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No difference between alfacalcidol and paricalcitol in the treatment of secondary hyperparathyroidism in hemodialysis patients: a randomized crossover trial

Ditte Hansen[1], Knud Rasmussen[1], Henning Danielsen[2], Helmut Meyer-Hofmann[3], Egidijus Bacevicius[3], Thomas G. Lauridsen[4], Jens K. Madsen[5], Birgitte G. Tougaard[5], Peter Marckmann[6], Peter Thye-Roenn[7], Jørgen E. Nielsen[8], Svend Kreiner[9] and Lisbet Brandi[1]

[1]Section of Nephrology, Department of Medicine, Roskilde Hospital, Roskilde, Denmark; [2]Section of Nephrology, Department of Medicine, Region Hospital Viborg, Viborg, Denmark; [3]Department of Nephrology, Aalborg Hospital - Århus University Hospital, Aalborg, Denmark; [4]Section of Nephrology, Department of Medicine, Region Hospital Holstebro, Holstebro, Denmark; [5]Department of Nephrology, Århus University Hospital Skejby, Århus, Denmark; [6]Department of Nephrology, Odense University Hospital, Odense, Denmark; [7]Section of Nephrology, Department of Medicine, Esbjerg Hospital of Southwest Denmark, Esbjerg, Denmark; [8]Section of Nephrology, Department of Medicine, Holbæk Hospital, Holbæk, Denmark and [9]Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark

Alfacalcidol and paricalcitol are vitamin D analogs used for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease, but have known dose-dependent side effects that cause hypercalcemia and hyperphosphatemia. In this investigator-initiated multicenter randomized clinical trial, we originally intended two crossover study periods with a washout interval in 86 chronic hemodialysis patients. These patients received increasing intravenous doses of either alfacalcidol or paricalcitol for 16 weeks, until parathyroid hormone was adequately suppressed or calcium or phosphate levels reached an upper threshold. Unfortunately, due to a period effect, only the initial 16-week intervention period for 80 patients was statistically analyzed. The proportion of patients achieving a 30% decrease in parathyroid hormone levels over the last four weeks of study was statistically indistinguishable between the two groups. Paricalcitol was more efficient at correcting low than high baseline parathyroid hormone levels, whereas alfacalcidol was equally effective at all levels. There were no differences in the incidence of hypercalcemia and hyperphosphatemia. Thus, alfacalcidol and paricalcitol were equally effective in the suppression of secondary hyperparathyroidism in hemodialysis patients while calcium and phosphorus were kept in the desired range.

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Correspondence: *Ditte Hansen, Section of Nephrology, Department of Medicine, Roskilde Hospital, Koegevej 7-13, DK-4000 Roskilde, Denmark. E-mail: dittehansen@dadlnet.dk*

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Patients with chronic kidney disease have increased risk of cardiovascular disease and mortality compared with patients with normal renal function.[1–3] Epidemiological studies have found this increased risk to be associated with the disturbances in the mineral metabolism, including poorer cardiovascular and mortality outcomes in patients with elevated calcium and phosphate levels.[4–10]

Secondary hyperparathyroidism is a common complication in patients with renal failure and is associated with renal osteodystrophy,[11,12] risk of bone fracture,[13] and higher risk of cardiovascular morbidity and mortality.[7,14]

Vitamin D analogs are used to treat secondary hyperparathyroidism. However, vitamin D analogs increase the calcium and phosphate levels by increasing the intestinal calcium and phosphate absorption, as well as increasing the calcium and phosphate mobilization from the bone.[15] To suppress the secondary hyperparathyroidism without increasing calcium and phosphate, treatment modalities such as non-calcium-containing phosphate binders, selective vitamin D analogs, and calcimimetics have been developed.

Alfacalcidol (1α-hydroxyvitamin D_3) and paricalcitol (19-nor-1α,25 dihydroxyvitamin D_2) are frequently used vitamin D analogs, especially in Europe. Alfacalcidol has been used for treatment of secondary hyperparathyroidism and renal osteodystrophy since 1978. Paricalcitol was registered in Denmark in 2004 and was introduced as a less calcemic and phosphatemic vitamin D analog. In uremic rats,[16] paricalcitol suppressed parathyroid hormone (PTH) levels with less hypercalcemic and hyperphosphatemic effects than calcitriol (1α,25 dihydroxyvitamin D_3). Until now, no randomized controlled study addressed possible differences between alfacalcidol and paricalcitol.[17]

This investigator-initiated clinical trial compared alfacalcidol and paricalcitol. In a crossover study with forced

titration, we tested whether there is any difference in the ability of paricalcitol and alfacalcidol to reduce secondary hyperparathyroidism in hemodialysis patients without increasing *p*-calcium and *p*-phosphate outside the desired range.

RESULTS

Patient characteristics

Patients were recruited from June 2007 through December 2009. Patients were followed up until the last study visit (the last patient visit was in October 2010).

Because of the lack of eligible patients, the trial was stopped early. This decision was taken by the steering committee. No interim analysis took place. A final inclusion date was set 3 months ahead, and all investigators made a final recruitment effort. A total of 86 patients were randomized, of whom 80 patients completed the first treatment period and 71 patients completed both treatment periods (Figures 1 and 2). Demographic characteristics for randomized and analyzed participants are presented in Table 1.

