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# Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism

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*Background.* Management of secondary hyperparathyroidism has included the use of active vitamin D or vitamin D analogs for the suppression of parathyroid hormone (PTH) secretion. Although, these agents are effective, therapy is frequently limited by hypercalcemia, hyperphosphatemia, and/or elevations in the calcium-phosphorus (Ca × P) product. In clinical studies, paricalcitol was shown to be effective at reducing PTH concentrations without causing significant hypercalcemia or hyperphosphatemia as compared to placebo. A comparative study was undertaken in order to determine whether paricalcitol provides a therapeutic advantage to calcitriol.

*Methods.* A double-blind, randomized, multicenter study comparing the safety and effectiveness of intravenous paricalcitol and calcitriol in suppressing PTH concentrations in hemodialysis patients was performed. A total of 263 randomized patients were enrolled at domestic and international sites. Following the baseline period, patients with serum Ca × P < 75, and a PTH level ≥300 pg/mL were randomly assigned to receive either paricalcitol or calcitriol in a dose-escalating fashion for up to 32 weeks. Dose adjustments were based on laboratory results for PTH, calcium, and Ca × P. The primary end point was the greater than 50% reduction in baseline PTH. Secondary end points were the occurrence of hypercalcemia and elevated Ca × P product.

*Results.* Paricalcitol-treated patients achieved a ≥50% reduction from baseline PTH significantly faster than did the calcitriol-treated patients ($P = 0.025$) and achieved a mean reduction of PTH into a desired therapeutic range (100 to 300 pg/mL) at approximately week 18, whereas the calcitriol-treated patients, as a group, were unable to achieve this range. Moreover, paricalcitol-treated patients had significantly fewer sustained episodes of hypercalcemia and/or increased Ca × P product than calcitriol patients ($P = 0.008$).

*Conclusion.* Paricalcitol treatment reduced PTH concentrations more rapidly with fewer sustained episodes of hypercalcemia and increased Ca × P product than calcitriol therapy.

**Key words:** paricalcitol, calcitriol, ESRD, secondary hyperparathyroidism, hemodialysis, hypercalcemia, hyperphosphatemia.

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Osteitis fibrosa cystica, resulting from poorly controlled secondary hyperparathyroidism, remains a common manifestation of renal osteodystrophy and causes significant morbidity in patients with chronic renal failure [1, 2]. Decreased renal production of calcitriol (1,25 vitamin $D_3$), hypocalcemia, and hyperphosphatemia are the major contributing factors to the development of secondary hyperparathyroidism [1, 3–5]. Calcitriol is synthesized from previtamin $D_3$ by hydroxylation on carbons 25 and 1 in the liver and kidney, respectively [6]. The administration of calcitriol decreases the synthesis and secretion of parathyroid hormone (PTH) directly by inhibition of the synthesis of PTH at the pre-promessenger RNA level [4] and indirectly by both increasing the serum calcium concentration and by increasing the sensitivity of PTH suppression to calcium.

Both oral and parenteral forms of calcitriol have been effective in treating and preventing secondary hyperparathyroidism [8–11]. However, in the United States, intravenous calcitriol has been more widely used and thought to be the more effective form. Serum calcium concentrations, however, are increased via vitamin D–enhanced intestinal calcium absorption and increased mineral resorption from bone [3, 7], thereby increasing serum calcium concentrations, which occasionally results in hypercalcemia. Calcitriol, especially in conjunction with calcium-containing phosphate binders, greatly increases the risk for hypercalcemia, hyperphosphatemia, and increased calcium-phosphorus (Ca × P) product as well as the development of adynamic bone disease [12–16]. These disturbances, in turn, can result in soft tissue and vascular calcifications, which contributes to increased mortality and cardiovascular morbidity [17–19].

