Intermittent oral 1α-hydroxyvitamin D2 is effective and safe for the suppression of secondary hyperparathyroidism in haemodialysis patients

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Abstract Calcitriol and alfacalcidol are useful in suppressing parathyroid hormone (PTH) in haemodialysis patients, but hypercalcaemia and hyperphosphataemia are frequent. The vitamin D analogue, 1α-hydroxyvitamin D2 (1αD2), has a higher therapeutic index in animal models. Previously, 1αD2, 4 μg/day or 4 μg/haemodialysis, lowered iPTH to the target range in 87.5% of 24 haemodialysis patients with moderate to severe secondary hyperparathyroidism (plasma iPTH, 359–1521 pg/ml). The incidences of hypercalcaemia (serum Ca > 2.8 mM) or hyperphosphataemia (serum P > 2.23 mM) were low. Later, 10 of these patients were re-treated with 1αD2, initial dose, 10 μg, thrice weekly with haemodialysis. The iPTH was suppressed as readily, and there was no greater incidence of hypercalcaemia and hyperphosphataemia. Based on these data, a large, multicentre study is ongoing in California and Tennessee/Mississippi, using 1αD2 in haemodialysis patients with iPTH > 400 pg/ml. In this and the earlier studies, only calcium-based phosphate binders were used to control serum phosphorus. The initial dose, 10 μg thrice weekly with haemodialysis, is adjusted to maintain a target iPTH within the range of 150–300 μg/ml; the final dose range is 2.5–20 μg per haemodialysis. The protocol includes 8 weeks of wash-out with no vitamin D, 16 weeks of open label treatment period with 1αD2, and finally 8 weeks of randomized double blinded treatment with either continued 1αD2 or placebo. Forty two patients from California and 38 from Tennessee/Mississippi have completed 16 weeks of open label treatment. In California, iPTH declined from 832 ± 95 pg/ml at baseline to 222 ± 71 pg/ml at the nadir and to 477 ± 117 pg/ml at week 16 of the treatment. In Tennessee/Mississippi, the iPTH declined from 977 ± 65 pg/ml to 286 ± 42 pg/ml at the lowest point and to 493 ± 79 at the end of the treatment. Plasma iPTH reached or fell below the target range in 84% of the 80 patients completing open treatment. Asymptomatic hypercalcaemia (serum Ca > 2.8 mM) increased from 0.3 episodes/100 weeks during wash-out to 3.6 episodes/100 treated weeks in California and from 0 to 3.7 episodes in Tennessee/Mississippi. In California and Tennessee, the episodes of hyperphosphataemia (serum P > 2.2 mM) increased from 5.0 and 5.0 episodes per 100 patient/week during wash-out to 10.1 and 10.9 episodes/100 treatment weeks, respectively, with 1αD2 treatment. There were no adverse events in association with 1αD2 treatment. Thus, oral 1αD2 is safe and highly effective for the treatment of secondary hyperparathyroidism.

Key words: haemodialysis; 1α-hydroxyvitamin D2; intact PTH; secondary hyperparathyroidism; therapeutic trial; vitamin D

Introduction

The two active vitamin D sterols, calcitriol and alfacalcidol or 1α(OH)-vitamin D3 (1αD3), are effective in suppressing intact parathyroid hormone (iPTH) and for the treatment of secondary hyperparathyroidism in dialysis patients, but they are associated with a significant incidence of hypercalcaemia and hyperphosphataemia. New vitamin D compounds that suppress the secretion of iPTH but exert minimal calcaemic and phosphataemic actions could theoretically be ideal for the treatment of secondary hyperparathyroidism in the haemodialysis patient. The advantages of a possible dissociation between the suppressive effect on iPTH and the hypercalcaemic effect have led to the study of several vitamin D analogues, including 22-oxacalcitriol [1], hexafluorocalcitriol [2] and 19-nor-1,25-dihydroxy-vitamin D [3]. Over the last 2 years, we have been involved in the study of the vitamin D sterol, 1α-hydroxyvitamin D3 (1αD3), and our results in dialysis patients with secondary hyperparathyroidism seem to hold promise. This discussion reviews the rationale and background for our renewed interest in this compound and the recent results with the
use of oral 1αD₃ for the treatment of secondary hyperparathyroidism in haemodialysis patients.