Mineral metabolism

Changes in PTH levels, ionized calcium (Ca), and phosphate (P) for the patients who completed the crossover study are shown in Figure 3. There was a significant difference between the baseline mean PTH levels in period 1 and period 2 (552 ± 202 and 453 ± 249 pg/ml, respectively; $P = 0.01$). The PTH level was significantly higher before beginning of washout period 1 (317 ± 155 pg/ml) compared with washout period 2 (219 ± 187 pg/ml; $P < 0.01$). The PTH levels before and after washout 2 were significantly correlated (0.398; $P = 0.001$). Only four patients were formerly untreated and included directly at week 6 (paricalcitol–alfacalcidol: $n = 3$; and alfacalcidol–paricalcitol: $n = 1$).

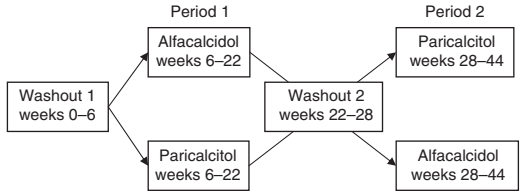


Figure 2 | Treatment periods and treatment arms.

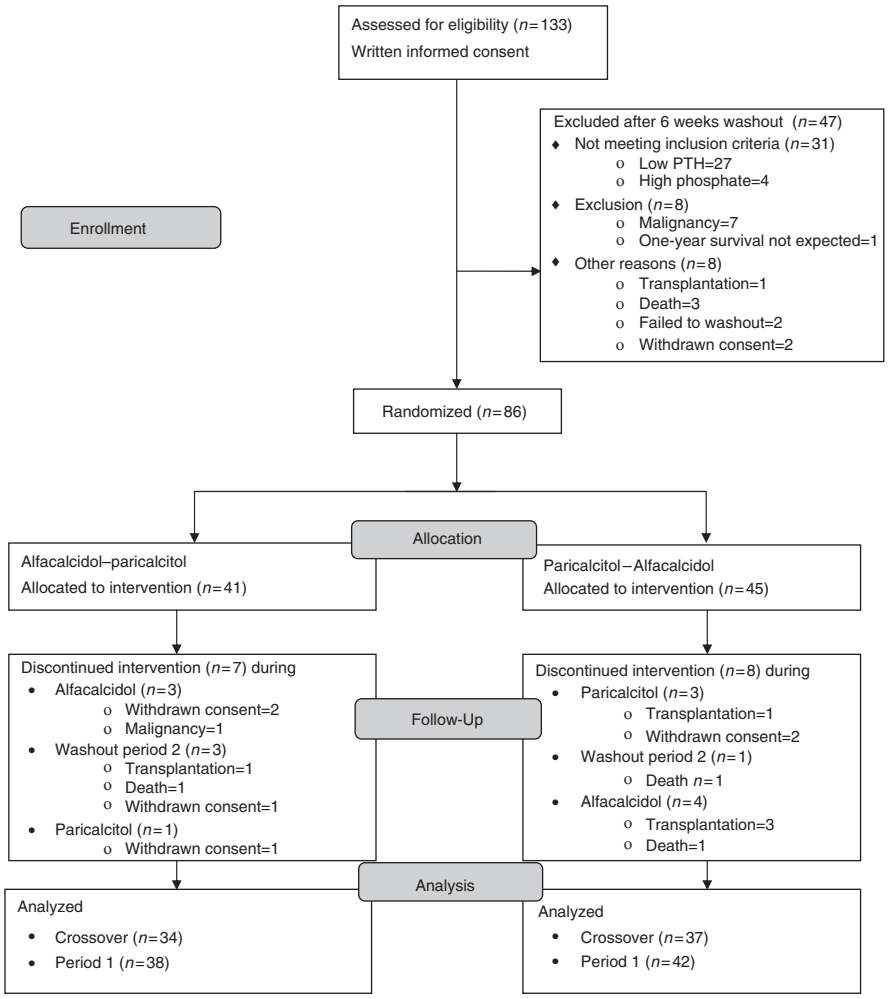


Figure 1 | Participants' flow through the study. PTH, parathyroid hormone.

Table 1 | Baseline demographic and clinical characteristics

	All randomized (*n*=86)		Analyzed period 1 (*n*=80)	
	Alfacalcidol–paricalcitol (*n*=41)	Paricalcitol–alfacalcidol (*n*=45)	Alfacalcidol (*n*=38)	Paricalcitol (*n*=42)
Age (years ± s.d.)	63.6 ± 13.7	63.5 ± 15.3	63.7 ± 14.0	63.7 ± 15.8
Gender (male/female (%/%))	27/14 (66/34)	28/17 (62/38)	25/13 (66/34)	26/16 (62/38)
Race				
Caucasian	41 (100%)	44 (97%)	38 (100%)	41 (98%)
Hispanic	0 (0%)	1 (3%)	0 (0%)	1 (2%)
Diabetes	6 (15%)	7 (16%)	6 (16%)	7 (17%)
Time on dialysis (months; median (range))	38 (3–236)	36 (3–262)	35.5 (3–236)	37.5 (3–240)
Etiology of end-stage kidney disease				
Diabetes	5 (12%)	7 (16%)	5 (13%)	7 (17%)
Nephrosclerosis	5 (12%)	8 (18%)	5 (13%)	8 (19%)
Polycystic	7 (17%)	7 (16%)	6 (16%)	6 (14%)
Chronic glomerulonephritis	9 (22%)	7 (15%)	9 (24%)	6 (14%)
Chronic interstitial	3 (8%)	3 (7%)	2 (5%)	2 (5%)
Postrenal	5 (12%)	4 (9%)	4 (11%)	4 (10%)
Unknown	7 (17%)	9 (20%)	7 (19%)	9 (21%)
Previous vitamin D therapy	40 (98%)	43 (96%)	37 (97%)	41 (98%)
Alfacalcidol oral	39 (95%)	39 (87%)	37 (97%)	37 (88%)
Mean dose (μg/week; median (range))	3.5 (1.5–18.0)	3.5 (0.5–12.0)	3.5 (1.5–18.0)	3.5 (0.5–10.5)
Alfacalcidol intravenous	1 (2%)	1 (2%)	0 (0%)	1 (2%)
Paricalcitol oral	0 (0%)	2 (4%)	0 (0%)	2 (5%)
Cholecalciferol oral	0 (0%)	2 (4%)	0 (0%)	2 (5%)
Ergocalciferol oral	0 (0%)	1 (2%)	0 (0%)	1 (2%)
p-Intact PTH (pg/ml ± s.d.)	566 ± 208	538 ± 190	571 ± 210	528 ± 176
p-Phosphate (mmol/l ± s.d.)	1.48 ± 0.27	1.46 ± 0.28	1.49 ± 0.25	1.45 ± 0.28
p-Calcium ionized (mmol/l ± s.d.)	1.16 ± 0.07	1.15 ± 0.07	1.15 ± 0.07	1.15 ± 0.07
p-Hemoglobin (mmol/l ± s.d.)	7.3 ± 0.76	7.3 ± 0.76	7.3 ± 0.76	7.3 ± 0.77
p-Albumin (g/l ± s.d.)	40.5 ± 3.6	40.0 ± 3.8	40.3 ± 3.6	39.7 ± 3.7
p-25 hydroxyvitamin D2+D3 (nmol/l ± s.d.)	42.1 ± 21.3	40.5 ± 24.0	41.1 ± 21.2	39.8 ± 24.2

