

Paricalcitol versus calcitriol treatment for hyperparathyroidism in pediatric hemodialysis patients

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Received: 3 March 2006 / Revised: 3 April 2006 / Accepted: 18 April 2006 / Published online: 10 August 2006
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Abstract Secondary hyperparathyroidism (SHPT) remains a treatment dilemma in pediatric dialysis patients. Recent experience with paricalcitol (P), a vitamin D analogue, in adults with SHPT has shown equal efficacy and improved survival compared to traditional treatment with calcitriol (C). We present our experience with (C) compared to (P) treatment in our pediatric dialysis patients with SHPT. Twenty-one patients (mean age 11.5 ± 5 years) with SHPT (intact parathyroid hormone (iPTH) averaging $1,228 \pm 496$ pg/ml) were studied. Seventeen received (C) followed by (P); while an additional four were treated with either (C=1) or (P=3) alone. After 26 ± 8 weeks, average percent (%) decrease in iPTH was similar with (C) and (P) ($-60.4 \pm 34\%$ versus $-65.4 \pm 28\%$, respectively; $p=0.6$). In the (P) group, the effective dose in children was greater than in adult trials based on kilogram weight. Episodes of hypercalcemia between the treatment groups were not different. However, episodes of elevated calcium \times phosphorus product ($\text{Ca} \times \text{P}$) ≥ 70 mg^2/dl^2 occurred more frequently in the (C) group (odds ratio=1.5; $p=0.01$). Paricalcitol appears to be safe and effective in pediatric patients. Data suggest that dosing should be gauged according to degree of SHPT. This should serve as impetus for future pharmacokinetic studies in pediatric dialysis patients.

Keywords Paricalcitol · Calcitriol · Hyperparathyroidism · Children · Young adults · Hemodialysis

Introduction

Secondary hyperparathyroidism (SHPT) is a major complication among children and adults undergoing dialysis. It often causes growth failure, bone deformities, fractures and soft tissue calcification [1–6]. Decreased levels of calcitriol (1,25-dihydroxy vitamin D) and phosphorus retention play major roles in SHPT [1, 2, 5, 6]. Thus, current management aims to provide adequate vitamin D supplementation while controlling hyperphosphatemia by dietary restriction and use of phosphate-binders [1–3]. Calcitriol has been shown to control SHPT effectively in both pediatric and adult patients [7–11]. It has a direct effect on suppressing the synthesis and secretion of parathyroid hormone [1–5]. Nevertheless, its potent actions on enhancing intestinal calcium and phosphorus absorption as well as increasing bone resorption often results in hypercalcemia and hyperphosphatemia, which limits its therapeutic dosing [2, 7–12]. Several studies in adults indicate that paricalcitol, a new analog of vitamin D, can control SHPT as effectively as calcitriol [13–16] with a reduced tendency to raise serum calcium and phosphorus [14, 16]. The different mechanism between paricalcitol and calcitriol might be from a selective action of paricalcitol on parathyroid glands with less action on bone and intestine [17, 18]. Furthermore, two recent studies have shown that paricalcitol provided a survival advantage over calcitriol treatment in adults on hemodialysis [19, 20]. The benefit of this novel therapy has not been adequately studied in a pediatric population.

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A substantial proportion of children in advanced stages of chronic kidney disease (CKD) (stages 3 to 5) have SHPT with concomitant growth failure and osteodystrophy [1–8]. A cross-sectional survey of our pediatric hemodialysis unit showed a high prevalence of SHPT and hyperphosphatemia, despite calcitriol treatment and extensive use of phosphate binders. Based upon the promising studies in adults, we developed a clinical protocol using paricalcitol in a select group of pediatric patients who had severe SHPT despite calcitriol treatment. To our knowledge, this is the first comparative study of calcitriol in a single center pediatric population.