Thus, current clinical practice is focused on developing therapies that do not cause increased body burdens of calcium and phosphorus. This has included the use of a noncalcium-containing phosphate binder, sevelamer hydrochloride, a hydrogel of cross-linked poly-allylamine

**Table 1.** Dose administration schedule

| | Dose adjustments[a] | | | | |
|---|---|---|---|---|---|
| Treatment | Initial dose | Increments | Escalation | Maximum dose | Reduction[b] |
| Paricalcitol | 0.04 μ/kg | 0.04 μg/kg | 4-week intervals | 0.24 μg | 1-week intervals |
| Calcitriol | 0.01 μ/kg | 0.01 μg/kg | 4-week intervals | 0.06 μg | 1-week intervals |

[a] Dose adjustment criteria were met prior to changes in study drug dosing. All doses, including the initial dose, were to be maintained for a minimum of 4 weeks unless safety parameters were met.
[b] Unless immediate reduction was necessary for safety reasons

hydrochloride [20], as well as analogs of calcitriol that have less effect on the absorption of calcium and phosphorus. One such analog, 19-nor-1α, 25-dihydroxyvitamin $D_2$ (paricalcitol), was approved for clinical use in hemodialysis patients in 1998. Preclinical studies with paricalcitol have demonstrated significant PTH suppression, comparable to that observed with intravenous calcitriol. Early studies evaluating paricalcitol dosing suggested that for comparable suppressive effects, paricalcitol should be dosed at a ratio of 4:1 to calcitriol [21]. However, a recently published study of dialysis patients resistant to calcitriol found that a more appropriate dosing ratio of paricalcitol to calcitriol would be 3:1 [22]. Nevertheless, in contrast to what has been observed with calcitriol, paricalcitol seems to exhibit less of a calcemic and phosphatemic effect with a reduction in parathyroid gland size and beneficial effects on bone remodeling in experimental studies [23–26].

In clinical studies, paricalcitol was shown to be effective at reducing PTH concentrations without causing significant hypercalcemia or hyperphosphatemia as compared to placebo [21]. In order to determine whether paricalcitol provides a therapeutic advantage to calcitriol, a double-blinded, randomized multicenter comparative study was undertaken. A preliminary report of our results from a subset of patients enrolled in this study at two dialysis centers affiliated with Northwestern University was recently published [27].

## METHODS

To compare the safety and effectiveness of intravenous paricalcitol with intravenous calcitriol in suppressing PTH in end-stage renal disease (ESRD) patients undergoing chronic hemodialysis, a phase III, prospective, comparative, double-blind, randomized, multicenter study was conducted during the years 1995 and 1996. The primary efficacy goal was the achievement of a 50% reduction in baseline PTH levels. Safety end points were to evaluate the occurrence of hypercalcemia and/or elevated Ca × P in these patients. Hypercalcemia was defined as a normalized serum total calcium ≥11.5 mg/dL and an elevated Ca × P was defined as being ≥75. All medically stable adult ESRD patients undergoing chronic hemodialysis three times a week for at least 6 months who had not previously been enrolled in a paricalcitol trial were eligible for enrollment. Subjects were excluded if any of the following conditions existed: (*1*) screening PTH value <250 pg/mL or 300 pg/mL if naïve to vitamin D therapy, (*2*) screening calcium value of >11.5 mg/dL, (*3*) screening Ca × P of greater than 70, (*4*) history of clinically significant allergic reaction to calcitriol or other vitamin D compounds, or (*5*) necessity for calcitonin, maintenance oral or intravenous glucocorticoids, or other drugs that could have affected calcium or bone metabolism, other than females on stable estrogen and/or progestin therapy. All clinical laboratories were performed in a central laboratory (Covance Central Laboratory Services, Indianapolis, IN, USA). All intact PTH measurements were performed at Covance (Covance Central Laboratory Services) using the Nichols immunoradiometric assay (IRMA). The Institutional Review Board at each center approved the protocol and consent form. Informed consent was obtained from each subject prior to enrolling into the study.

The study consisted of a pretreatment (washout/baseline) phase and a treatment phase. During pretreatment, patients receiving calcitriol (intravenous or oral), dihydrotachysterol, α−calcidol, or calcitonin prior to enrollment underwent a 2-week washout period which was followed by a 2- to 6-week baseline period. Weekly measurements of serum calcium, phosphorous, albumin, and PTH concentrations were performed and final adjustments to pertinent medications (i.e., phosphate binders and dialysate calcium concentration) were made in order to maintain these medicines as constant as possible during the study. Patients not receiving calcitriol, dihydrotachysterol, α–calcidol, or calcitonin prior to enrollment directly entered the baseline period. Following the pretreatment phase, patients with normalized total serum calcium concentration <11.5 mg/dL, serum Ca × P ≤ 75, and a PTH level ≥300 pg/mL were randomized to receive either paricalcitol or calcitriol for the treatment phase. The treatment phase lasted 12 to 32 weeks and subjects were dosed in a 4:1 ratio of paricalcitol to calcitriol as shown in Table 1.

