Opposite Effects of Calcitriol and Paricalcitol on the Parathyroid Hormone-(1-84)/Large Carboxy-Terminal-Parathyroid Hormone Fragments Ratio in Patients with Stage 5 Chronic Kidney Disease

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Background and objectives: The effects of calcitriol and paricalcitol on circulating levels of intact parathyroid hormone, parathyroid hormone-(1-84), the large carboxy-terminal-parathyroid hormone fragments, and the parathyroid hormone-(1-84)/carboxy-terminal-parathyroid hormone fragments were studied.

Design, setting, participants, & measurements: In the longitudinal study, 31 hemodialysis patients who were receiving intravenous calcitriol or paricalcitol were followed for 6 to 8 wk. After a washout period, patients were treated with the other vitamin D compound for 6 to 8 wk. Plasma intact parathyroid hormone and parathyroid hormone-(1-84) were measured, and the parathyroid hormone ratio was calculated. In the cross-sectional study, results of intact parathyroid hormone, parathyroid hormone-(1-84), and parathyroid hormone ratio were compared between patients who were treated with paricalcitol ($n = 49$) *versus* no vitamin D therapy ($n = 44$).

Results: In the longitudinal study, the parathyroid hormone ratio was significantly lower in patients who were treated with calcitriol and higher with paricalcitol treatment compared with values that were obtained during washout. In the cross-sectional study, intact parathyroid hormone levels were identical in both groups, whereas parathyroid hormone-(1-84) and thus parathyroid hormone ratio values were higher in patients who were given paricalcitol than in patients who were not receiving vitamin D.

Conclusions: These data show that at similar intact parathyroid hormone values, the active parathyroid hormone-(1-84) compound is lower with calcitriol than with paricalcitol treatment. This finding might be relevant for choice of vitamin D compound in patients with stage 5 chronic kidney disease.

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Calcitriol and its analogs are widely used to treat secondary hyperparathyroidism in patients with stage 5 chronic kidney disease (CKD) that requires dialysis. Calcitriol and paricalcitol equally suppress circulating levels of parathyroid hormone (PTH) (1–3); however, calcitriol treatment often induces hypercalcemia, hyperphosphatemia (1,2), and low bone turnover (4,5). Paricalcitol has less hypercalcemic and hyperphosphatemic effects (6,7) and did not induce low bone turnover in a rat model of renal failure (3).

It is of note that the commercially available PTH assays (intact PTH [iPTH]) used during the past decade not only measure the whole molecule [PTH-(1-84)] but also large carboxy-terminal-PTH (C-PTH) fragments, which have been shown to be closely related to PTH-(7-84) (8–10). Moreover, PTH- (7-84) has been shown to antagonize the effects of PTH-(1-84) on serum calcium and bone turnover (11–13). Recently, new assays that specifically detect PTH-(1-84) have been developed (14,15). This study was undertaken to elucidate whether calcitriol and paricalcitol therapy have different effects on circulating levels of PTH-(1-84) and its large C-PTH fragments and the PTH-(1-84)/C-PTH fragments ratio.

Concise Methods

Two separate studies were conducted, one prospective and one cross-sectional. Both studies were conducted in accordance with the Declaration of Helsinki and were approved by the internal review board of the University of Kentucky.

Longitudinal Study

Study Patients. Patients were recruited prospectively from local dialysis clinics during 2001 to 2005. The inclusion criteria were age >18 yr, on long-term maintenance hemodialysis for at least 3 mo, in stable condition, and willing to participate in the study. The exclusion criteria were serum calcium >10.5 mg/dl, calcium phosphate product >65, blood iPTH <150 pg/ml, hematocrit <30%, treatment (during last 6 mo) with medications that are known to affect calcium and bone metabolism (with the exception of vitamin D compounds), systemic illnesses or organ diseases (except for diabetes) that may affect calcium and bone metabolism (*e.g.*, gastrointestinal diseases, liver disease, ma-

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lignancies, tuberculosis, HIV/AIDS), chronic alcoholism, drug addiction, failed transplant or parathyroidectomy within the past 6 mo, and participation in other studies.

