum calcium concentration using a lower dialysate calcium and thereby prevent the tendency to develop hypercalcemia observed with more prolonged use of calcitriol.

Serum phosphorus concentration was effectively controlled with combined oral therapy. This may in part be due to the chelation of dietary phosphate by calcium carbonate. The amount of calcium carbonate administered was appreciably less than that reported effective in controlling serum phosphorus concentrations [1]. The suppression of PTH and the consequent reduction in bone turnover may also have contributed to the decline in serum phosphorus analogous to that observed following parathyroidectomy. Continuation of phosphate binders was necessary to control the serum phosphorus concentration in the majority of patients.

Although the majority of patients showed dramatic reductions in PTH, the degree of suppression was less in the three patients with the highest baseline concentrations of PTH. Additional time may be necessary to achieve control of hyperparathyroidism in these patients. Alternatively, these patients may represent a subset with more severe parathyroid hyperplasia who continue to have elevated PTH release because of increased gland mass, in spite of maximal suppression of PTH secretion. Observations which demonstrate a correlation between PTH secretion and gland mass support this possibility [23]. The normalization of PTH concentrations in several patients without hypercalcemia, as demonstrated in our study, however, is consistent with regression of the parathyroid gland hyperplasia in some of the patients.

Our results differ from studies which have demonstrated the ineffectiveness of oral calcitriol. This may be due to differences in patient selection or intensity of treatment. Studies showing little effect of oral calcitriol may be confounded by the failure to document that: 1) sufficient doses of this hormone were administered; 2) adequate dietary calcium was provided; or 3) patients with similar degrees of hyperplasia were selected [7, 8]. PTH suppression by oral therapy has been reported in other investigations in association with substantial degrees of hypercalcemia [6, 7]. In our study, the calcemic response was less for the degree of PTH suppression and similar to that observed with intravenous therapy (vida infra) [8]. This may result from the co-administration of aluminum containing phosphate binders and calcium with meals. In this regard, aluminum has recently been shown to interfere with calcium absorption in a setting of vitamin D repletion [24]. Nevertheless, as demonstrated by this study, hypercalcemia is not a universal occurrence following oral calcitriol therapy. Nonetheless, reductions in the dialysate calcium concentration and/or oral calcium supplementation may be needed with any form of vitamin D therapy in order to minimize the tendency to hypercalcemia following prolonged therapy.

Our observations highlight the need to resolve the role of oral versus intravenous calcitriol administration in the management of hyperparathyroidism in patients with ESRD. The intravenous administration of calcitriol has recently been advocated because oral therapies have been reported ineffective in achieving adequate serum calcitriol concentrations and suppressing PTH secretion without the concurrence of significant hypercalcemia [8, 9], a contention not supported by our observations. Central to this issue is whether the pharmacologic concentrations achieved with intravenous therapy offers any advantage in PTH suppression. To date an additional benefit of such extremely high concentrations has not been unequivocally established. On the other hand, in vitro studies show maximum inhibition of PTH mRNA synthesis at physiologic concentrations of 1,25 dihydroxyvitamin D [20, 21]. Moreover, the degree of PTH suppression with low physiologic concentration of calcitriol as demonstrated in our study is equivalent to that observed following the parenteral administration of calcitriol [8, 9]. In addition, the potential untoward effects of the supraphysiologic concentrations attendant upon intravenous therapy have not been fully explored. Indeed, high concentrations of calcitriol do increase bone resorption in vitro [25].

In conclusion, recent experimental evidence supports a vital role for calcitriol in the normal feedback suppression of both PTH synthesis and secretion, in addition to its established effects on the gastrointestinal absorption of calcium. While our results are preliminary and involve relatively small numbers of patients, our studies suggest that attaining low normal circulating concentrations of this vitamin D metabolite, along with dietary calcium supplementation in the form of calcium carbonate, is sufficient to adequately control the biochemical manifestations of hyperparathyroidism in selected patients with ESRD. A prospective controlled trial, which compares the relative
effectiveness of oral versus intravenous calcitriol, should be performed in patients with comparable degrees of parathyroid hyperplasia with similar dietary calcium intake and dialysate calcium concentrations and with attention to the serum concentration of 1,25(OH)2D achieved, in order to determine the optimal route of calcitriol administration.

References