ORAL CALCITRIOL VERSUS ORAL ALFACALCIDOL FOR THE TREATMENT OF SECONDARY HYPERPARATHYROIDISM IN PATIENTS RECEIVING HEMODIALYSIS: A RANDOMIZED, CROSSOVER TRIAL

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ABSTRACT

Background
Secondary hyperparathyroidism is a common complication in patients with chronic kidney disease and treatment with vitamin D analogues is a mainstay of therapy. Although oral calcitriol and alfacalcidol are used extensively in Canada, there is little published data comparing equal doses of these agents.

Objectives
To compare the effect of equal doses of oral calcitriol and alfacalcidol on intact parathyroid hormone concentrations (iPTH) in the treatment of secondary hyperparathyroidism due to chronic kidney disease. Secondary endpoints included serum 1,25-dihydroxyvitamin D_3, calcium and phosphate concentrations, achievement of target iPTH concentrations, and need for phosphate binder dose increases.

Methods
Five adult hemodialysis subjects who were naïve to vitamin D analogues and had iPTH concentrations ≥ 20 pmol/L were enrolled in a prospective, randomized 16-week crossover pilot study. Subjects were randomized to either oral calcitriol or oral alfacalcidol 0.75 mcg three times weekly for six weeks. After a four-week washout period, patients were crossed over to the alternate drug for six weeks.

Results
Oral calcitriol significantly suppressed iPTH after six weeks of therapy (p=0.003), while no significant change in iPTH was observed with oral alfacalcidol.

Conclusions
This small randomized crossover study provides preliminary evidence that equal doses of oral alfacalcidol and calcitriol may demonstrate differences in iPTH suppression during the first six weeks in dialysis patients treated for secondary hyperparathyroidism. Further comparative trials are required to confirm this finding and to determine whether important differences in parathyroid hormone suppression exist between oral calcitriol and alfacalcidol beyond the six-week period.

Key words: *Vitamin D analogues, alfacalcidol, calcitriol, secondary hyperparathyroidism, renal dialysis*

Secondary hyperparathyroidism is a common complication in patients with chronic kidney disease. Decreased production of 1,25-dihydroxyvitamin D_3 is one of the factors that contributes to this disorder.[1] Two vitamin D_3 analogues are currently available in Canada for the treatment of secondary hyperparathyroidism – calcitriol and alfacalcidol. There is little published

data comparing the efficacy of equivalent doses of oral calcitriol and alfacalcidol.[2] Additionally, there are cost implications as alfacalcidol is significantly less expensive than oral calcitriol at equal doses.[3] The objective of this study was to compare the effect of equal doses of oral calcitriol and alfacalcidol on iPTH concentrations in the treatment of secondary hyperparathyroidism in patients receiving hemodialysis who were naïve to vitamin D analogues.

Secondary endpoints examined included serum 1,25-dihydroxyvitamin D_3, calcium, and phosphate concentrations, achievement of therapeutic iPTH concentrations, and phosphate binder dose increases.

METHODS

Patients

Inclusion and exclusion criteria are listed in Table 1. All patients provided written informed consent prior to enrolment. The University of Western Ontario Ethics Review Board approved this study.

Study Design

Subjects in this pilot study were prospectively and randomly assigned to receive either oral calcitriol (Rocaltrol®, Hoffman LaRoche) or oral alfacalcidol (One-Alpha®, Leo Pharma) 0.75 mcg three times weekly for six weeks (period 1). It has been previously reported that daily oral doses of 0.25 mcg to 0.5 mcg (1.75 mcg to 3.5 mcg per week) of calcitriol or alfacalcidol were well tolerated and reversed the biochemical and histologic features of secondary hyperparathyroidism.[2] Our dose of 0.75 mcg three times weekly (2.25 mcg per week) was in the midpoint range of these effective and well tolerated doses. Additionally, studies have reported that three times a week administration of these vitamin D_3 analogues is as effective and safe as once daily dosing.[4,5] Three times a week administration also ensured medication compliance as the doses were administered in the hemodialysis unit.