**Animal and human background**

In the past, vitamin D₂, which is produced by the irradiation of the plant sterol, ergosterol, enjoyed widespread use in comparison with cholecalciferol (vitamin D₃), the natural form of vitamin D that is synthesized in the skin; the reason was ease and lower cost of production of vitamin D₂ compared with vitamin D₃. The development of efficient methods for the production of vitamin D₃ has led to much greater use of the naturally occurring, mammalian form, vitamin D₃. Vitamin D₂ and vitamin D₃ are believed to be equally potent in humans and other mammals except for in New World monkeys [5]. The vitamin D sterols 1αD₂ and 1αD₃ are both converted by the liver into the corresponding 1,25-dihydroxylated sterols. In vitamin D-deficient rats, 1αD₃ is equipotent to 1αD₂ in stimulating intestinal calcium absorption, in mobilizing bone calcium and in leading to the healing of rickets [6], however, 5- to 6-fold larger doses of 1αD₂ than 1αD₃ are required to produce hypercalcemia and toxicity in normal rats [7] and normal mice [8].

In a study done in 15 post-menopausal women [9], an increase in the urinary calcium was noted with the oral administration of progressively larger doses of 1αD₂. These patients received oral 1αD₂, beginning with 0.5 µg/day; the dose was then increased at weekly intervals to 1.0, 2.0, 4.0 and 5.0 µg/day. The doses were increased further to 8 and 10 µg/day, each in five and four patients, respectively. There was a small but linear increase in the urinary calcium excretion with doses between 0.5 and 5 µg/day, but hypercalciuria, defined as urinary calcium >350 mg/24 h, did not occur with doses <5.0 µg/day. Moreover, there was hypercalcemia in only four of the 15 subjects receiving a dose of 5.0 µg/day. There were progressive increases in serum osteocalcin, an index of osteoblastic activity, that reached significance at a dose of 2.0 µg/day; osteocalcin levels increased substantially with larger doses. There was no increase in the excretion of urinary hydroxyproline during treatment with 1αD₂, an observation consistent with no augmentation in bone resorption. This study did not compare 1αD₂ with other sterols, but the increments of urinary calcium were substantially less than those reported in osteoporotic patients receiving 1αD₂ in doses of 2.0 µg/day [10,11]. These observations suggest that 1αD₂ exerts less stimulatory effect on intestinal calcium absorption than 1αD₃.

Based on the above observations, an initial study was done using oral 1αD₂ in haemodialysis patients with secondary hyperparathyroidism [12]. After 8 weeks of wash-out without calcitriol, oral 1αD₂, either 4 µg per day or 4 µg thrice weekly, was given to 24 haemodialysis patients with moderate to severe secondary hyperparathyroidism, defined as pre-treatment plasma intact parathyroid hormone (iPTH) ranging from 359 to 1521 pg/ml. The dose of 1αD₂ was then adjusted over 12 weeks in an effort to maintain the plasma iPTH between 130 and 250 pg/ml, values associated with normal bone turnover [13–15]. In six of the 14 patients initially treated with 4 µg three times per week, the dose was increased to 4 µg/day, the maximum dose given, after 6–8 weeks when there had been little or no reduction in the plasma iPTH. The pre-treatment plasma iPTH declined from 672 ± 70 pg/ml to 289 ± 36 pg/ml at the end of treatment (P < 0.05) (Figure 1). The maximal decrease in plasma iPTH was 48–96%, moreover, 87.5% of the patients reached the target iPTH range. Pre-treatment serum calcium rose modestly from 2.20 ± 0.05 to 2.37 ± 0.05 mM after treatment. Only once did modest hypercalcemia, with a serum Ca of 3.07 mM, necessitate the interruption of treatment. This occurred in a patient who was hospitalized for pneumonia and placed at bed rest; otherwise, no serum Ca exceeded 2.80 mM. Oral 1αD₂, in a dose of 4 µg per day or 4 µg thrice weekly, was shown to be highly efficacious in suppressing secondary hyperparathyroidism in haemodialysis patients and to be safe despite the exclusive use of calcium-based, phosphate-binding agents.