Thirty-one patients who were on hemodialysis qualified, agreed to participate in the study, and signed informed consent forms. There were 17 men and 14 women with a mean age of 54.9 ± 4.91 and 52.8 ± 5.61 yr, respectively. There were 23 black (12 men and 11 women) and eight white patients (five men and three women). The mean dialysis vintage was 51.1 ± 8.25 mo (5 to 140 mo). Underlying kidney diseases were diabetic nephropathy ($n = 13$), hypertensive nephropathy ($n = 10$), obstructive nephropathy ($n = 1$), glomerulopathy ($n = 1$), and unknown origin ($n = 6$). Patients underwent dialysis three times a week for 3 to 4 h. Calcium dialysate concentration was 2.5 mEq/L. Phosphate binding was achieved with calcium acetate (PhosLo; $n = 14$, Fresenius Medical Care, Waltham, MA), sevelamer hydrochloride (Renagel; $n = 10$, Genzyme Corporation, Cambridge, MA), or both calcium acetate and sevelamer hydrochloride ($n = 7$).

Study Protocol. Patients who were treated with intravenous calcitriol (Calcijex; $n = 8$, Abbott Laboratories, Abbott Park, IL) three times a week continued to be treated with the same dosage of calcitriol for 6 to 8 wk. Calcitriol was then discontinued for the next 6 to 8 wk (washout period). In the subsequent 6 to 8 wk, the patients were treated with paricalcitol (Zemplar, Abbott Laboratories) at a dosage equipotent to calcitriol (four to five times) based on previous clinical studies that compared the two vitamin D compounds (1,16). Patients who were administered paricalcitol ($n = 23$) followed the same protocol and were switched to calcitriol at the end of the washout period. During the washout period, it was anticipated that serum calcium levels would decrease and PTH levels would increase. For maintaining serum calcium and phosphorus levels similar to the calcitriol or paricalcitol treatment period, phosphate binders were adjusted during the washout period. Blood draws were done twice a week during the first 2 wk of each period and once weekly thereafter. Determinations of blood ionized and serum total calcium and phosphorus and plasma total and whole PTH were performed. The large C-PTH fragment levels were obtained by subtracting PTH-(1-84) from iPTH levels. The PTH-(1-84)/C-PTH fragment ratio was then calculated (17). Blood was drawn at the same time points for determinations of bone-specific alkaline phosphatase (BSAP) and tartrate-resistant acid phosphatase 5 (TRAP-5) in the last eight patients who completed the study. For all biochemical and hormonal parameters, the mean values during each experimental phase (paricalcitol, washout, and calcitriol) were calculated.

Cross-Sectional Study

In this study iPTH, PTH-(1-84), and the PTH-(1-84)/C-PTH fragments ratio values were compared in patients who had stage 5 CKD and were on long-term maintenance hemodialysis and treated with paricalcitol or naive to vitamin D. There were no selection criteria. All patients who agreed to participate in the study were enrolled. Ninety-three patients were enrolled in the study: 49 men and 44 women with a mean age of 59 ± 2 and 64 ± 2 yr, respectively. There were 78 black and 15 white patients. There were 59 with and 34 without diabetes. Dialysis vintage was 35.1 ± 5.0 mo. During the study, blood samples were collected before dialysis every 3 mo for at least 9 mo. Results are given as the mean values of PTH peptides during the 9 mo of the study.

Determination of Biochemical Parameters

Blood ionized calcium was measured using an ICA113 Ionized Calcium System (Radiometer Copenhagen, Copenhagen, Denmark). Serum total calcium and phosphorus were measured using routine laboratory techniques.

Table 1. Biochemical parameters obtained during paricalcitol, washout, and calcitriol phases in 23 black and eight white patients with stage 5 CKD[a]

Parameter	Paricalcitol	Washout	Calcitriol
Blood Ca^{2+} (mg/dl)			
black	4.12 ± 0.08	4.09 ± 0.09	4.11 ± 0.06
white	4.31 ± 0.16	4.22 ± 0.12	4.45 ± 0.16
all	4.18 ± 0.08	4.13 ± 0.07	4.21 ± 0.06
Serum total calcium (mg/dl)			
black	8.27 ± 0.25	8.39 ± 0.23	8.74 ± 0.23
white	8.71 ± 0.27	8.37 ± 0.17	8.96 ± 0.26
all	8.43 ± 0.19	8.39 ± 0.16	8.81 ± 0.17
Serum phosphorus (mg/dl)			
black	5.26 ± 0.46	5.26 ± 0.44	5.25 ± 0.47
white	6.48 ± 0.28	6.05 ± 0.41	6.64 ± 0.64
all	5.60 ± 0.36	5.47 ± 0.34	5.65 ± 0.40
Plasma iPTH (pg/ml)			
black	493.00 ± 61.9	523.00 ± 61.40	539.00 ± 69.50
white	648.00 ± 112.00	646.00 ± 77.10	738.00 ± 121.00
all	533.00 ± 54.70	555.00 ± 50.10	591.00 ± 61.40
Plasma PTH (1-84) (pg/ml)			
black	289.00 ± 37.50	276.00 ± 32.60	281.00 ± 41.10
white	365.00 ± 60.60	345.00 ± 54.40	374.00 ± 66.60
all	308.00 ± 31.80	294.00 ± 28.10	305.00 ± 35.20