TABLE 1 Inclusion and Exclusion Criteria

Inclusion Criteria
• ≥18 years old
• Receiving chronic hemodialysis three times weekly
• PTH ≥ 20 pmol/L
• No previous use of vitamin D analogues
• Dialysate calcium concentration = 1.25 mmol/L
• Serum aluminum concentration <2,000 nmol/L
• Stable dose of calcium containing phosphate binder in previous 4 weeks
Exclusion Criteria
• Hypersensitivity to calcitriol or alfacalcidol
• Baseline serum corrected calcium > 2.5mmol/L
• Baseline serum phosphorus >2.0mmol/L
• Pregnant or breastfeeding women
• Women of childbearing age not using an adequate method of birth control
• Previous parathyroidectomy
• Liver cirrhosis
• Concurrent use of phenytoin, phenobarbital, or primidone*

*Drug Interaction: Higher doses of vitamin D may be required. Mechanism is not known

Randomization was performed by computerized code by a researcher not involved in providing care to the patients. The healthcare providers were not blinded to patient allocation, as the study was not placebo-controlled. A four-week washout phase followed the first six weeks of therapy, during which patients did not receive any vitamin D therapy. After the washout interval, patients were crossed over to the alternate drug for a further six weeks (period 2). The total duration of the study was 16 weeks.

If hypercalcaemia (defined as serum corrected calcium ≥ 2.7 mmol/L) developed, the dose of the calcium containing phosphate binder was decreased at the prescriber's discretion. If hyperphosphatemia (defined as serum phosphate >1.8 mmol/L) developed, the dose of the calcium containing phosphate binder was increased or a non-calcium containing phosphate binder was added, also at the discretion of the prescriber.

Biochemical Assessment

Baseline measurements for alkaline phosphatase, creatinine and aluminum were taken from the subjects' routine bloodwork at the time of randomization. Blood samples for iPTH and 1,25-dihydroxyvitamin D_3 were drawn at baseline, 6, 10 and 16 weeks. Blood samples for the measurement of serum calcium, phosphate and albumin were drawn at baseline and every 2 weeks during periods 1 and 2. Serum corrected calcium was calculated using the following formula: 0.02 (40-albumin (g/L)) + serum calcium (mmol/L).

The Immulite 2000® intact PTH assay was used for the quantitative measurement of iPTH concentrations. The test is a solid-phase, two-site chemiluminescent enzyme-labelled immunometric assay that requires antibodies to bind to specific C-terminal and N-terminal fragments of the parathyroid hormone. The sensitivity of the assay is 0.1 pmol/L. The intraassay coefficient of variation ranged from 4.2% to 5.7%; the interassay coefficient of variation ranged from 6.3% to 8.8%.[6] A calf-thymus receptor, prepared by the Hospitals In-Common (Toronto, Canada) was used for the quantitative measurement of serum 1,25-dihydroxyvitamin D_3. The lower limit of this assay was 20 pmol/L.[7]

Statistical Analysis

For both iPTH and 1,25-dihydroxyvitamin D_3 concentrations, paired t-tests were used to compare the mean differences in serum concentration from baseline to six weeks in the calcitriol versus alfacalcidol groups. Paired t-tests were also used to calculate within group differences from baseline to six weeks for calcitriol and alfacalcidol separately. The Fisher's exact test was used to calculate differences in proportions for the other secondary outcomes. All p-values were two-tailed and $p \leq 0.05$ was defined as statistically significant.

RESULTS

Baseline Characteristics

A total of five subjects (four male, 1 female) were eligible and enrolled during the study period. Subject recruitment was more difficult than originally planned due to the fact that many patients receiving dialysis were already on a vitamin D analogue. Due to time limitations, a decision was made to close the study. This decision was made before the results were unblinded and analysed.