The next pilot study was done to evaluate the efficacy and safety of a single, higher pulse oral dose of 10 µg, given thrice weekly with haemodialysis. Ten patients who had participated in the earlier study were re-treated with oral 1αD₂, using an initial dose of 10 µg per haemodialysis treatment [16]. This study demonstrated that oral 1αD₂, at this dose of 10 µg three times a week, was as efficacious and as safe as 4 µg given daily; thus, the weekly doses of 28 or 30 µg were quite similar. The prevalence of hypercalcemia did not differ between the two dosage regimens.

**The ongoing clinical trial**

These two initial clinical trials provided the background for a multicentre, phase 3, clinical trial designed...
to evaluate the efficacy and safety of oral 1αD₂ in the treatment of moderate to severe secondary hyperparathyroidism in a larger number of haemodialysis patients. Preliminary results have been reported [17]. During 8 weeks of wash-out, the patients received no vitamin D compounds. Patients with plasma iPTH levels >400 pg/ml were then treated with oral 1αD₂ for 16 weeks. The starting dose was 10 μg, three times a week taken after haemodialysis; the dose was adjusted thereafter to maintain the iPTH within the range of 150–300 pg/ml. The final dose ranged from <2.5 to 20 μg per haemodialysis. After the 16 weeks of open label treatment, the patients were randomly crossed-over to 8 weeks of double blinded treatment with either continued 1αD₂ or placebo; the data from this last double-blinded phase are not yet available. Throughout the study, the study patients received only calcium carbonate or calcium acetate as phosphate binders, with the dose adjusted to maintain the serum phosphorus level at <2.22 mM.

The two geographic areas of the US involved are Southern California and Tennessee/Mississippi. Fifty one haemodialysis patients from California and 70 from Tennessee/Mississippi have qualified to enter the 16 week phase of open treatment. To this date, 42 patients have completed 16 weeks of open label treatment in California. From a baseline value of 832±95 pg/ml, the mean (±SE) of plasma iPTH declined to 222±71 pg/ml at the lowest point, and was 477±117 pg/ml at the end of week 16. In the Tennessee and Mississippi group, 38 patients have completed the 16 weeks of open label treatment with 1αD₂. The mean baseline plasma iPTH of 977±65 pg/ml declined to 286±42 pg/ml at the nadir and was 493±79 pg/ml at the end of week 16. Among the total of 80 patients who completed 16 weeks of treatment, plasma iPTH reached or fell below the target range in 84% of them.

In California, the baseline serum calcium was 2.22±0.03 mM; this increased to 2.62±0.05 mM at the time of maximum iPTH suppression and was 2.42±0.03 mM at the end of 16 weeks of treatment. The incidence of episodes of asymptomatic hypercalcaemia, defined as a serum Ca >2.80 mM, increased from 0.3 episodes per 100 patient/week during the wash-out period to 3.6 episodes per 100 patient/week during treatment with 1αD₂. In the Tennessee and Mississippi sites, the baseline serum calcium was 2.27±0.03 mM; it increased to 2.57±0.03 mM at the nadir of iPTH suppression and was 2.42±0.05 mM at the end of the treatment period. The number of asymptomatic hypercalcaemic episodes increased from zero episodes per 100 patient/week during the washout period to 3.7 episodes per 100 patient/week during treatment with 1αD₂.