Patients and methods

In a retrospective review of 49 patients who were on regular hemodialysis at Holtz Children’s Hospital, University of Miami Miller School of Medicine, between January 1999 and January 2006, 21 had SHPT with a baseline serum intact parathyroid hormone (iPTH)>150 pg/mL and calcium-phosphorus product (Ca × P)<70 mg²/dl². This was an observational retrospective clinical study approved by the institutional review board of the University of Miami Miller School of Medicine. All subjects were assured anonymity in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

Patients included 13 females and 8 males. Mean age was 11.5±5 years (range from 1.5 to 20 years). Mean duration of dialysis was 68±62 months (range 16 months to 3.5 years). There was an ethnic predominance with 14 of African descent and 7 Hispanics. Etiology of end stage renal disease

included chronic glomerulonephritis (n=4), focal glomerulosclerosis (n=7), renal dysplasia (n=6), HIV-nephropathy (n=2), Alport’s syndrome and Wilms tumor (n=1, each). All underwent hemodialysis three times weekly with calcium dialysate concentration at 3 mEq/L (1.5 mmol/L).

Seventeen patients had treatment with calcitriol (C) before beginning treatment with paricalcitol (P). An additional patient received only calcitriol and three received only paricalcitol during the treatment period. Twelve had radiographic bone changes consistent with renal osteodystrophy including four with pathological fractures. Two patients had soft tissue calcification. Five patients received concurrent treatment with recombinant human growth hormone (rhGH) during one or both treatment periods. Growth is not reported due to the short period of observation, although the bone disease activity and response to treatment were considered separately.

Intravenous calcitriol was administered three times weekly at a dose of 0.5–2 mcg/dose or 40±20 ng/kg/dose. The dose of calcitriol was adjusted according to the degree of SHPT and to maintain the appropriate levels of serum calcium and phosphorus. Only calcium-based or polymer phosphate-binders were prescribed before and during treatment to control serum phosphate levels.

The clinical protocol of paricalcitol shown in Fig. 1 was adapted from the adult study [13]. After calcitriol was withdrawn, intravenous paricalcitol was given at a dose of 0.04 mcg/kg, three times weekly post-dialysis. The dose was increased by 0.04–0.1 mcg/kg at least every 4 weeks to achieve an effective dose aimed at reducing iPTH levels>30% from baseline with a target iPTH level>150<300 pg/ml [1]. Conversely, the dose was reduced by 0.02–0.05 mcg/kg/dose

Fig. 1 Protocol for treatment with paricalcitol in adults [13]