Doses were escalated every 4 weeks up to a maximum of five dose escalations. Patients were dose titrated to achieve at least a 50% reduction in PTH concentration into a clinically appropriate range (>100 pg/mL). The

**Table 2.** Dose adjustment criteria

| Dose maintained | Dose increased | Dose reduced |
|---|---|---|
| PTH ≥100 pg/mL | Minimum of 4 weeks at the given dose | PTH <100 pg/mL after 2 consecutive weeks of treatment on a given dose level |
| -and- | -and- | -or- |
| PTH level reduced ≥50% from baseline | PTH level did not decrease ≥50% | Calcium is >11.5 mg |
| -and- | -or- | -or- |
| Calcium is ≤11.5 mg/dL | If the PTH level had previously been reduced ≥50% has subsequently increased and is no longer less than 50% of baseline. | All Ca × P levels in a consecutive 2-week period at a given dose level are >75 |
| -and- | -and- | |
| At least one Ca × P within the preceding consecutive 2-week period is ≤75 | Calcium is ≤11.5 mg/dL | |
| | -and- | |
| | At least one Ca × P within the preceding consecutive 2-week period is ≤75 | |

PTH is parathyroid hormone.

"maintenance" dose was defined as the dose whereby a patient's PTH was reduced by ≥50% from baseline (or was the fifth dose escalation, whichever occurred first). The dose would be reduced if PTH levels decreased to less than 100 pg/mL, or if Ca × P became greater than 75 for 2 consecutive weeks, or if a single episode of serum calcium greater than 11.5 mg/dL occurred. Once a patient reached the maintenance dose via the dose adjustment criteria, the patient was to remain at that dose for 12 weeks provided all the maintenance criteria continued to be met (Table 2). This 12-week period was an attempt to allow for equivalent treatment of the disease through PTH reduction for both treatment groups. Ca × P levels were measured twice weekly, whereas PTH concentrations were assessed weekly. Investigators were instructed to maintain phosphate binder usage, which was predominantly calcium carbonate or acetate (sevelamer HCL was not yet available), as constant as possible (chronic use of phosphate binders containing aluminum was not permitted), and centers were required to maintain calcium concentration in the dialysate bath at 2.5 mEq/L.

### Statistics

All analyses were performed with SAS® version 6.12 (SAS Institute, Cary, NC, USA) procedures GLM, FREQ, LIFETEST, MEANS, and UNIVARIATE (SAS Institute, Inc., Cary, NC, USA). All statistical tests were two-tailed and $P$ values ≤0.050 were considered statistically significant.

A Fisher's exact test was used to test for a difference in incidence rates for categorical variables with a dichotomous outcome. A one-way analysis of variance was used to test for a difference between treatment groups in continuous variables such as the change from baseline in laboratory variables and vital signs. The Kaplan-Meier method of generating survival curves was used to evaluate the time (in days) to the first occurrence of four consecutive 50% decreases from baseline in PTH. The independent variable was treatment. Patients who did not meet the end point prior to study end or were prematurely terminated were censored at their last day of treatment. The log-rank test was used to test for the equality of survival curves between treatments.

A total of 100 patients per treatment group were required to detect a 15% difference between the two treatment groups in the proportions of patients experiencing at least one incidence of hypercalcemia and/or an elevated Ca × P ≥ 75 during the study, with an $\alpha$ level of 5% and a power of 80%. This assumed a 10% incidence rate in the paricalcitol treatment group and a 25% incidence rate in the calcitriol treatment group.

## RESULTS

After providing consent to participate, a total of 476 patients were enrolled at 27 centers in the United States, The Netherlands, Spain, and Switzerland. A total of 266 subjects met eligibility criteria and were randomized to treatment with either paricalcitol or calcitriol. Baseline characteristics are presented in Table 3. There were no differences between groups with respect to gender, race, age, history of prior vitamin D exposure, length of time on dialysis, and major causes of chronic renal failure. Baseline values for PTH, calcium, phosphorus, and albumin were also comparable between treatment groups.