A significant period effect was found between period 1 and period 2. Therefore, the crossover data were not accessible for further analysis. The analysis was performed for data from period 1 ($n = 80$). As there were no laboratory data from dropout patients, these were not included in the analysis.

After 16 weeks of treatment, a 30% decrease in PTH level during the last 4 weeks was reached in 82 and 93% of alfacalcidol- and paricalcitol-treated patients, respectively ($P = 0.180$). A total of 68% and 83% of alfacalcidol- and paricalcitol-treated patients reached a level of PTH <300 pg/ml ($P = 0.188$). Success criteria defined as PTH <300 pg/ml with phosphate <1.8 mmol/l and ionized calcium <1.30 mmol/l was reached in 18 and 31% of alfacalcidol- and paricalcitol-treated patients, respectively ($P = 0.301$).

Baseline measurements, mean measurements of the last 4 weeks of treatment, and comparisons of changes for primary and secondary end points are presented in Table 2.

When analyzing the PTH changes with the baseline values as covariates, there was a significant interaction between the effect of baseline PTH level and the effect of treatment ($P = 0.012$). The effect of the interaction is shown in Figure 4, where mean measurements of the last 4 weeks are plotted against baseline PTH levels. The difference between treatments in patients with high versus low baseline PTH levels is illustrated in Figure 5. The analysis was also performed for period 2 in the 71 patients who fulfilled the study and the same interaction was found, although not statistically significant ($P = 0.10$).

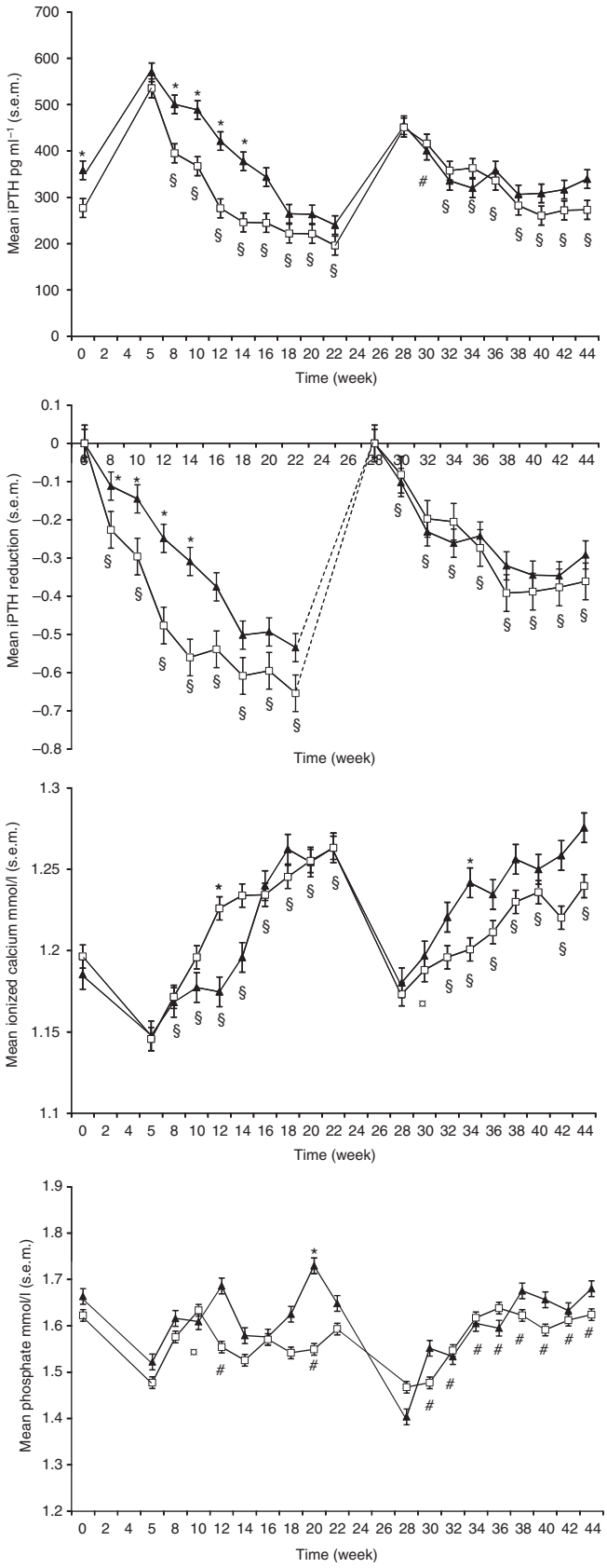
Overall, the mean PTH levels decreased faster in the paricalcitol group. A 30% decrease in mean PTH level was reached after 4 weeks of treatment in the paricalcitol group and after 8 weeks of treatment in the alfacalcidol group. Mean PTH levels were suppressed beneath 300 pg/ml after 6 weeks of treatment in the paricalcitol group and after 12 weeks of alfacalcidol treatment.