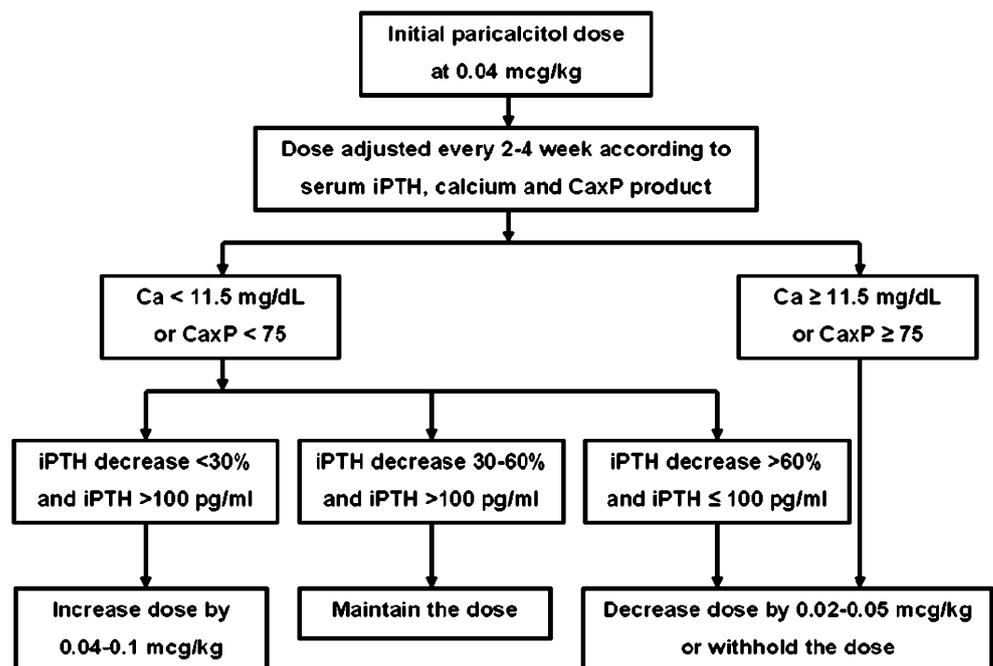


Table 1 Demographics and treatment response in pediatric dialysis patients treated with Calcitriol versus Paricalcitol for secondary hyperparathyroidism

Parameter	Calcitriol <i>n</i> =18	Paricalcitol <i>n</i> =20
Age (yr)	11±4	13±4
Weight (kg)	37±21	37±16
Initial iPTH (pg/ml)	1,114±721	1,228±579
Final iPTH (pg/ml)	503±529	422±388
Calcium (mg/dl)	9.0±0.8	9.0±0.8
Phosphorus (mg/dl)	6.9±1.2	6.8±1.4
Ca×P product (mg ² /dl ²)	61±10	61±14
Weeks of treatment	22±11	26±8

Indicates significant difference from initial iPTH in the same treatment group

or temporarily withheld if there was excessive suppression of iPTH (level decrease more than 60% or iPTH level ≤60 pg/mL, hypercalcemia (serum calcium ≥11.5 mg/dL or 2.87 mmol/L) or Ca×P ≥75.

Calcium and phosphorus with calculation of their product (Ca × P) was measured at least every 2 weeks to monitor for episodes of hypercalcemia and excessive Ca × P. For the purposes of reporting, hypercalcemia was noted if any calcium was ≥11 mg/dl. Average treatment period was 22±11 weeks for the calcitriol group and 26±8 weeks for the paricalcitol group. Data for Ca × P was retrieved in 84% (331/393 treatment weeks) for the calcitriol group and 98.8% (517/523 treatment weeks) for the paricalcitol group.

During treatment, serum iPTH was measured by immunoradiometric assay (normal 12–72 pg/mL) at least every 4 weeks until the appropriate level was achieved. Serum alkaline phosphatase, serum electrolytes, and adequacy of hemodialysis (urea reduction ratio) were evaluated monthly.

Response to calcitriol and paricalcitol was defined as a reduction of iPTH more than 30% from the baseline [13]. Since many of these patients had been treated solely with calcitriol for many months, the “baseline” iPTH was taken as the maximum for the observation period. For the purposes of comparison, “effective” response to calcitriol was taken as the maximum decline in iPTH during the period of treatment. If the dose of calcitriol was suspended as per protocol, the “rebound” increase in iPTH was not taken as an adverse event. Paricalcitol was initiated after discontinuing calcitriol when the iPTH rebounded to >150 pg/ml or if the SHPT was uncontrolled by calcitriol therapy.

Statistical methods

All data sets were analyzed for Gaussian distribution using the D’Agostino-Pearson omnibus test for normality. The data were calculated into average values at baseline and

after achieving maximum dosing and/or maximum response. Variables at baseline and over time were compared by one way analysis of variance (ANOVA) with Tukey’s multiple comparisons post tests. Differences in parameters between the two independent groups were analyzed using Mann-Whitney and the Friedman test with Dunn’s multiple comparisons post tests for repeated measures of nonparametric data. Comparison of toxicity parameters was made by analyzing contingency tables with the Fisher’s exact test and calculation of odds ratios with 95% confidence intervals (CI). *P* values of less than 0.05 were considered significant. All results are expressed as mean± standard deviation (SD). All graphs and statistical analyses were determined using GraphPad Prism v. 4.00 for Windows (GraphPad Software, San Diego, California, USA).