A decrease in mean PTH concentrations was observed in both treatment groups (Fig. 1). The primary treatment goal was to achieve a 50% reduction in baseline PTH levels. A mean reduction from baseline PTH concentration of ≥50% was achieved at week 15 in the paricalcitol group compared to week 23 in the calcitriol-treated subjects. Thus, paricalcitol dosed at a 4:1 ratio to calcitriol resulted in a more rapid decrease in PTH concentrations. PTH concentrations between 100 and 300 pg/mL are considered a desirable therapeutic range for patients with ESRD. Subjects receiving paricalcitol achieved this

**Table 3.** Baseline patient characteristics

| | Paricalcitol ($N$ = 130) | Calcitriol ($N$ = 133) |
|---|---|---|
| Male | 70 (54%) | 80 (60%) |
| Female | 60 (46%) | 53 (40%) |
| Race | | |
| Caucasian | 34 (26%) | 40 (30%) |
| African American | 81 (62%) | 76 (57%) |
| Other | 15 (12%) | 17 (13%) |
| Age (mean ± SD) | 56.7 ± 15.5 | 56.6 ± 14.3 |
| Previous vitamin D therapy[a] | | |
| Oral calcitriol | 28 (22%) | 30 (23%) |
| Oral dihydrotachysterol | 2 (2%) | 2 (2%) |
| Intravenous calcitriol | 87 (67%) | 90 (68%) |
| Other vitamin D analogues | 10 (8%) | 3 (2%) |
| No vitamin D analogues | 22 (17%) | 21 (16%) |
| Duration of dialysis *years* | | |
| Less than 1 year | 31 (24%) | 32 (24%) |
| One year but less than 5 years | 58 (45%) | 53 (40%) |
| Five years but less than 10 years | 21 (16%) | 39 (29%) |
| Ten years or longer | 20 (15%) | 9 (7%) |
| PTH (mean ± SE) *pg/mL* | 648 ± 30.5 | 675 ± 35.0 |
| Calcium (mean ± SE) *mg/dL* | 9.0 ± 0.08 | 9.0 ± 0.09 |
| Phosphorous (mean ± SE) *mg/dL* | 5.9 ± 0.12 | 5.8 ± 0.13 |
| Albumin (mean ± SE) *g/dL* | 3.6 ± 0.04 | 3.6 ± 0.03 |

[a] A patient may have received one, more than one, or no previous vitamin D treatment

PTH range by week 18, whereas calcitriol-treated subjects never achieved this "therapeutic" range.

The graph of mean percent change from baseline in PTH over time indicated that paricalcitol reduces PTH levels more rapidly than calcitriol. To further validate this observation, the number of days to the first period of four consecutive values consistent with a 50% reduction from baseline in PTH levels (event) was analyzed by the Kaplan-Meier method of survival analysis. Figure 2 shows estimates over time of the proportions of all-treated patients not yet attaining a period of four consecutive values consistent with a ≥50% reduction from baseline PTH levels. The median number of days to the event was significantly less ($P$ = 0.025) for the paricalcitol group (87 days) compared to the calcitriol group (108 days).

The treatment groups were also evaluated by analyzing the proportions of subjects achieving a ≥50% reduction from baseline in PTH levels: (*1*) at least once during treatment; (*2*) for one or more periods of four consecutive PTH laboratory draws; and (*3*) at the final laboratory draw. More than 80% of all-treated subjects in each treatment group achieved a ≥50% reduction from baseline in PTH levels at least once during treatment. A slightly higher proportion of subjects in the paricalcitol group achieved a 50% decrease in PTH for at least one period of four consecutive laboratory draws (paricalcitol 62%, calcitriol 54%). In total, approximately 60% of patients in each treatment group achieved a ≥50% reduction from baseline in PTH levels at the final blood draw. These results were not significantly different.

Since hypercalcemia, hyperphosphatemia and/or increased Ca × P product are the major limitations to effective vitamin D therapy, the incidence of hypercalcemia and/or elevated Ca × P (>75) during the treatment phase was analyzed. No significant differences were observed between treatment groups in the proportions of patients who became hypercalcemic and/or experienced elevated Ca × P at least once during treatment (Table 4). However, on further analysis, the incidence of hypercalcemia and/or Ca × P > 75 for two consecutive laboratory draws and the incidence of hypercalcemia and/or Ca × P > 75 for four consecutive laboratory draws was significantly lower in the paricalcitol group compared to the calcitriol group (18% vs. 33%) ($P$ = 0.008). There was no difference in the incidence of hyperphosphatemia between treatment groups.