Four subjects were randomized to receive calcitriol during period 1 and alfacalcidol during period 2; one subject was randomized to receive alfacalcidol in period 1 and calcitriol in period 2. Each patient received hemodialysis three times weekly through the Renal Program at London Health Sciences Centre, London, Ontario, Canada. The median duration of hemodialysis prior to study commencement was four weeks. The etiologies of renal disease included reflux nephropathy (1), diabetic nephropathy (1), renal carcinoma (1) and cyclosporine-induced renal failure (2). Other baseline characteristics are outlined in Table 2.

TABLE 2 Baseline Characteristics of Patients at Study Entry

Baseline Characteristic	Median	Interquartile Range Difference
Age (years)	61	51,71 (20)
1,25-dihydroxyvitamin D_3(pmol/L)	33.0	18, 36 (18)
iPTH (pmol/L)	35.8	33.0, 39.3 (6.3)
Corrected calcium (mmol/L)	2.3	2.3, 2.4 (0.2)
Phosphate (mmol/L)	1.8	1.8, 1.9 (0.1)
Albumin (g/L)	30.0	29, 31 (3.0)
Calcium x Phosphate ($mmol^2/L^2$)	4.4	4.0, 4.5 (0.5)
Alkaline Phosphatase (u/L)	61.0	57.5, 66.8 (9.3)
Aluminum (nmol/L)	133.0	104, 189 (85)

Abbreviations: iPTH = intact parathyroid hormone

Primary Endpoint: Change in iPTH Concentration

Table 3 presents the changes in iPTH concentrations at baseline and after six weeks of therapy in both the calcitriol and alfacalcidol groups. At baseline, there was no difference in iPTH concentrations between the calcitriol and alfacalcidol phases (p=0.30). After six weeks of therapy, the iPTH concentrations were significantly different between the groups, with the calcitriol group having a significantly lower iPTH concentration as compared with the alfacalcidol group (p=0.009). The mean reduction in iPTH concentration from baseline to six weeks was significant for calcitriol (p=0.003). The iPTH concentration at six weeks in the alfacalcidol group was not significantly different from baseline (p=0.57).

Secondary Endpoints

Table 4 presents the changes in serum 1,25-dihydroxyvitamin D_3 concentrations. At baseline, there was no significant difference observed in 1,25-dihdyroxyvitamin D_3 concentrations between the calcitriol and alfacalcidol phases of the study (p=0.97). Similarly, there was no significant difference in the final 1,25-dihydroxyvitamin D_3 concentrations between groups (p=0.12). The baseline 1,25-dihdyroxyvitamin D_3 concentrations in the calcitriol group did not differ from the six-week concentrations (p=0.98). However, the 1,25-dihdyroxyvitamin D_3 concentrations in the alfacalcidol group significantly increased after six weeks of therapy (p=0.038).

There was no difference between the groups with respect to the serum corrected calcium at baseline (p=0.262) or at six weeks (p=0.10). Corrected calcium for the calcitriol group did not change significantly from baseline to six weeks (p=0.13). Similarly, there was no significant difference in corrected calcium between the baseline and six-week concentrations for the alfacalcidol group (p=0.80).

Serum phosphate did not differ between the calcitriol and alfacalcidol group at baseline (p=0.41) or at six weeks (p=0.10). There was no observed difference between the baseline and six-week serum phosphate for either the calcitriol group (p=0.44) or the alfacalcidol group (p=0.14). The calcium phosphate product did not differ between the calcitriol and alfacalcidol groups at baseline (p=0.55) and or at six weeks (p=0.60). There was no observed difference between baseline and six week calcium phosphate product for either the calcitriol group (p=0.86) or the alfacalcidol group (p=0.18).