In California, the serum phosphorus was 1.61±0.06 mM at the end of baseline, 1.64±0.06 mM at the time of maximal iPTH suppression and 1.90±0.09 mM at the end of 16 weeks of treatment. In Tennessee and Mississippi, the serum phosphorus was 1.64±0.03 mM/l at baseline, 1.70±0.06 mM at the nadir of iPTH suppression and 1.87±0.09 mM at the end of treatment. In both the California and Tennessee/Mississippi areas, the number of episodes of hyperphosphataemia, defined as a serum phosphorus >2.22 mM, increased from 5.0 and 5.0 episodes per 100 patient/week, respectively, during the washout period, to 10.1 and 10.9 episodes per 100 patient/week during the treatment period.

Despite the exclusive use of calcium-based phosphate-binding agents, the increase in serum calcium was mild, and asymptomatic hypercalcaemia was easily controlled by dose reduction. Mean serum phosphorus was not changed; mild hyperphosphataemia was more common during treatment with 1αD₂, but this did not prevent the effective reduction of plasma iPTH.

How do the efficacy and safety of 1αD₂ compare with previous data reported on pulse treatment with either calcitriol or 1αD₂ in haemodialysis patients? This cannot be answered conclusively since studies that directly compare these compounds are not available. In our earlier report [12], the results of 12 prospective studies of the effect of calcitriol in 309 adult ESRD patients were analysed and compared with our observations. The comparisons were limited to studies using the iPTH assay, determined with an immunoradiometric method, and reports of treating patients with minimal or mild hyperparathyroidism, as indicated by average iPTH <450 pg/ml [18,19], were also excluded. Only in studies done in single dialysis centres [20–23] did the results of PTH suppression compare with our observations in a multicentre study; the results of multicentre studies using calcitriol have shown a maximum suppression of iPTH <50% [24,25]. Several of these studies employed an aluminium-containing phosphate binder, either alone or in combination with calcium carbonate or calcium acetate, for the control of serum phosphorus [20–25]; it is likely that the use of aluminium gels would reduce the incidence of hypercalcaemia but with a risk of aluminium accumulation.

In both our ongoing study and the earlier reports [12,16], only calcium-based phosphate binders were used, and our results were more favourable than those in one report of i.v. calcitriol combined with calcium carbonate as a phosphate-binder [26]. Other investigators have continued vitamin D treatment until the hypercalcaemia was more marked, or they noted greater hyperphosphataemia when (i.v.) calcitriol was given in combination with calcium-based phosphate-binding agents [27–29].

1αD₂, or alfalcaldiol, has been widely used in Canada, Europe and Japan for the management of secondary hyperparathyroidism. Before exerting its action, this sterol, like 1αD₂, must undergo hepatic 25-hydroxylation; therefore, a comparison of results of treatment with these two sterols is of interest. Most early reports with 1αD₂ utilized various PTH antisera that led to results that cannot be compared with studies using the iPTH assay. Three studies have reported on the use of pulse, i.v. doses of 1αD₂ with the measurements of iPTH [30–32]. In two of these reports, the iPTH was only mildly elevated [30,31]; there were reductions of serum iPTH, but the prevalence of hyper-
calcaemia and/or hyperphosphataemia was high. Moriri et al. [32] reported a 74% reduction of intact PTH from the mean value of 486 pg/ml after pulse i.v. treatment with 1αD₂ of patients whose serum phosphorus was managed with only calcium-based phosphate binders. These results of i.v. alfalcacidol from a single centre are comparable with those of our multicentre studies [12,17]: however, the ranges of values for serum Ca and P during treatment were not reported.

Conclusion

The present study and our earlier observations [12,16,17] demonstrate that 1αD₂, when given at the dosage regimen studied, is efficacious and safe in the treatment of haemodialysis patients with moderate to severe secondary hyperparathyroidism. The final results and data analysis of this ongoing study, using a large number of patients, will further establish the proper dosing. Further studies comparing the efficacy and safety of 1αD₂ with either calcitriol or alfalcacidol are clearly warranted. This agent appears to have a greater safety profile than other available vitamin D sterols, calcitriol or alfalcacidol. 1αD₂ seems to be a preferred alternative to calcitriol in uraemic patients with secondary hyperparathyroidism.

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