Treatment outcomes are further illustrated through group comparison of the total days on study drug relative to PTH suppression. Despite a disparity of >1600 patient-treatment days and similar PTH values at baseline, patients in the paricalcitol treatment group achieved a greater number of days in the optimal therapeutic range (100 to 300 pg/mL) than patients receiving calcitriol (Table 5). Furthermore, paricalcitol patients experienced fewer episodes of hypercalcemia, fewer incidences of elevated Ca × P, and a greater incidence of decreased Ca × P product (<50) than subjects receiving calcitriol while in the optimal PTH therapeutic range.

As a marker for bone remodeling activity, alkaline phosphatase activity provides an additional efficacy variable. Mean reductions in total alkaline phosphatase were observed for both treatment groups. At week 16 of the treatment phase, mean reductions from baseline observed were 26.3 U/L in the paricalcitol group ($N$ = 91) and 27.3 U/L in the calcitriol group ($N$ = 84). At follow-up, mean reductions from baseline observed were 37.4 U/L in the paricalcitol group ($N$ = 122) and 44.0 U/L in the calcitriol group ($N$ = 115). The safety profiles presented during the study by each compound were comparable. No meaningful differences were observed between treatment groups in the incidence, severity, or relationship of adverse events occurring during treatment. Similarly, other laboratory values (change from baseline) and vital signs assessments were comparable.

## DISCUSSION

Previous clinical studies of paricalcitol have demonstrated its effectiveness and safety in reducing PTH concentrations in patients with moderate to severe hyperparathyroidism [21, 28]. This study is the first blinded, randomized, multicenter clinical trial comparing a vitamin D analog with calcitriol, and shows that paricalcitol, dosed at a 4:1 ratio to calcitriol, results in a greater and more rapid decrease in PTH concentrations than calcitriol (Figs. 1 and 2). The rapid decrease in PTH is

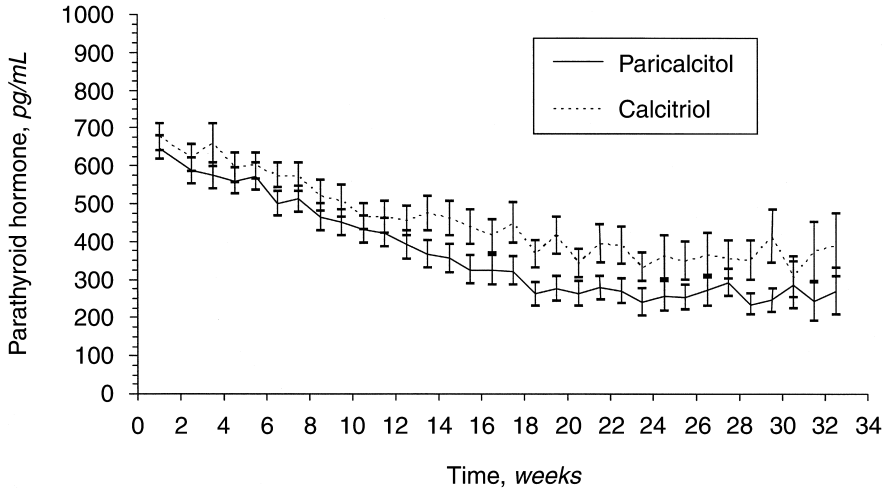


**Fig. 1. Mean parathyroid hormone (PTH) (±SEM) during the 32 weeks of drug administration.** Paricalcitol patients (solid line) experienced a more rapid reduction over time in mean PTH levels, resulting in more days in the effective therapeutic range (100 to 300 pg/mL) than patients in the calcitriol treatment group (whose mean values did not enter this target range).