The incidence levels of hyperphosphatemia, hypercalcemia, and elevated Ca × P are described in Table 3.

The median (range) final doses for the last 4 weeks were as follows: alfacalcidol 5.3 μg/week (0.0–33.0 μg/week), and paricalcitol 18.1 μg/week (6.8–60.0 μg/week).

Phosphate-binder usage is presented in Table 4. No patient received magnesium- or aluminum-containing phosphate binders. No patient entered the use of calcimimetics, nor were they referred for parathyroidectomy during the study.

Based on the present changes in PTH, calcium and phosphate levels, in the alfacalcidol group ($n = 38$) and



paricalcitol group ($n = 42$), and on the basis of the results of the two-tailed test, $\alpha = 0.05$, a power of 33, 86, and 99.6% is calculated to detect a difference in PTH reduction of 10, 20, and 30% between groups, respectively. A calcium increase of 5 and 10% is detected with a power of 77.5 and 99.9%, respectively, and a phosphate increase of 5, 10, and 20% is detected with a power of 11, 28, and 79%, respectively.

Hemodynamic parameters

The baseline systolic pressure, diastolic pressure, pulse pressure, and pulse were equal between groups. There was no change in these parameters during the treatment, and no difference in changes between groups (Supplementary Material, Table 3S online).

Safety measures and adverse events

There were no clinical relevant differences in changes in safety parameters. These are shown in detail in Supplementary Material, Table 2S online.

During the study, 490 adverse events (AEs) were registered. There was a higher report of skin-related AEs in alfacalcidol-treated patients, consisting of various kinds of complaints. In total 132 of the AEs were considered as a serious AE, including six deaths. Three patients died during the primary washout period, before randomization, and two during the second washout period: three because of septicemia, one because of herpes simplex virus encephalitis, and one because of sudden death. One patient receiving alfacalcidol decided to withdraw from dialysis treatment during second treatment period, and died from pneumonia. The remaining 126 serious AEs occurred due to hospitalization or prolonged hospitalization.

Six patients withdrew from the study of their own accord. No patients were withdrawn by the investigators.

The AEs and withdrawals are further specified in Supplementary Material, Table 1S online).

DISCUSSION

This study is the first randomized clinical trial comparing alfacalcidol and paricalcitol. Hemodialysis patients with secondary hyperparathyroidism were treated with alfacalcidol and paricalcitol under forced titration until PTH were sufficiently suppressed or calcium and/or phosphate passed a maximal threshold. In the uncorrected analysis, there were no statistically significant differences in the ability of the two compounds to suppress PTH after 16 weeks of treatment, whereas calcium and phosphate were maintained within the

Figure 3 | Changes in parathyroid hormone (PTH), % reduction in PTH, changes in ionized calcium and phosphate during the 44-week study period. Alfacalcidol–paricalcitol (AP, ▲), $n = 34$. Paricalcitol–alfacalcidol (PA, □), $n = 37$. Weeks 0–6 and weeks 22–28 were washout periods. Comparison between groups; $^{*}P < 0.05$, unpaired t-test. Comparison with baseline (week 6 in period 1 and week 28 in period 2); $^{\S}P < 0.05$, paired t-test for both AP and PA group. $^{\#}P < 0.05$, paired t-test AP group. $^{¤}P < 0.05$, paired t-test PA group.

