Original Article

Paricalcitol in Dialysis Patients with Calcitriol - Resistant Secondary Hyperparathyroidism

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Abstract

Background. Clinical studies in dialysis patients with secondary hyperparathyroidism (SHPT) showed that paricalcitol (19-nor-1α, 25-dihydroxyvitamin D3), a vitamin D analog, suppresses parathyroid hormone (PTH) levels as effectively as intravenous calcitriol without resulting in significant increases in serum Ca and P. The aim of the present study is to investigate whether paricalcitol could provide long-term control of moderate to severe SHPT in hemodialysis patients considered resistant to intravenous calcitriol/alfacalcidol therapy. We also assess the incidence of hypercalcemia and hyperphosphatemia during treatment with paricalcitol in this group of patients.

Methods. Thirty-one stable hemodialysis patients of mean age 54±10 with persistent intact PTH (iPTH) levels of 600 pg/ml or greater for at least 6 months despite treatment with intravenous alfalcacidol were included into the study. All patients underwent hemodialysis three times weekly. Paricalcitol was administered intravenously 3 times per week at the end of hemodialysis session. Therapy with paricalcitol was not initiated until a patient’s serum P level was less than 6.5 mg/dl (2.1 mmol/L). Nutritional counseling and phosphate binders (calcium acetate and/or sevelamer) were used for phosphate control. The initial dose of paricalcitol in mcg per hemodialysis session was calculated according to the formula: iPTH/100. Subsequent doses were titrated according to serum levels of iPTH, Ca and P. The follow-up of the patients was 12-18 months. During the study serum levels of Ca and P were measured every month and iPTH every 1-3 months. The serum Ca concentration was corrected according to the formula: total Ca + 0.8 × (4 – serum albumin).

Results. Mean iPTH levels (baseline mean 933±294 pg/ml) decreased rapidly during the first months of therapy and this decrease reached statistical significance already by the first month of treatment with paricalcitol. Mean iPTH levels reached the designated target range (100-300 pg/ml) by month 3 (mean 242±199 pg/ml). Mean Ca and P levels did not change significantly over the 14 months of paricalcitol therapy. The baseline mean Ca level of 9.3±0.8 mg/dl (2.3±0.2 mmol/L) increased to 9.7±0.9 mg/dl (2.4±0.2 mmol/L) (P = 0.86) and P level increased from 6.1±0.9 mg/dl (1.9±0.3 mmol/L) to 6.4±1.3 mg/dl (2.0±0.4 mmol/L) (P = 0.77) after 14 months of therapy. The initial dose of paricalcitol (iPTH/100) was less than previously recommended to avoid excessive iPTH suppression and resultant hypercalcemia. Mean doses of paricalcitol decreased significantly throughout the course of therapy while maintaining acceptable iPTH suppression. Six patients experienced episodes of severe hypercalcemia (Ca > 12 mg/dl or 3 mmol/L), mainly within the first 2 months and when iPTH levels decreased rapidly to less than 150 pg/ml. All these episodes were successfully managed by dietary counseling, phosphate-binder adjustment and paricalcitol dose reduction. Ten patients developed severe hyperphos-phatemia (P > 6.5 mg/dl or 2.1 mmol/L); 6 patients responded adequately to the dietary manipulation and phosphate binders, but 4 patients had repeated episodes. Three patients did not respond adequately to paricalcitol therapy and were switched on cinacalcet therapy.

Conclusion. Paricalcitol is effective in controlling SHPT in patients resistant to calcitriol therapy with minimal impact on calcium and phosphorus homeostasis.