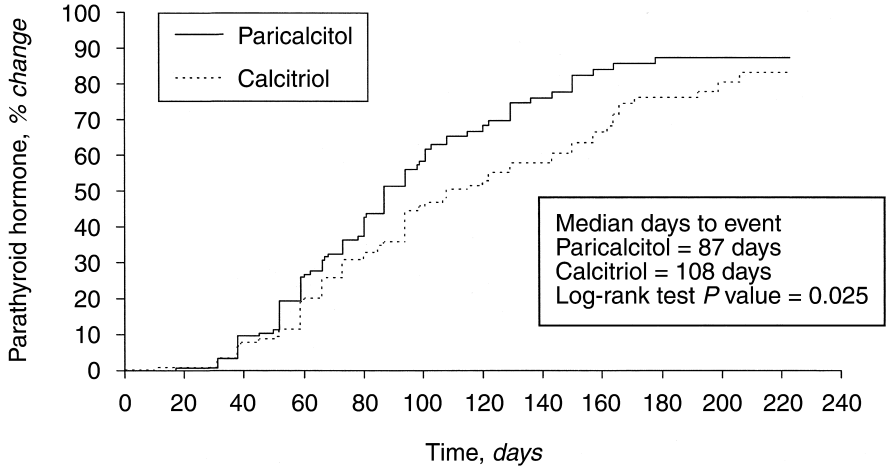


**Fig. 2. Kaplan-Meier curves to first period of four consecutive values consistent with a ≥50% reduction from baseline in parathyroid hormone (PTH) levels**. Patients in the paricalcitol treatment group achieved the first of four consecutive 50% reductions from baseline PTH levels in a median of 87 days compared to 108 days for calcitriol patients. All-treated patients, paricalcitol ($N$ = 130), calcitriol ($N$ = 133). The significance of this difference ($P$ = 0.025) attests to the rapidity of overall PTH reduction for patients treated with paricalcitol.

**Table 4.** Incidence of hypercalcemia and elevated Ca × P

| End point | Number (%) of patients | | |
|---|---|---|---|
| | Calcitriol ($N$ = 133) | Paricalcitol ($N$ = 130) | $P$ value[a] |
| Hypercalcemic and/or a Ca × P > 75 at least once during treatment | 90 (68%) | 83 (64%) | 0.519 |
| Hypercalcemic and/or a Ca × P > 75 for at least two consecutive blood draws | 67 (50%) | 50 (38%) | 0.034 |
| Hypercalcemic for at least two consecutive blood draws and/or a Ca × P > 75 for at least one period of four consecutive blood draws | 44 (33%) | 24 (18%) | 0.008 |

[a] $P$ values comparing the proportions between treatment groups are from a 2 × 2 Fisher's Exact Test.

similar to what we observed when we analyzed a subgroup of 38 subjects from a single center [27].

Furthermore, in the present study a higher proportion of the paricalcitol-treated patients achieved a mean PTH concentration in the clinically desirable target range of 100 to 300 pg/mL (Table 5). By reducing serum concentrations of PTH more rapidly than calcitriol, paricalcitol may offer an important clinical advantage to calcitriol. Unlike the findings in our previous subgroup analysis, in which the percentage of subjects experiencing severe hyperphosphatemia (serum phosphorus greater than 8.0 mg/dL) was higher in the subjects receiving calcitriol compared to those receiving paricalcitol [27], the occurrence of hyperphosphatemic episodes was comparable in both groups. Although persistent hypercalcemia and/or elevated Ca × P product was observed less in the paricalcitol group (Table 4) in this multicenter analysis. The difference in incidence of hyperphosphatemia and hyper-

**Table 5.** Calcium, phosphorus, and Ca × P levels relative to days on study drug and overall parathyroid hormone (PTH) suppression

| | Paricalcitol ($N$ = 130) | Calcitriol ($N$ = 133) |
|---|---|---|
| Total days on study drug | 16,030 | 17,718 |
| Total days of PTH suppression (target range of 100 to 300 pg/mL) | 4505 | 4269 |
| Percent of time in target range | 28.1 | 24.1 |
| Incidences of hypercalcemia while PTH suppressed (per 1000 patient-day) | 30 (6.7) | 39 (9.2) |
| Number of patients who became hypercalcemic while PTH suppressed | 13 | 19 |
| Incidences of hyperphosphatemia while PTH suppressed (per 1000 patient-day) | 446 (99) | 436 (102) |
| Number of patients who became hyperphosphatemic while PTH suppressed | 66 | 71 |
| Incidences of elevated Ca × P while PTH suppressed (per 1000 patient-day) | 153 (33.9) | 170 (39.8) |
| Number of patients with elevated Ca × P while PTH suppressed | 43 | 43 |
| Incidences of decreased Ca × P (<50) while PTH suppressed (per 1000 patient-day) | 507 (112.5) | 394 (92.3) |
| Number of patients with decreased Ca × P (<50) while PTH suppressed | 71 | 70 |

calcemia and/or elevated Ca × P product between the subgroup analysis and the multicenter analysis is an interesting observation and may reflect the peculiarities of treatment at a single center. The multicenter nature of this study should negate any such peculiarities.