Results

Of the 18 patients treated with calcitriol, 13 responded to treatment and 5 remained stable with an average decline in iPTH from 1,114±721 to 503±529 pg/ml (*p*<0.001) equivalent to an average reduction of 60.4±34% (Table 1, Fig. 2). Average treatment duration was 22±11 weeks with a total of 393 patient weeks. Five patients experienced a decline in iPTH to <60 pg/ml requiring discontinuation of therapy. All average parameters of treatment including calcium, phosphorus, Ca × P, alkaline phosphatase, albumin, and urea reduction ratio did not differ from the other treatment group (Table 1).

Of the 20 patients treated with paricalcitol, 19 responded with a significant drop in iPTH from baseline after attaining an effective dose ranging from 0.1 to 0.9 mcg/kg/dose

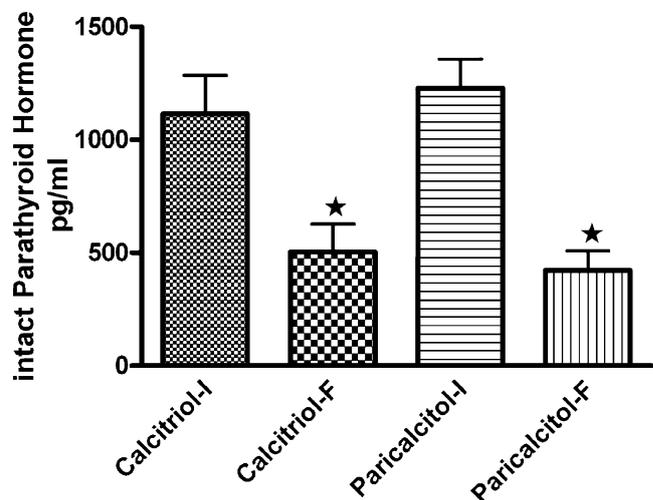


Fig. 2 Absolute values of iPTH at baseline (I) and after treatment (F) with either calcitriol or paricalcitol in pediatric hemodialysis patients. ★ Significantly different from baseline values of iPTH

(average 0.2 ± 0.7 mcg/kg/dose) (Fig. 3). During the first few months after initiation of slowly escalating dose of paricalcitol treatment, there was an unsustained increase in serum iPTH levels in almost all patients (Fig. 4). However, the levels subsequently declined as the dose of paricalcitol was increased. After the 12th week of treatment, the iPTH levels were significantly less than baseline and the 8 week escalation ($p=0.002$). Serum iPTH fell from baseline levels of $1,228 \pm 579$ to 422 ± 388 pg/mL ($p < 0.001$) equivalent to a reduction of $-65.4 \pm 28\%$ ($p < 0.01$) (Figs. 2, 4). Average treatment duration was 26 ± 8 weeks with a total of 523 patient weeks. All patients tolerated paricalcitol without serious adverse effects. Five patients had iPTH levels drop to less than < 60 pg/mL, but improved within 4 weeks after the medication was withheld.

As shown in Table 1, average serum calcium, phosphorus and $Ca \times P$ product did not differ for either treatment group. Episodes of hypercalcemia, defined as serum calcium ≥ 11 mg/dl, occurred rarely (1%) in both treatment groups with a slightly increased rate in the calcitriol group (odds ratio=1.5; 95% CI=0.6 to 3.7; $p=0.5$). Hyperphosphatemia, defined as serum phosphorus ≥ 6.5 mg/dl, also occurred with equal frequency (32%) in both treatment groups. However, episodes of elevated $Ca \times P$ product ≥ 70 mg^2/dl^2 were significantly increased in the calcitriol group compared to the paricalcitol group (101/331 versus 117/517, respectively; odds ratio =1.5; 95% CI 1.1 to 2.1; $p=0.01$).