Keywords: Calcitriol/alfalcacidol, paricalcitol, hemodialysis, hypercalcemia, hyperphosphatemia, sec. Hyperparathyroidism

Introduction

Severe renal osteodystrophy, resulting from poorly controlled secondary hyperparathyroidism, is a potentially disabling disease and causes significant morbidity in patients with chronic renal failure [1,2]. Decreased renal production of calcitriol (1,25 vitamin D3), hypocalcemia and hyperphosphatemia are the major contributing factors to the development of secondary hyperparathyroidism [3,4]. The administration of calcitriol has a direct inhibitory effect on the parathyroid gland; directly by suppressing the synthesis of parathyroid hormone (PTH) messenger RNA at the transcription level and indirectly by both increasing the serum calcium concentration and by increasing the sensitivity of PTH suppression to calcium [5]. Medical management of secondary hyperparathyroidism relies on the control of hyperphosphatemia and adequate dosing of calcitriol or one of the newer vitamin D analogues. Phosphorus control is accomplished by phosphorus restricted diets and the use of oral phosphate binders. Intravenous calcitriol has a proven efficacy in the severe cases of secondary hyperparathyroidism [6]. Serum calcium concentrations, however, are increased via vitamin D-enhanced intestinal calcium absorption, which occasionally results in hypercalce-mia [7]. 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 [8,9]. These disturbances, in turn, can result in soft tissue and vascular calcification, which contributes to an increased mortality and cardiovascular morbidity [10]. At the same time the above mentioned adverse events limit the use and effectiveness of calcitriol. Thus, current clinical practice is focused on developing therapies that do not cause increased body burden of calcium and phosphorus. This has included the use of non-calciating phosphate binders, as well as vitamin D analogues that has less calcemic and phosphatemic effect. One such analogue, 19-nor-1α, 25-dihydroxyvitamin D₃ (paricalcitol), was approved for clinical use in hemodialysis patients in 1998. Preclinical and clinical studies with paricalcitol demonstrated significant PTH suppression with only mild effects on serum calcium and phosphorus levels [11-13]. A recent double-blinded, randomized multicenter comparative study suggested that paricalcitol provides a therapeutic advantage to calcitriol because it reduced PTH concentration more rapidly and with fewer sustained episodes of hypercalcemia and increased Ca×P product than calcitriol [14]. The aim of the present study was to investigate whether paricalcitol could provide long-term control of moderate to severe SHPT in hemodialysis patients considered resistant to intravenous calcitriol/alfacalcidol therapy. We also assessed the incidence of hypercalcemia and hyperphosphatemia during the treatment with paricalcitol in this group of patients.

Patients and methods

Thirty-one stable hemodialysis patients with mean age of 54±10 with persistent intact PTH (iPTH) levels of 600 pg/ml or greater for at least 6 months despite treatment with intravenous alfalcaldiol were included into the study. All patients evaluated came from the same dialysis unit that represents a dialysis population of approximately 250 patients. Informed consent was obtained from all patients before entering the study.

All patients were dialyzed three times 4 hours per week with a calcium dialysate concentration of 2,5 mEq/l. Paricalcitol was administered intravenously 3 times per week at the end of hemodialysis session. Therapy with paricalcitol was not initiated until a patient’s serum P level was less than 6,5 mg/dl (2,1 mmol/L). Nutritional counseling and phosphate binders [calcium acetate and sevelamer] were used for the phosphate control. The initial dose of paricalcitol in mcg per hemodialysis session was calculated according to the formula: iPTH/100. However, the recommended paricalcitol dosing (iPTH/80) according to our previous experience, resulted in an unacceptably rapid suppression of iPTH and frequent hypercalcemic episodes.

The initial paricalcitol dose was maintained for a minimum of 4 weeks. Subsequent doses were titrated according to serum levels of iPTH, Ca and P. The follow-up of the patients was 12-18 months. During the study serum levels of Ca and P were measured every month and iPTH every 1-3 months. iPTH was measured by means of an intact hormone radioimmunoassay. The serum Ca concentration was corrected according to the formula: total Ca + 0,8× (4 – serum albumin).