The importance of finding hypercalcemia and/or elevated Ca × P product is further appreciated if one considers that the development of hypercalcemia is more likely to occur when PTH levels are rapidly lowered and/or suppressed to levels below those considered to be therapeutic. In this regard, recent long-term studies have shown that paricalcitol dosed at a 3:1 ratio may be as effective in suppressing PTH but may significantly minimize the hypercalcemia [22]. Yet, the present study demonstrates that in subjects receiving paricalcitol there was a lower incidence of sustained hypercalcemia and/or elevated Ca × P product while PTH had decreased to the target range more rapidly than in those receiving calcitriol (Table 5). The exact dosing in relation to prior calcitriol usage may not be as high as the 4:1 ratio employed in this study. Lower doses may be just as effective but with fewer accompanying side effects.

Recent understanding of the role of calcium and phosphorous in the morbidity and mortality in patients with chronic renal failure [17] has led to important refinements in the therapeutic approach toward hyperparathyroidism. These analyses suggest that increased mortality is related to the severity of hyperphosphatemia and elevation of Ca × P [29]. Calcitriol, especially in conjunction with calcium-containing phosphate binders, greatly increases the risk for hypercalcemia, hyperphosphatemia, and increased Ca × P [13, 19]. These disturbances, in turn, can cause soft tissue and vascular calcifications and contribute to increased mortality and cardiovascular morbidity [18, 29, 30]. Thus, recent efforts have focused on developing therapies that do not precipitate an increase in overall calcium load. This has included the introduction of the noncalcium-containing phosphate binder sevelamer hydrochloride [20]. Analogues of calcitriol that have less effect on the absorption of calcium and phosphorus, such as paricalcitol, are also desirable in terms of suppressing PTH with a decreased incidence of hypercalcemia and/or elevations in the Ca × P product.

We would like to emphasize that the study design of this comparative analysis was reflective of the dose-reactive practice used by nephrologists in the early to mid-1990s, whereby vitamin D administration was adjusted in order to reduce or avoid incidences of hypercalcemia and elevated Ca × P product resulting from treatment. Such an approach favored a slow and steady methodology that resulted in a gradual decline of PTH with what were considered "manageable" occurrences of hypercalcemia and elevated Ca × P. At that time, management of hypercalcemia commonly consisted of reducing or withholding vitamin D therapy until calcium and phosphorus levels returned to clinically acceptable ranges as there were no safe and effective noncalcium-containing phosphate binders available. Furthermore, the acceptable levels of calcium and Ca × P allowed in the study (11.5 mg/dL and 75 mg/dL, respectively), which were at that time considered acceptable for initiating vitamin D therapy, certainly fall outside of what is currently considered suitable as a goal of patient management. The dose of vitamin D necessary to effectively treat a particular patient's PTH level often induced an excessively high calcium level. In cases where vitamin D treatment was insufficient, the outcome for such patients was further progression of their hyperparathyroidism and, in extreme cases, surgical parathyroidectomy. The concomitant occurrence of hypercalcemia or elevated Ca × P was a rate-limiting factor rather than a true measure of a patient's ability to respond to treatment. The shortcoming of this approach was the creation of a significant subset of patients who were considered "refractory" to vitamin D treatment.

Other studies have revealed the critical importance of rapid reduction of PTH levels in order to preserve remaining vitamin D receptor function [30–32] and the value of early identification of true "responders" versus potential nonresponders. ESRD patients commonly ex-

hibit a lack of vitamin D receptors in the more severe and nodular forms of parathyroid hyperplasia. Coupled with the increasing risks of extraosseous calcification, it is necessary in clinical practice to promptly and accurately identify which patients will respond to vitamin D treatment [30, 33, 34].

Bearing these issues in mind, results for this comparator trial are interesting and relevant in that they reflect the subtle shift from the reactive modalities of calcitriol therapy to the interactive regimen made possible by a selective analog such as paricalcitol. While the primary endpoint of this study (single incidence of hypercalcemia and/or elevated Ca × P) failed to differentiate paricalcitol from calcitriol, this end point was ultimately shortsighted in that it did not capture the clinical significance of overall maintenance of appropriate PTH levels. The clinical meaningfulness of a single episode of elevated calcium and/or Ca × P product, occurrences routinely associated with hemodialysis patients, is doubtful. As evidenced by a secondary, and perhaps more meaningful, end point (the incidence of hypercalcemia for two consecutive laboratory draws and/or Ca × P > 75 for four consecutive laboratory draws), there was a statistically significant difference ($P = 0.008$) in the number of patients who experienced prolonged hypercalcemia and increased Ca × P product (Table 4).