Table 2 | Outcome table of primary end points

	Alfacalcidol			Paricalcitol			
	Baseline	16 Weeks	Changes (s.e.m.)	Baseline	16 Weeks	Changes (s.e.m.)	Difference in changes after 16 weeks (95% CI)
PTH (pg/ml), mean (s.d.)	571 (210) n=38	249 (174) n=38	−323 (41)*	528 (176) n=42	199 (166) n=42	−329 (23)*	−6.8 (−99.2 to 85.6)
% change			−53.1 (5.4)			−63.8 (3.6)	−10.7 (−23.6 to −2.2)
Ionized calcium (mmol/l), mean (s.d.)	1.15 (0.07) n=38	1.26 (0.09) n=38	0.10 (0.02)*	1.15 (0.07) n=42	1.26 (0.09) n=42	0.11 (0.01)*	−0.01 (−0.05 to −0.03)
% change (s.e.m.)			9.3 (1.5)			9.9 (1.1)	−0.6 (−4.2 to 3.1)
Phosphate (mmol/l), mean (s.d.)	1.49 (0.25) n=38	1.67 (0.32) n=38	0.18 (0.06)*	1.45 (0.28) n=42	1.58 (0.34) n=42	0.13 (0.06)*	0.05 (−0.12 to 0.22)
% change (s.e.m.)			15.1 (4.7)			13.4 (5.4)	1.7 (−12.7 to 16.0)
Calcium × phosphate (mmol/l)^2, mean (s.d.)	1.72 (0.32) n=38	2.09 (0.38) n=38	0.38 (0.07)*	1.67 (0.35) n=42	2.00 (0.46) n=42	0.32 (0.08)*	−0.01 (−0.23 to 0.21)
% change (s.e.m.)			25.4 (5.0)			24.3 (5.7)	1.1 (−14.2 to 16.4)
Alkaline-phosphatase (U/l), mean (s.d.)	88.4 (34.1) n=38	82.7 (40.3) n=38	−5.7 (5.8)	91.4 (29.9) n=41	86.1 (35.1) n=41	−5.8 (3.5)	−4.2 (−14.8 to 6.5)
% change (s.e.m.)			−2.3 (7.2)			−5.4 (3.7)	−3.1 (−18.8 to 12.6)
25-(OH) vitamin D (nmol/l), mean (s.d.)	41.1 (21.2) n=33	42.8 (27.0) n=33	2.9 (4.2)	39.8 (24.2) n=39	36.4 (25.9) n=39	−4.6 (4.1)	7.4 (−4.3 to 19.2)
% change (s.e.m.)			42.7 (26.5)			−0.9 (9.2)	41.8 (−14.8 to 98.5)
1,25 $(OH)_2$ vitamin D (pmol/l), median (range)	6.0 (19.5) n=8	21.0 (77.5) n=8	13.5 (30.0)**	5.0 (8.5) n=10	2.5 (10.5) n=10	0.3 (13.0)	***
% change (s.e.m.)			267.3 (105.6)			6.9 (28.2)	***

Abbreviations: CI, confidence interval; PTH, parathroid harmone.
Change from baseline within group; *P<0.05, paired t-test. Change from baseline within group; **P<0.05, Wilcoxon test. Comparison of changes between groups; ***P<0.05, Mann–Whitney U test.

desired range. With a sufficient power to detect a 20% difference in PTH suppression, this indicates that overall alfacalcidol and paricalcitol are equally effective.

Paricalcitol has, almost exclusively, been compared with calcitriol in both animal[16,18,19] and human[20–30] studies. In a large north American–European (n = 263) randomized trial, Sprague *et al.*[28] compared paricalcitol and calcitriol. Similar to our study in which the end point was a 30% reduction, no difference in the proportion of subjects reaching a PTH suppression of 50% was found. Sprague *et al.* found a reduced incidence of sustained hypercalcemia and elevated Ca × P in the paricalcitol-treated group. In contrast, we did not find any difference in the incidence of hypercalcemia, hyperphosphatemia, or elevated Ca × P between alfacalcidol and paricalcitol. The results from the comparative studies of paricalcitol and calcitriol have been applied to alfacalcidol, classically considered as a prohormone, exerting its effects after 25 hydroxylations in the liver into calcitriol.[31] The differences between the present study and the study by Sprague *et al.* may be explained by an innate effect of alfacalcidol, which does not induce elevated phosphate and calcium. Indeed, acute intravenous administration of equal doses of alfacalcidol and calcitriol suppressed PTH to the same level, whereas the plasma concentrations of 1,25$(OH)_2$vitaminD raised to a lower level after alfacalcidol than after calcitriol.[32] Furthermore a direct suppressive effect of alfacalcidol on PTH production in bovine parathyroid cells has been observed.[33] Alfacalcidol and calcitriol have been compared in small long-term studies in hemodialysis patients.[34–36] Alfacalcidol and calcitriol were administered intravenously by El-Rashaid *et al.*[34] and intermittent orally by Kiattisunthorn *et al.*[35] Both found equal PTH suppression, with equal changes in calcium and phosphate levels. Equal doses of both drugs were applied by El-Rashaid *et al.*, arguing for alfacalcidol being a prodrug to calcitriol. On the other hand, the oral dose of alfacalcidol in the study by Kiattisunthorn *et al.* was half that predicted from pharmacokinetic studies,[32] arguing for a direct effect of alfacalcidol.

When correcting for baseline PTH level, we found that alfacalcidol suppressed PTH throughout the entire range of PTH levels, whereas paricalcitol was more efficient at the lower PTH levels than at the higher PTH levels. The differentiated paricalcitol response is in accordance with a switch study from ordinary calcitriol to scheduled paricalcitol in hemodialysis patients. The patients with the highest PTH responded least to paricalcitol treatment and the baseline PTH level was independently associated with response to paricalcitol treatment.[30] The baseline-independent PTH-lowering effect was not found in randomized studies comparing oral paricalcitol with placebo in stages 3–4 CKD patients, [37] and oral alfacalcidol with calcitriol in hemodialysis patients.[35] Other randomized studies examining paricalcitol or alfacalcidol have used baseline PTH as covariate, but did not report whether interaction between baseline and treatment was present.[38–40]

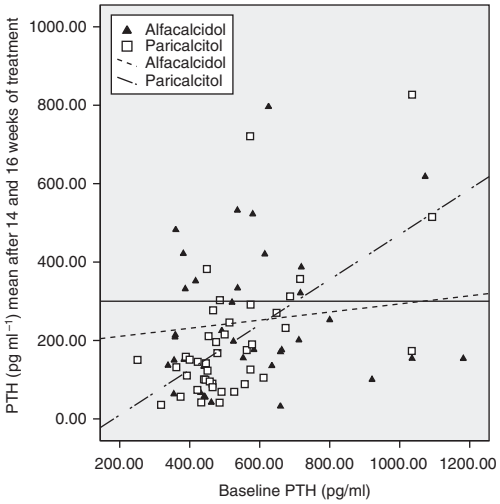


Figure 4 | Relation between baseline parathyroid hormone (PTH) and final PTH in treatment groups. Regression line for mean PTH after 14 and 16 weeks of treatment as a function of baseline PTH in the alfacalcidol (▲———) and paricalcitol (□ · — ·) treated groups ($P = 0.012$). The upper desired PTH level (bold line).