If a patient’s serum calcium concentration level increased to greater than 11 mg/dl (2,7 mmol/L), paricalcitol dose was decreased by approximately 30%. Paricalcitol was withheld if serum calcium levels increased to greater than 12 mg/dl (3 mmol/L) or symptomatic hypercalcemia was suspected. Paricalcitol was also withheld if serum phosphorus levels increased to greater than 7,5 mg/dl (2,4 mmol/L) or calcium-phosphorus product was greater than 75. When calcium levels decreased to 10 mg/dl (2,5 mmol/L) or less, phosphorus levels decreased to 6,5 mg/dl (2,1 mmol/L) or less, or calcium-phosphorus product decreased to 65 or less, paricalcitol therapy was restarted. The designated target was to correct iPTH levels to a range of 100-300 pg/ml. Student’s t-test was used for statistical analysis of biochemical data before, during and after therapy. Statistical significance threshold was set at 0,05. Results are expressed as mean ± SD.

Results

Thirty-one patients with end-stage renal disease on maintenance hemodialysis therapy with moderate to severe secondary hyperparathyroidism were included into the study. Demographic data for patients are listed in Table 1. Before entering the study, all patients were treated with intravenous alfalcaldiol for at least 6 months, but alfalcaldiol failed to control secondary hyperparathyroidism. Just before alfalcaldiol therapy was discontinued, the mean iPTH level was 933±294 pg/ml.

Recruited patients had experienced hypercalcemia (Ca > 11,5 mg/dl or 2,8 mmol/L), hyperphosphatemia (P > 6,5 mg/dl or 2,1 mmol/L), or both during the previous 6 months of therapy with alfalcaldiol. Twenty patients (64%) experienced repeated episodes of hyperphosphatemia, 16 patients repeated episodes of hypercalcemia (52%) and 15 patients (48%) experienced both before being converted to paricalcitol therapy. Patients were followed up for 12-18 months. Twenty-eight patients were evaluated for the full 12 months of paricalcitol therapy.

Mean iPTH levels (baseline mean 933±294 pg/ml) decreased rapidly during the first months of therapy and this decrease reached statistical significance already by the first month of treatment with paricalcitol. Mean iPTH levels reached the designated target range (100-300 pg/ml) by month 5 (mean 242±199 pg/ml). Mean iPTH levels at 6, 12,
and 16 months of paricalcitol treatment were statistically lower than mean iPTH levels at baseline (p<0.001). Figure 1 shows mean iPTH levels over the 18 months of paricalcitol therapy.

![Fig. 1. Mean iPTH levels throughout the study in paricalcitol-treated patients](image)

Mean Ca and P levels did not change significantly over the 14 months of paricalcitol therapy. The baseline mean Ca level of 9,3±0,8 mg/dl (2,3±0,2 mmol/L) increased to 9,7±0,9 mg/dl (2,4±0,2 mmol/L) (P = 0,86) and P level increased from 6,1±0,9 mg/dl (1,9±0,3 mmol/L) to 6,4±1,3 mg/dl (2,0±0,4 mmol/L) (P = 0,77) after 14 months of therapy. Figures 2 and 3 show the variations of mean Ca, P and Ca×P throughout the study. The initial dose of paricalcitol (iPTH/100) was less than previously recommended to avoid excessive iPTH suppression and resultant hypercalcemia. Mean doses of paricalcitol decreased significantly throughout the course of therapy while maintaining acceptable iPTH suppression.

![Fig. 2. Mean Ca and P responses over time in paricalcitol-treated patients](image)

![Fig. 3. Mean Ca×P responses over time in paricalcitol-treated patients](image)

Six patients experienced episodes of severe hypercalcemia (Ca > 12 mg/dl or 3 mmol/L), mainly within the first 2 months and when iPTH levels decreased rapidly to less than 150 pg/ml. All these episodes were successfully managed by dietary counseling, phosphate-binder adjustment and paricalcitol dose reduction. Ten patients developed severe hyperphosphatemia (P > 6,5 mg/dl or 2,1 mmol/L), 6 patients responded adequately to dietary manipulation and phosphate binders, but 4 patients had repeated episodes. Three patients did not respond adequately to paricalcitol therapy, their iPTH levels remained greater than 900 pg/ml and are now on cinacalcet. One of the patients with persistent hyperphosphatemia is now also on cinacalcet.