In addition to this crucial finding, paricalcitol reduced serum levels of PTH much more rapidly than calcitriol. Patients in the paricalcitol treatment group achieved a mean reduction in PTH of ≥50% at week 15 versus week 23 for calcitriol-treated patients. This finding was reinforced by a Kaplan-Meier analysis that indicated the median number of days to achieve a ≥50% reduction was 87 for paricalcitol patients versus 108 for calcitriol patients, a statistically significant finding ($P = 0.025$). While of potential clinical benefit, the rapid reduction of PTH exhibited by the paricalcitol group in this study increased the difficulty of making an adequate comparison to calcitriol. The dose-increase criteria resulted in PTH levels <100 pg/mL, with some patients having PTH concentrations as low as 10 to 20 pg/mL. These results were well below the target range and are actually below the normal range for healthy subjects. Dosing criteria further required that no dose reduction could take place until two consecutive PTH results were <100 pg/mL. Physiologically, when PTH is oversuppressed (<100 pg/mL), the risk of hypercalcemia is greatly increased. Yet paricalcitol-treated patients experienced significantly fewer episodes of sustained hypercalcemia and/or elevated Ca × P compared to calcitriol-treated patients, clearly indicating a therapeutic advantage over calcitriol.

Analyzing the results in terms of achieving an optimal PTH concentration (100 to 300 pg/mL) allows for a more complete evaluation of the effectiveness of therapy. There were several differences between the two groups, which suggest that paricalcitol might be safer. The paricalcitol patients tended to experience a greater number of days in the optimal range of PTH than did patients in the calcitriol group. In comparison to the calcitriol-treated patients, paricalcitol patients received fewer days of study drug treatment, experienced fewer incidences of hypercalcemia while in the therapeutic range, and experienced fewer incidences of elevated Ca × P while in this range. In addition, the paricalcitol patients experienced greater incidences of decreased Ca × P (<50) while in the therapeutic range. To emphasize the importance of these findings, one must consider that these results were achieved without protocol-specified adjustments in the chronic use of phosphate binders and that serum phosphorus was controlled solely with the use of calcium-containing phosphate binders since sevelamer HCl was not yet available. Although these findings were not statistically significant, they suggest a therapeutic advantage to the use of paricalcitol. It should be noted that PTH concentrations are used as a surrogate marker of bone disease. Thus, PTH suppression to a target level is presumed evidence for therapeutic efficacy. Clearly, further studies that include the use of bone histomorphometry should be designed to confirm this therapeutic advantage.

Given the difference in our understanding and approach to the treatment of hyperparathyroidism today compared to when this protocol was designed years ago, it is powerful to note that these results distinguish a significant difference in outcomes in patients treated with paricalcitol as opposed to calcitriol. Such a study was difficult to design and clearly would not be conducted in the same fashion today. Nevertheless, the results of this study reinforce the current trends demonstrated in clinical practice (i.e., the desire to reduce PTH levels expeditiously while maintaining patient safety and the maintenance of PTH levels within a clinically acceptable range). Furthermore, noncalcium-containing phosphate binders were not available, thus differences observed in the incidence of hypercalcemia and/or elevated Ca × P product occurred with both groups receiving similar doses of calcium containing binders to control serum phosphorus concentrations. The incidence of hypercalcemia and elevated Ca × P product may be different with the use of the newer noncalcium-containing phosphate binders.

The therapeutic advantage of paricalcitol demonstrated by this study is consistent with studies in experimental animals demonstrating that the administration of paricalcitol can result in suppression of PTH without increasing the intestinal vitamin D receptor [24]. The lack of increased expression of intestinal vitamin D receptor could limit the gastrointestinal absorption of calcium and phosphorus [23]. In addition, calcitriol appears

to be more potent than paricalcitol in mobilizing calcium resorption from bone in vivo [23, 25] (abstract; Slatopolsky E et al, *J Am Soc Nephrol* 11:583A, 2000) and in vitro [26]. Further studies should seek to elicit the differences of vitamin D analogs through studies of their mechanism of actions including gastrointestinal absorption and bone resorption.

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