Of the patients treated concurrently with rhGH, time averaged iPTH for each treatment period was higher than that of patients who did not receive rhGH (903 ± 620 pg/ml versus 805 ± 357 pg/ml, respectively), although the difference was not significant ($p=0.7$). Similarly, their response

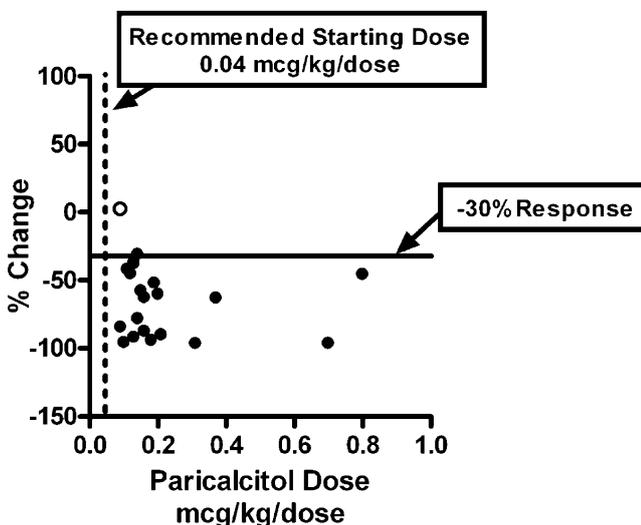


Fig. 3 Dose response in pediatric patients treated with paricalcitol. All “responders” (closed circles) required greater than 0.1 mcg/kg/dose. The “non-responder” is shown as the open circle

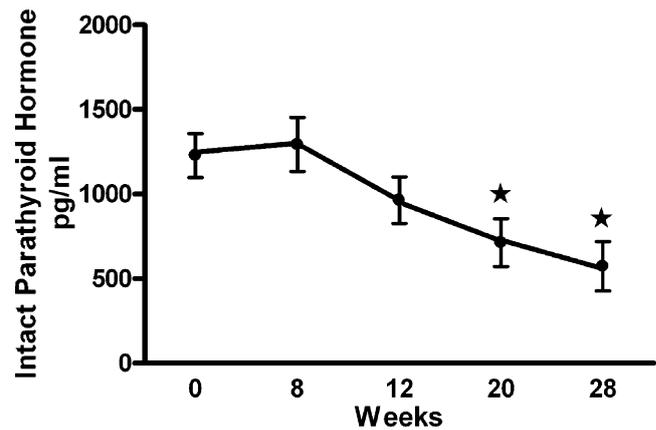


Fig. 4 Time line for response of iPTH to paricalcitol treatment of 20 pediatric hemodialysis patients from baseline to 28 weeks. ★ Significantly different from baseline or 8 week values of iPTH

to treatment was equal to that of patients not receiving growth hormone ($-77 \pm 26\%$ versus $-63 \pm 28\%$, respectively; $p=0.4$) Follow-up of patients treated with paricalcitol ranges from 7 to 222 months. Ten of the original patients continue on hemodialysis and intermittent treatment with paricalcitol as per protocol with a goal to maintain $iPTH > 150 < 300$ pg/ml [1, 13]. The remainder of the patients have been terminated from the study protocol due to transplantation (5), death (2), transfer (2), and change to peritoneal dialysis (1).

Discussion

While extensive clinical studies in adults indicate that paricalcitol can safely and effectively suppress SHPT, there is a paucity of information on experience in pediatric patients [11–15]. In the current report, we used this novel vitamin D analogue in a particular group of children who had poorly controlled SHPT despite calcitriol therapy. After an average of 26 weeks of paricalcitol treatment, overall serum iPTH in these patients fell by 65% from baseline, without significant alterations in serum calcium and phosphorus.