TABLE 3 Intact PTH

Mean iPTH concentration ± standard deviation (pmol/L)

	0 weeks	**6 weeks**	**Mean Change (95% Confidence Interval)**	**Within Group Differences (p-value)**
Calcitriol Group	31.7 ± 6.7	5.44 ± 7.44	26.22 (14.9 to 37.5)	0.003
Alfacalcidol Group	19.9 ± 20.2	13.7 ± 6.98	6.12 (-21.05 to 33.3)	0.57
Between group differences (p-value)	0.30	0.009	0.13	Not applicable

Abbreviations: iPTH = intact parathyroid hormone

TABLE 4 1,25 Dihydroxyvitamin D_3 Concentrations

Mean 1,25-dihydroxyvitamin D_3 concentration ± standard deviation (pmol/L)

	0 weeks	**6 weeks**	**Median Change**	**Within Group Differences (p-value)**
Calcitriol Group	25.6 ± 9.4	25.8 ± 13.6	2.20 ±14.8	0.98
Alfacalcidol Group	25.2 ± 9.6	41.6 ± 13.8	16.4 ±16.8	0.038
Between group differences (p-value)	0.97	0.12	0.23	Not applicable

TABLE 5 Additional Secondary Endpoints

Number of Patients	**Calcitriol n=5**	**Alfacalcidol n=5**	**p-value**
In iPTH range (10-20pmol/L)	1	2	0.6
Who became hypercalcemic (cCa> 2.5mmol/L)	2	1	0.6
Who became hyperphosphatemic (P>1.8mmol/L)	2	2	1.0
Who developed elevated CaxP product (Ca x P>4.8$mmol^2/L^2$)	1	2	0.6
Who required an increased dose of phosphate binder	2	1	0.6

Abbreviations: iPTH =intact parathyroid hormone; cCa= corrected calcium; P=phosphorus; Ca x P=calcium phosphate product

Table 5 summarizes the results for the remaining secondary outcomes. There was no observed difference between alfacalcidol and calcitriol groups in the proportion of patients achieving a therapeutic iPTH range of 10-20 pmol/L. Similarly, there were no differences in the incidences of hypercalcaemia, hyperphosphatemia, elevated calcium phosphate product, and need for increasing doses of phosphate binders between the alfacalcidol and calcitriol periods.

DISCUSSION

Few studies comparing equal doses of alfacalcidol and calcitriol have been published. One prospective, randomized, crossover trial compared equal doses of intravenous calcitriol and alfacalcidol (1 mcg three times weekly) in twenty subjects receiving chronic hemodialysis.[8] In this study, the two vitamin D_3 analogues were equipotent in regards to suppression of iPTH concentrations after three months of intravenous therapy. Serum concentrations of 1,25-dihydroxyvitamin D_3, measured 48 hours after intravenous injection, were not different between the two groups.

A more recent single dose study compared equal doses (10 mcg) of intravenous calcitriol and alfacalcidol.[9] Twenty-four hours after administration, the percentage suppression of iPTH was approximately 60% with calcitriol and 20% with alfacalcidol. Effects on serum 1,25-dihydroxyvitamin D_3 concentrations were not examined in this study. Although iPTH may be more rapidly suppressed with intravenous calcitriol in the first 24 hours, this study does not provide information on the long-term suppression of parathyroid hormone with these agents.

Another retrospective study of 21 hemodialysis subjects with stable secondary hyperparathyroidism examined the effect of changing from intravenous calcitriol to intravenous alfacalcidol as a result of a hospital drug formulary decision.[10] In the alfacalcidol period, mean parathyroid hormone concentrations increased significantly from 30.3 pmol/L to 48.6 pmol/L ($p<0.001$) despite a significant increase in the mean alfacalcidol dose (1.7 mcg versus 2.3 mcg three times weekly, $p<0.05$). Serum calcium concentrations did not show significant differences but phosphorus control was improved in the alfacalcidol period. However, the non-randomized, retrospective design of this trial is a weakness.