A difference in the PTH response across the range of baseline PTH may have several possible mechanisms. The vitamin D analogs may differ in their direct effect on parathyroid glands and the production of PTH or indirectly by differences in calcium and phosphate levels. In addition, FGF23, a recently discovered phosphate-regulating hormone,[41] was shown to suppress PTH secretion in rats, parathyroid rat culture, and bovine parathyroid cells.[42,43] It is unknown whether alfacalcidol and paricalcitol differ in their induction of the synthesis of FGF23.

Only some of the possible areas in which alfacalcidol and paricalcitol may differ in their direct effect on the parathyroid gland have been explored. Alfacalcidol binds to the vitamin D receptor, with 0.4% of the affinity of calcitriol,[44] whereas the affinity for paricalcitol is 33% of calcitriol.[45] This difference may be compensated by intracellular accumulation of alfacalcidol. Indeed, paricalcitol has the same affinity for vitamin D-binding protein as calcitriol, whereas alfacalcidol has a low affinity for vitamin D-binding protein and may rapidly be taken up by the parathyroid gland before 25 hydroxylations by the liver.[46] Non-genomic actions[15] of vitamin D analogs and actions not involving the vitamin D receptor[47] have been described and may be affected variously by different analogs. Other issues that remain to be explored are different conformational changes in VDR when binding, different interaction with corepressor and co-activators required for VDR function, different binding to intracellular proteins, and different induction of catabolic enzymes.[46]

In comparative studies of paricalcitol and calcitriol, a decreased calcium mobilization from bone in parathyroidectomized rats,[19] decreased intestinal calcium uptake in hemodialysis patients[23] and in normal rats,[18] and decreased

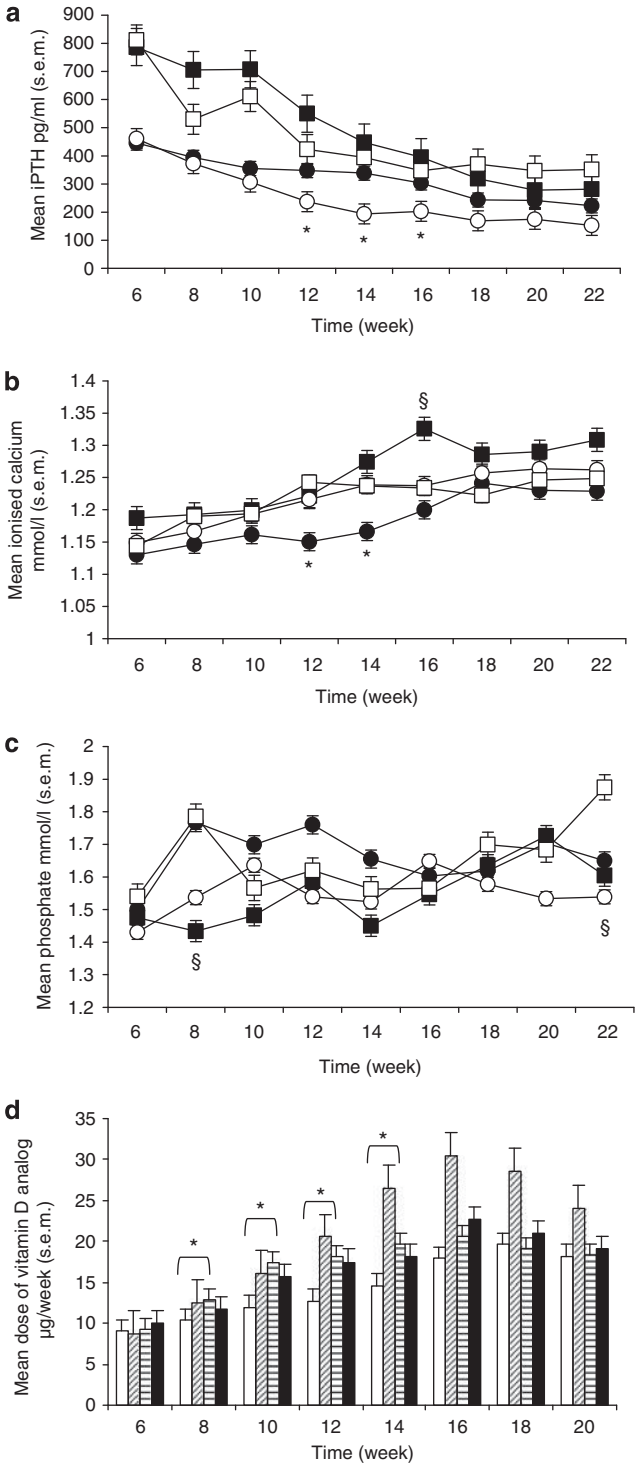


Figure 5 | Changes in parathyroid hormone (PTH), ionized calcium, phosphate, and vitamin D analog dose during first treatment period, divided according to the level of PTH at baseline. Changes separated into low baseline PTH ⩽600 pg/ml (alfacalcidol, $n = 24$, ●; paricalcitol, $n = 34$, ○) and high baseline PTH >600 pg/ml (alfacalcidol, $n = 14$, ■; paricalcitol, $n = 8$, □). (**a**) PTH; (**b**) ionized calcium; (**c**) phosphate; (**d**) vitamin D analog dose. Alfacalcidol dose is multiplied by 3, because alfacalcidol: paricalcitol dosing is 1:3. Alfacalcidol, low PTH (white); alfacalcidol, high PTH (diagonal lines); paricalcitol, low PTH (horizontal lines); paricalcitol, high PTH (black). Comparison between low PTH groups; $^{*}P < 0.05$ and high PTH groups; $^{§}P < 0.05$ (unpaired *t*-test.).