Although the response of SHPT seemed to be similar to the experience in adults [13], our patients required a much higher dose of paricalcitol per unit body weight to achieve the target reduction of serum iPTH. The effective dose of paricalcitol in our study averaged 0.2 ± 0.7 mcg/kg/dose (total 5–20 mcg/dose), compared to 0.12 mcg/kg in the adult study [13]. In that report, however, the severity of SHPT was less than in our study (baseline iPTH was 785 versus 1,228 pg/mL). Hence, lower age and severity of SHPT might be an important factor in appropriate dosing of paricalcitol.

In fact, we found that a higher dose of paricalcitol was required to suppress serum iPTH towards optimum levels in patients with severe SHPT, similar to the adult experience [14]. The refractory response to vitamin D treatment in patients with severe SHPT might be related to a decrease in vitamin D receptor density in hyperplastic parathyroid glands, demonstrated in several studies [21–23]. Furthermore, a recent study indicated that dosing of paricalcitol based on the severity of SHPT could be more favorable than weight-based dosing [24].

Our data also show a poor correlation between body weight and the magnitude of changes in serum iPTH. Since the protocol for paricalcitol dosing was based on body weight, the smaller the patient, the lower the total dose of paricalcitol given at initiation of treatment. It seems possible that these small children might have received an inadequate initial dose of paricalcitol for their degree of SHPT. Also, the vast difference in basal metabolism of growing children should be considered in their response to all medications. Therefore, pharmacokinetic studies are imperative for determining appropriate dosing of paricalcitol in children.

Although too few patients were treated concurrently with growth hormone in the current experience, there are important issues that should be addressed in future studies. As reported previously in adults and children, growth hormone increases endogenous parathyroid hormone and higher doses of vitamin D analogues may be required to control the SHPT [25–27].

Paricalcitol was well tolerated by each of our patients without serious adverse events. No significant hypercalcemia was observed during paricalcitol treatment. Despite dietary advice and provision of phosphate-binders, the incidence of hyperphosphatemia remained high in both treatment groups. Only the incidence of elevated $\text{Ca} \times \text{P}$ product was greater in the calcitriol group, suggesting an increased absorption of dietary phosphorus with this vitamin D sterol. Although improvement of compliance with diet and phosphate binders could be responsible for the difference, we believe this to be unlikely as most patients in our study remained poorly compliant throughout.

An ancillary issue with the introduction of new and various vitamin D analogues is the differential cost per patient, especially when equal efficacy is demonstrated. In a recent comparative analysis of dosing regimens in adults, monthly costs for paricalcitol dosed at 5 to 10 mcg/dialysis compared to calcitriol dosed at 0.5 to 2.0 mcg/dialysis would cost 32 to 52% more per month (\$299 compared to \$180, respectively) [28]. Nevertheless, clinical studies are demonstrating a possible safety and survival advantage to paricalcitol that may save medical costs of hospitalizations in compensation for absolute drug expenses [20, 29].

Since there was no information on paricalcitol treatment in children reported previously, our clinical protocol was developed for highly selected patients who had severe SHPT despite calcitriol therapy. Thus, a limited number of patients was included. In addition, the relatively slow escalation of paricalcitol dose might have delayed the response to paricalcitol in this patient group. Therefore, long-term studies in larger samples with selective dosing are needed to evaluate the relative benefit of paricalcitol in children undergoing hemodialysis.

In conclusion, this pilot study showed that paricalcitol therapy could effectively control SHPT in pediatric patients on chronic hemodialysis with minimal effect on serum calcium and phosphorus. Moreover, it appears that smaller children with severe SHPT require higher doses per body weight to achieve an effective end point. Future studies directed towards determining optimum effective dosing of paricalcitol are very much warranted including the use of the oral form of the analogue in peritoneal dialysis patients and those with earlier stage chronic kidney disease.

Acknowledgement This study was supported in part by a grant from Florida's Department of Health, Children's Medical Services.

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