[a]Data are means ± SEM of all results during each phase. Ca^{2+}, ionized calcium; CKD, chronic kidney disease. iPTH, intact parathyroid hormone.

Table 2. Biochemical parameters obtained during paricalcitol, washout, and calcitriol phases in 13 patients with and 18 patients without diabetes and with stage 5 CKD[a]

Parameter	Paricalcitol	Washout	Calcitriol
Blood Ca^{2+} (mg/dl)			
ND	4.18 ± 0.10	4.13 ± 0.10	4.23 ± 0.07
D	4.18 ± 0.12	4.13 ± 0.11	4.19 ± 0.11
Serum total calcium (mg/dl)			
ND	8.39 ± 0.30	8.32 ± 0.24	8.68 ± 0.25
D	8.51 ± 0.13	8.46 ± 0.24	8.90 ± 0.25
Serum phosphorus (mg/dl)			
ND	5.62 ± 0.38	5.50 ± 0.42	5.88 ± 0.48
D	5.56 ± 0.75	5.44 ± 0.61	5.34 ± 0.69
Plasma iPTH (pg/ml)			
ND	494.00 ± 49.20	517.00 ± 41.40	586.00 ± 64.40
D	588.00 ± 112.00	606.00 ± 105.00	597.00 ± 119.00
Plasma PTH (1-84) (pg/ml)			
ND	288.00 ± 30.90	273.00 ± 28.10	303.00 ± 41.50
D	337.00 ± 63.60	323.00 ± 55.10	306.00 ± 63.40

[a]Data are means ± SEM of all results during each phase. D, patients with diabetes; ND, patients with no diabetes.

Plasma whole PTH levels were measured with the IRMA assay using radiolabeled detection antibodies raised against 1 to 6 PTH (Whole PTH; Scantibodies, Santee, CA) (14,15). The normal range of the assay is 5 to 39 pg/ml. Intra- and interassay coefficients of variation were <5 and <7%, respectively. Plasma total PTH was determined using Total PTH assay (Scantibodies). The normal range of the assay is 14 to 66 pg/ml, and the intra- and interassay coefficients of variation were <5 and <7%, respectively.

BSAP levels were determined using an immuno-capture enzyme activity assay (Metra BAP EIA kit; Quidel Corp., San Diego, CA). The normal range of the assay is 11.6 to 29.6 U/L for premenopausal women, 14.2 to 42.7 U/L for postmenopausal women, and 15.0 to 41.3 U/L for men. The intra- and interassay coefficients of variation were <6 and <8%, respectively.

TRAP-5 levels were determined using an immuno-capture enzyme activity assay (Human Trap 5 Assay; BioVendor, Candler, NC). The normal values are 2.12 to 11.69 U/L for women and 1.56 to 12.50 U/L for men. The intra- and interassay coefficients of variation were <4 and <8%, respectively.

Statistical Analyses

Results are expressed as means ± SEM. All statistical tests were two-sided. An assigned significance level of 0.05 was used. Comparisons of values of biochemical parameters in the longitudinal study were done using a nonparametric ANOVA for repeated measurements the Friedman test with subsequent Wilcoxon sign-rank tests. Comparisons of values of biochemical parameters between demographic groups in both studies (longitudinal and cross-sectional) were performed using the Mann-Whitney *U* rank-sum test. Computations and analyses were performed using SPSS 7.5 software package for Windows (SPSS, Chicago, IL).