incidence of hypercalcemia and hyperphosphatemia in hemodialysis patients[28] were found during paricalcitol treatment. Differences in other treatment modalities could compensate for differences in calcium and phosphate levels in the present study. Importantly, the only difference in phosphate binders was a decreased sevelamer usage in the alfacalcidol group, arguing for a less hyperphosphatemic tendency. Changes in urea reduction rate as an indicator of dialysis dose were equal. Further assessment of dialysis dose was not performed. We did not carry out registration of dietary intervention and advice. This could be a bias with respect to the phosphate level, as the study was unblinded.

The dosing of alfacalcidol:paricalcitol was given in 1:3 ratio, according to the present recommendation, when switching from calcitriol to paricalcitol.[22] This ratio may be questioned,[48] but the forced titration should secure a sufficient dose increase in both groups.

Paricalcitol decreased PTH faster than alfacalcidol in the first treatment period. As illustrated in Figures 3 and 5, the level of ionized calcium was increased at the same time, which probably explains the different effect on PTH. A non-equipotent dose titration could be the reason. Whether a difference of 4 to 6 weeks before reaching the goal has any clinical importance for the long-term prognosis regarding bone fracture, and the cardiovascular disease risk associated with elevated PTH,[6,49,50] is not known.

As in earlier interventional studies,[29,51] the PTH apparently reached a plateau after 14–16 weeks of treatment. Prolonging the study period may have led to further PTH suppression even after 16 months,[22] possibly through a reduction in the parathyroid hyperplasia.

The period effect observed was not due to a pharmacological effect of the analogs.[32,52] Apparently, a biological effect persists after 6 weeks washout as the rise in PTH depends on the degree of the preceding PTH suppression. Vitamin D treatment upregulates the vitamin D receptors,[53,54] and this may make the parathyroid glands more sensitive to the small amounts of endogenous vitamin D, withholding the PTH suppression.

In conclusion, this randomized study found alfacalcidol and paricalcitol to be overall equally effective in suppressing

Table 3 | Incidence of hypercalcemia, hyperphosphatemia, and elevated Ca × P product

	Number of patients		
	Alfacalcidol (n=38; %)	Paricalcitol (n=42; %)	P-value
Hypercalcemia (ionized calcium > 1.30 mmol/l) at least once	21 (55)	24 (57)	0.866
Hypercalcemia (ionized calcium > 1.30 mmol/l) at least two consecutive measurements	12 (32)	16 (38)	0.542
Hyperphosphatemia (phosphate ⩾ 1.80 mmol/l) at least once	29 (76)	29 (69)	0.467
Hyperphosphatemia (phosphate ⩾ 1.80 mmol/l) at least two consecutive measurements	17 (45)	14 (33)	0.296
Elevated Ca × P ⩾ 2.3 $(mmol/l)^2$ at least once	25 (66)	29 (69)	0.756
Elevated Ca × P ⩾ 2.3 $(mmol/l)^2$ at least two consecutive measurements	14 (37)	16 (38)	0.908

Comparison of proportions between groups by Fisher's exact test.

Table 4 | Phosphate binder use in treatment groups

Number of patients receiving phosphate binder	Alfacalcidol (n=38)		Paricalcitol (n=42)	
Median daily dose, mg (range)	Before treatment	After 16 weeks treatment	Before treatment	After 16 weeks treatment
Any binder	33 (87%)	34 (89%)	38 (90%)	39 (93%)
Calcium containing	28 (74%) 1500 (540–4000)	26 (68%) 1500 (540–4000)	34 (81%) 1440 (500–4000)	31 (74%) 1440 (500–4800)
Begin or increase		3 (8%)		1 (2%)
Stop or decrease		6 (16%)		6 (14%)
Sevelamer	17 (45%) 2400 (1600–7200)	18 (47%) 4800 (1600–7200)	22 (52%) 4800 (1600–7200)	25 (60%) 4800 (1600–7200)
Begin or increase		6 (16%)		5 (12%)
Stop or decrease		4 (11%)*		0
Lanthanum	5 (13%) 2250 (1500–3000)	8 (21%) 2250 (2250–4500)	7 (17%) 2250 (1500–4500)	7 (17%) 2250 (2250–4500)
Begin or increase		6 (16%)		2 (5%)
Stop or decrease		1 (3%)		0

Comparison between groups and within groups, number of patients receiving phosphate binder treatment; no difference ($P<0.05$, Fisher's exact test). No difference between groups in dose of phosphate binder ($P<0.05$, Mann–Whitney test). No difference in dose before and after treatment within groups ($P<0.05$, Wilcoxon signed rank test). Number of patients who 1: began phosphate binder or increased dose; 2: stopped phosphate binder or decreased dose (*$P<0.05$, Fisher's exact test).