**Discussion**

The present study evaluated 31 patients with persistent moderate to severe secondary hyperparathyroidism that did not respond to intravenous alfalcacidol and were converted to paricalcitol therapy. In summary, paricalcitol was successful in controlling secondary hyperparathyroidism over a long-term period in patients resistant to alfalcacidol therapy with minimal impact on calcium and phosphorus homeostasis.

The initial dose of paricalcitol (iPTH/100) was less than previously recommended because, according to our experience, higher doses of paricalcitol resulted in excessive iPTH suppression and subsequent hypercalcemia. It seems that lower doses of paricalcitol cause more gradual decrease in iPTH levels and thus severe hypercalcemic episodes are avoided. The dramatic iPTH suppression most likely induced a state of the low bone turnover that resulted in hypercalcemia.

The maintenance dose of paricalcitol was also dictated by the severity of secondary hyperparathyroidism. Paricalcitol dose decreased gradually as iPTH levels decreased but anyway the dose was lower in patients with an initial iPTH level between 600-800 pg/ml. Patients with more severe secondary hyperparathyroidism require greater doses of paricalcitol, which may reflect the severity of parathyroid hyperplasia in these patients.

Among the patients recruited in our study, six patients developed severe hypercalcemia (Ca > 12 mg/dl or 3 mmol/L), mainly within the first 2 months and when iPTH levels decreased rapidly to less than 150 pg/ml. iPTH values after 2 months of paricalcitol therapy had decreased to 175±75 pg/ml in this group of hypercalcemic patients. All these episodes of hypercalcemia were successfully managed by dietary counseling, phosphate-binder adjustment and paricalcitol dose reduction. After the maintenance dose of paricalcitol is established, the incidence of hypercalcemia appears to be negligible. Over the 1-year period only one episode of mild hypercalcemia (Ca 10,8 mg/dl or 2,7 mmol/L) occurred.

Ten patients experienced severe hyperphosphatemia (P > 6,5 mg/dl or 2,1 mmol/L) mostly due to a lack of compliance with dietary phosphorus restrictions and inappropriate phosphorus-binder use, 6 patients responded adequately to dietary manipulation and phosphate binders, but 4 patients had repeated episodes that necessitated temporary or definitive discontinuation of paricalcitol therapy. One of these patients with persistent hyperphosphatemia is now also on cinacalcet. Parathyroidectomy was not performed in any patient at least up to now.

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The results of our study are consistent with that of previous clinical studies, which demonstrated that paricalcitol provides profound PTH suppression and at the same time does not cause significant increases in serum Ca or P\textsuperscript{12-14}. However, our study was designed to evaluate the effectiveness and safety of paricalcitol specifically in patients considered to be resistant to calcitriol/alfacalcidol therapy. This subgroup of patients is deemed to have severe secondary hyperparathyroidism and therefore the role of paricalcitol in these difficult-to-manage patients is of particular interest. Additionally, the experience in this area is - according to our knowledge - limited.

In conclusion, paricalcitol is effective in controlling persistent moderate to severe secondary hyperparathyroidism in patients resistant to intravenous alfacalcidol therapy with minimal impact on calcium and phosphorus levels. This control was appreciated over a period of up to 18 months. The administered dose of paricalcitol was less than previously recommended in order to avoid excessive iPTH suppression and resultant hypercalcemia. Our experience shows that dose adjustment after the first month of therapy is mandatory because of the rapid iPTH suppression afforded by paricalcitol.

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Conflict of interest statement. None declared.

References