Results

Longitudinal Study

There were no differences in demographic characteristics and biochemical data between patients who started the study with calcitriol and those who were treated with paricalcitol; therefore, data were analyzed together. The mean dosages of paricalcitol and calcitriol were 13.5 ± 1.68 and 2.30 ± 0.41 μg/wk, respectively. Serum ionized and total calcium as well as phosphorus levels did not change during the study in both black and white patients (Table 1) and in both patients with and without diabetes (Table 2). iPTH and PTH-(1-84) did not rise significantly during the washout period, probably because of adjustment of serum calcium and phosphorus (Tables 1 and 2). The mean dosage of elemental calcium administered was 842 ± 128 mg/d. The PTH-(1-84)/C-PTH fragments ratio was significantly lower when patients were treated with calcitriol (1.14 ± 0.08) and significantly higher with paricalcitol treatment (1.75 ± 0.17) compared with values that were obtained during the washout period (1.33 ± 0.17; $P < 0.001$). ANOVA for

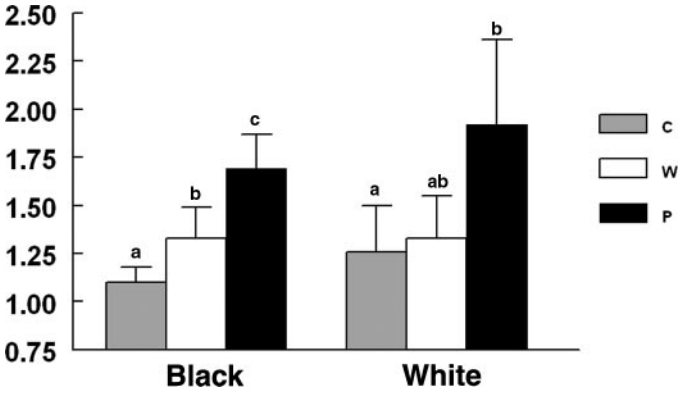

Figure 1. Mean parathyroid hormone (PTH)-(1-84)/carboxy-terminal-PTH (C-PTH) fragments ratio obtained during paricalcitol (P), washout (W), and calcitriol (C) phases in black ($n = 23$) and white ($n = 8$) patients with stage 5 chronic kidney disease (CKD). Results with different letters are significantly different; $P < 0.01$, ANOVA for repeated measurements.

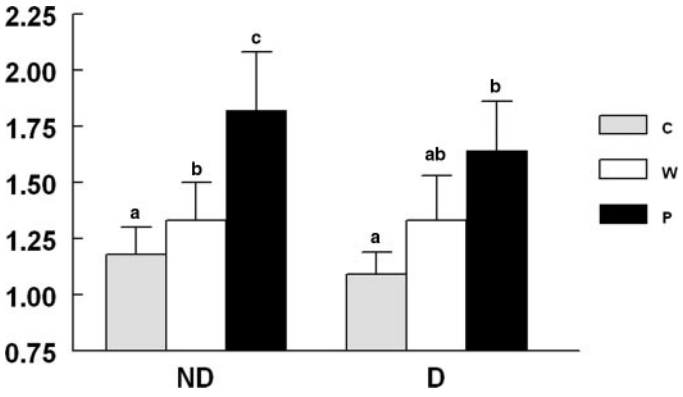

Figure 2. Mean PTH-(1-84)/C-PTH fragments ratio obtained during paricalcitol (P), washout (W), and calcitriol (C) phases in patients without (ND; $n = 18$) and with diabetes (D; $n = 13$) and stage 5 CKD. Results with different letters are significantly different; $P < 0.01$, ANOVA for repeated measurements.

repeated measurements showed a similar statistically significant trend in black and white patients ($P < 0.01$) and patients with and without diabetes ($P < 0.01$). Significant differences in PTH-(1-84)/C-PTH fragments ratio among the three phases of the study were observed in black patients and patients without diabetes (Figures 1 and 2), whereas in white patients and patients with diabetes, PTH-(1-84)/C-PTH fragments ratio values were significantly different only between calcitriol and paricalcitol treatment phases (Figures 1 and 2). There was no difference in variance of the PTH-(1-84)/C-PTH fragments ratio among the experimental phases (calcitriol 0.29 ± 0.12; washout 0.36 ± 0.13; paricalcitol 0.44 ± 0.15). Serum BSAP and TRAP-5 levels in a subset of patients showed a similar trend (*i.e.*, values were higher when patients were treated with paricalcitol than during the washout period or the calcitriol period); however, this did not reach statistical significance, probably because of the relatively low number of patients ($n = 8$; Table 3).