Table 5 | Dosing schedule

Start dose Alfacalcidol 3 μg/week Paricalcitol 9 μg/week		
Dose titration	iPTH > 150 pg/ml	iPTH ⩽ 150 pg/ml
p-Calcium <1.30 mmol/l and *p*-phosphate <1.80 mmol/l	Increase 50%	Unchanged dose
1.35 mmol/l⩾*p*-calcium ⩾1.30 mmol/l and *p*-phosphate <1.80 mmol/l	Unchanged dose	Unchanged dose
p-Calcium >1.35 mmol/l and/or *p*-phosphate ⩾1.80 mmol/l persist after control	Decrease 33%	Decrease 33%
p-Phosphate >2.00 mmol/l or *p*-calcium >1.40 mmol/l during 4 weeks	Pause treatment for 2 weeks	Pause treatment for 2 weeks

secondary hyperparathyroidism in hemodialysis patients. No difference in calcium and phosphate increase or episodes of hypercalcemia or hyperphosphatemia was observed. Alfacalcidol suppressed hyperparathyroidism independent of baseline PTH level, whereas paricalcitol was most effective at the lower PTH levels.

MATERIALS AND METHODS

This was an investigator-initiated, multicenter, block-randomized (1:1), crossover trial. The study design has been earlier described and discussed,[55] and is briefly summarized. The trial was set to identify a superiority of paricalcitol compared with alfacalcidol. The study took place in Danish public hospital dialysis departments.

The study was initiated in 11 departments; one center was dropped because of poor data quality, and analysis of data from this center was not possible.

Eligible subjects were >18 years old and were receiving chronic hemodialysis therapy. After a minimum of 6 weeks washout, without any kind of vitamin D supplement, and sufficiently regulated *p*-phosphate (<1.8 mmol/l) and ionized *p*-calcium (<1.25 mmol/l) levels, the patients were included if *p*-PTH was >350 pg/ml (37.1 pmol/l). The maximal daily dose of elementary calcium in phosphate binders was 1600 mg. Calcimimetics were not allowed.

Intervention was carried out as shown in Figure 2 and Table 5. Alfacalcidol (Etalpha, LEO Pharma A/S, Ballerup, Denmark) and paricalcitol (Zemplar, Abbott Scandinavia AB, Solna, Sweden) were given at the end of hemodialysis treatment two or three times a week depending on the frequency of hemodialysis treatment.

Elevated *p*-phosphate was treated with calcium-free phosphate binders, dietary intervention, and re-evaluation of the dialysis dose. Elevated *p*-calcium led to dietary intervention and reduction of calcium-containing phosphate binders. The calcium concentration of dialysate was fixed to 1.25 mmol/l.

The primary efficacy end point was the proportion of patients achieving ⩾30% reduction in PTH from baseline until the last 4 weeks of treatment with alfacalcidol or paricalcitol. The secondary outcomes were changes in ionized *p*-calcium, *p*-phosphate, calcium × phosphate product, *p*-alkaline phosphatase, *p*-25(OH) vitamin D, *p*-1,25$(OH)_2$ vitamin D, blood pressure, pulse, and pulse pressure from baseline until the end of treatment with alfacalcidol or paricalcitol, respectively.

p-PTH, ionized *p*-calcium, and *p*-phosphate were measured every second week during the treatment periods; the other parameters were measured at the beginning and the end of each treatment period. All laboratory analyses were performed at the local laboratories of the participating departments. The local assays for PTH were all second-generation assays: Elecsys 2010 (Roche Diagnostics GmbH, Mannheim, Germany), Immulite 2000 (Siemens Healthcare Diagnostics, Llanberis, UK), and Architect (Abbott Laboratories, Abbott Park, IL).

AEs were registered every second week. The registration procedure and procedure for classification are described in detail in Supplementary Material online.

A sample size of 117 was planned.[55] The patients were randomized in blocks of 10, to secure equal distribution in the two groups in each department. The trialists were aware of the block size. No stratification was performed. Assignments were enclosed in sequentially numbered, opaque, sealed envelopes. Envelopes were opened sequentially and the patient's initials and identification number written on the assignment. The patients were enrolled and treatment assignment ascertained by the primary investigator or a delegate at each center. The envelopes were generated by the study coordinator and the allocation list was packed afterward in a sealed, opaque envelope, and stored by the study coordinator. The study was an open-label study.

Statistics

Continuous data are described as mean (s.d.), and for differences as mean (s.e.m.), if normally distributed, and as median (range) if not normally distributed and for very small groups. Paired *t*-test for normally distributed and Wilcoxon test for not normally distributed data were used for comparing changes before and after treatment within groups. Unpaired *t*-test for normal distributed and Mann–Whitney test for not normal distributed data compared changes between groups. Proportions were compared by using Fischer's Exact Test. All tests were two sided. A *P*-value <0.05 was considered statistically significant.

The correlation between PTH values before and after washout 2 were described by Pearson's correlation coefficient, comparing the mean value with the change in these parameters.[56]

General linear models and multiple logistic regression models were used for the analyses of differences between effects of treatment by alfacalcidol and paricalcitol.

Statistical analysis was performed using SPSS Statistics 17.0 (SPSS, Chicago, IL) software.

The study is in compliance with the Helsinki Declaration of 1975, revised 1983, and approved by the Danish National Committee on Biomedical Research Ethics (SJ-27), the Danish Medicines Agency (EudraCT: 2006-005981-37), Danish Data Protection Agency (2007-41-0503), and registered in ClinicalTrials.gov (NCT004695).

DISCLOSURE

This study was supported by a research grant of 34,000 US$ from Abbott Laboratories A/S without restrictions on publications. Abbott Laboratories A/S has financed investigator meetings.
DH has received a research grant for additional studies of the collected biobank from Abbott Laboratories A/S. LB has received honoraria for lectures from LEO Pharmaceutical, Genzyme, Abbott

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SUPPLEMENTARY MATERIAL

Table S1. Adverse events.
Table S2. Safety parameters.
Table S3. Hemodynamic parameters.
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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