There is only one previously published study that compared the effects of similar doses of oral calcitriol and oral alfacalcidol on calcium, phosphorus, parathyroid hormone, and alkaline phosphatase in 40 chronic kidney disease patients (31 receiving hemodialysis; 9 not on dialysis with creatinine clearance <25 mL/min).[11] The doses of oral alfacalcidol and oral calcitriol ranged from 2 mcg to 2.5 mcg daily. The mean dose requirements for both agents decreased progressively throughout treatment from 2 mcg daily at the start to less than 1 mcg daily after two years. No significant differences in the outcomes of patients on the different agents were observed over 7 to 49 months so the data for the two compounds were pooled. However, this study is limited, as the doses used largely exceed currently prescribed doses and only the pooled data is reported, therefore it is difficult to assess equivalency.

As oral vitamin D_3 analogues are used first-line in Canada, we wanted to design a trial using the oral route. The bioavailability of oral alfacalcidol is 71% and 62% for oral calcitriol.[12,13] However, a limitation of this study is that there is likely patient to patient variability in the bioavailability of these agents especially as a previous study has shown that oral calcitriol can undergo substantial degradation by intestinal cells.[14]

Strengths of our study design include the fact that it was a prospective, randomized, crossover trial. Medication compliance was documented by administering the doses of medication in the hemodialysis unit. Although our study had a small sample size, a statistically significant difference was found, and this may be due to the fact that patients served as their own controls. Nevertheless, since the trial was small and of short duration, the possibility of a chance finding or transient effect cannot be ruled out.

While the previously mentioned prospective, randomized crossover trial of intravenous calcitriol and alfacalcidol suggested that these agents produce similar clinical effects on iPTH after three months of therapy,[8] our study suggests

that during the first six weeks of therapy, oral calcitriol is more effective at suppressing iPTH than oral alfacalcidol. However, secondary hyperparathyroidism is a chronic disease and it is unclear if early rapid suppression of iPTH is required to prevent complications. Thus, while our study suggests there are differences in iPTH suppression early in therapy, studies are required to assess whether the clinical differences between oral formulations are maintained after prolonged therapy.

In the present study, oral alfacalcidol therapy was associated with a significantly increased serum concentration of 1,25-dihydroxyvitamin D_3 after six weeks. However, this accumulation of 1,25-dihydroxyvitamin D_3 did not translate into suppression of iPTH concentrations. Conversely, calcitriol therapy significantly suppressed iPTH after six weeks of therapy; however, no differences in 1,25-dihydroxyvitamin D_3 concentrations were observed. This lack of relationship between 1,25-dihydroxyvitamin D_3 concentrations and iPTH has been previously described in chronic kidney disease.[15] This particular study reported that no correlation was found between serum 1,25 dihydroxyvitamin D_3 concentrations and either intact PTH or midregion/C-terminal PTH concentrations.[15]

A four-week washout period was used to allow adequate clearance of the first study drug prior to administration of the second study drug. The half-lives of alfacalcidol and calcitriol are 35 hours and 12 hours, respectively. This same washout period was also used in the previous intravenous crossover study.[8] In addition, there was no significant difference seen between the groups with respect to the baseline iPTH concentrations. This would suggest that the washout period was adequate. However, given the small sample size, it is possible that no difference was observed between baseline iPTH concentrations because there were too few patients to detect differences at baseline.

Overall, this study raises an important hypothesis that should be studied in future randomized trials of adequate sample size to determine whether clinically-important differences between alfacalcidol and calcitriol exist over the longer term. Additionally, dose-equivalence trials should be carried out to determine whether suboptimal doses of alfacalcidol are being used.

CONCLUSIONS

This small randomized crossover study provides preliminary evidence that equal doses of oral alfacalcidol and calcitriol may demonstrate differences in iPTH suppression during the first six weeks in dialysis patients treated for secondary hyperparathyroidism. Further comparative trials are required to confirm this finding and to determine whether important differences in parathyroid hormone suppression exist between oral calcitriol and alfacalcidol beyond the six-week period.

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