Cross-Sectional Study

Forty-nine patients were treated with paricalcitol, and 44 patients were naive to vitamin D. There were no significant differences in intact PTH, PTH-(1-84), and PTH-(1-84)/C-PTH fragments ratio between black and white patients and between patients with and without diabetes in both groups; therefore, all patients were analyzed together. iPTH levels were similar in patients who were not treated with vitamin D and patients who were treated with paricalcitol, whereas PTH-(1-84) was significantly higher in patients who were treated with paricalcitol (Table 4). The C-PTH fragments were similar in both groups; therefore, the PTH-(1-84)/C-PTH fragments ratio was significantly higher in patients who were treated with the vitamin D analog than in patients who were not treated with vitamin D (Table 4).

Discussion

These studies show that vitamin D treatment affects the ratio between PTH-(1-84) and its large C-PTH fragments. Moreover, calcitriol and its analog, paricalcitol, influence the PTH-(1-84)/C-PTH fragments ratio in an opposite manner as evidenced by the results of the longitudinal study in both black and white patients as well as in patients with and without diabetes. Paricalcitol has been shown to exert different effects compared with calcitriol on intestinal calcium absorption. This was found in experimental rats with and without renal insufficiency (18,19). Also, the affinity of paricalcitol for the vitamin D receptor is three times less than that of calcitriol, but its calcemic and phosphatemic effects have been shown to be 10 times lower (20). Affinity for vitamin D–binding protein is also three times less than that of calcitriol, whereas the pharmacokinetics are

Table 3. BSAP and TRAP obtained during paricalcitol, washout, and calcitriol phases in eight patients with stage 5 CKD[a]

Parameter	Paricalcitol	Washout	Calcitriol
Serum BSAP (U/L)	55.20 ± 21.30	47.50 ± 24.30	39.30 ± 21.90
Serum TRAP (U/L)	6.57 ± 2.90	6.24 ± 2.71	5.22 ± 1.78

[a]Data are means ± SEM of all results during each phase. BSAP, bone-specific alkaline phosphatase; TRAP, tartrate-resistant acid phosphatase.

Table 4. PTH peptides in patients who were treated with paricalcitol or were naive to vitamin D[a]

Parameter	No Vitamin D ($n = 44$)	Paricalcitol ($n = 49$)
Plasma iPTH (pg/ml)	269.00 ± 24.60	292.00 ± 19.20
PTH-(1-84) (pg/ml)	142.00 ± 13.40	170.00 ± 11.00[b]
Carboxy-terminal-PTH fragment (pg/ml)	128.00 ± 12.10	122.00 ± 8.93
PTH-(1-84)/C-PTH fragments ratio	1.37 ± 0.10	1.60 ± 0.06[b]

[a]Data are means ± SEM.
[b]Different from values obtained in patients who were naive to vitamin D, $P < 0.001$.

similar (21). It is conceivable that differences also exist in the effects on modulation of parathyroid chief cells. Also, it is not known whether intracellular calcium concentrations in the parathyroid glands are affected differently by paricalcitol than calcitriol (22). This could explain our observation of different relative concentrations of PTH-(1-84)/C-PTH fragments ratio in the circulation at similar blood levels of calcium. *In vitro* studies are needed for further elucidation of mechanisms underlying the observed results. The PTH-(1-84)/C-PTH fragments ratio was shown to be a good indicator of bone turnover in patients who were naive to vitamin D (17). A lower PTH-(1-84)/C-PTH fragments ratio with calcitriol administration than during the washout period is in keeping with the known suppressive effect of calcitriol on bone turnover and in some cases induction of adynamic bone disease (4,5). A higher PTH-(1-84)/C-PTH fragments ratio with paricalcitol in the longitudinal and cross-sectional studies is in agreement with data obtained in a rat model of renal failure showing that paricalcitol can prevent and treat secondary hyperparathyroidism and renal osteodystrophy without major decrease in bone turnover (3). This finding was also observed with another vitamin D analog, 22-oxacalcitriol, which controlled circulating levels of iPTH without affecting bone turnover in a canine model of renal failure (23).

Conclusions

The two vitamin D compounds studied affect the PTH-(1-84)/C-PTH fragments ratio in an opposite manner. Of course, bone biopsies are needed to prove that the differences in PTH-(1-84)/C-PTH fragments ratios are accompanied by different levels of bone turnover states. Given the known suppressive effects of PTH-(7-84) on the bone effects of PTH-(1-84) (12), these findings might be relevant for the choice of vitamin D compounds used in patients with stage 5 CKD.

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Disclosures

None.

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See related editorial, "Whole or Fragmentary Information on Parathyroid Hormone?" on pages 1106–1107.