

# Long-Term Outcomes of Cinacalcet and Paricalcitol Titration Protocol for Treatment of Secondary Hyperparathyroidism

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## Key Words

Vitamin D · End-stage renal disease · Osteodystrophy · Cinacalcet

## Abstract

Long-term outcomes of combined cinacalcet and paricalcitol therapy for secondary hyperparathyroidism (SHPT) in patients failing traditional therapies with phosphate binders and active vitamin D compound analogs are not well described. We implemented a titration protocol for cinacalcet and paricalcitol and assessed its long-term effects on bone metabolism and disease in hemodialysis (HD) patients. Thirty-five patients were started on 30 mg of cinacalcet daily. After 12 months, median cinacalcet dose was 60 mg. There was a 33% increase in number of patients receiving paricalcitol. Average corrected serum calcium (Ca) decreased from 9.5 to 8.8 mg/dl ( $p = 0.003$ , 95% CI 0.34–1.04); phosphorus (P) from 6.2 to 5.5 mg/dl ( $p = 0.047$ , 95% CI 0.01–1.34); Ca  $\times$  P product from 58 to 48 ( $p = 0.001$ , 95% CI 4.2–15.7); and intact PTH (iPTH) from  $426 \pm 274$  to  $300 \pm 228$  pg/ml ( $p = 0.03$ , 95% CI 19.3–401.7). Number of patients achieving three or more K/DOQI criteria increased by 29% ( $p = 0.009$ ).

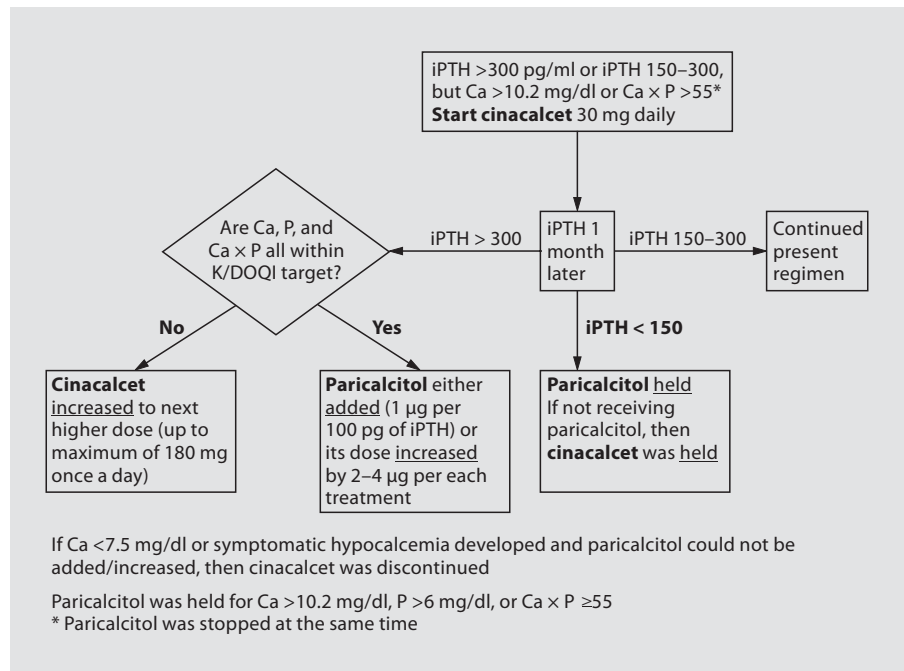
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## Background

Treatment results of SHPT in HD patients remain inadequate, with less than 30% of all patients achieving at least three and just over 5% reaching all four K/DOQI bone metabolism and disease clinical practice guidelines [1, 2]. Introduction of cinacalcet into clinical practice opened a novel pathway in SHPT therapy [3, 4]. The precise role of cinacalcet in SHPT management, its impact on active vitamin D use patterns and overall bone metabolism remains to be determined. Previously completed studies [5–7] mostly held active vitamin D dose constant. No titration protocols for combined therapy with cinacalcet and active vitamin D preparations have been proposed to date. The objective of this study is to describe the long-term effect of a combined therapy, using cinacalcet and paricalcitol titration protocol on achieving the K/DOQI bone metabolism and disease targets in patients failing traditional SHPT treatments.

## Methods

Two categories of patients were started on a calcimimetic: the first had iPTH >300 pg/ml (while on phosphate binders and paricalcitol) and the second had iPTH in the target range 150–300 pg/ml, but they became ineligible to continue paricalcitol therapy due to Ca >10.2 mg/dl or Ca  $\times$  P >55 (paricalcitol was discontinued in these patients). Treatment goals were established according



**Fig. 1.** Simultaneous titration algorithm for cinacalcet and paricalcitol.

**Table 1.** Patients achieving K/DOQI targets (in %)

Outcomes	Baseline	12 months
Calcium, mg/dl	40	54
Phosphorus, mg/dl	43	51
iPTH, pg/ml	43	66
Ca × P product	51	77
Three or more targets combined	14	43*

\* p < 0.01

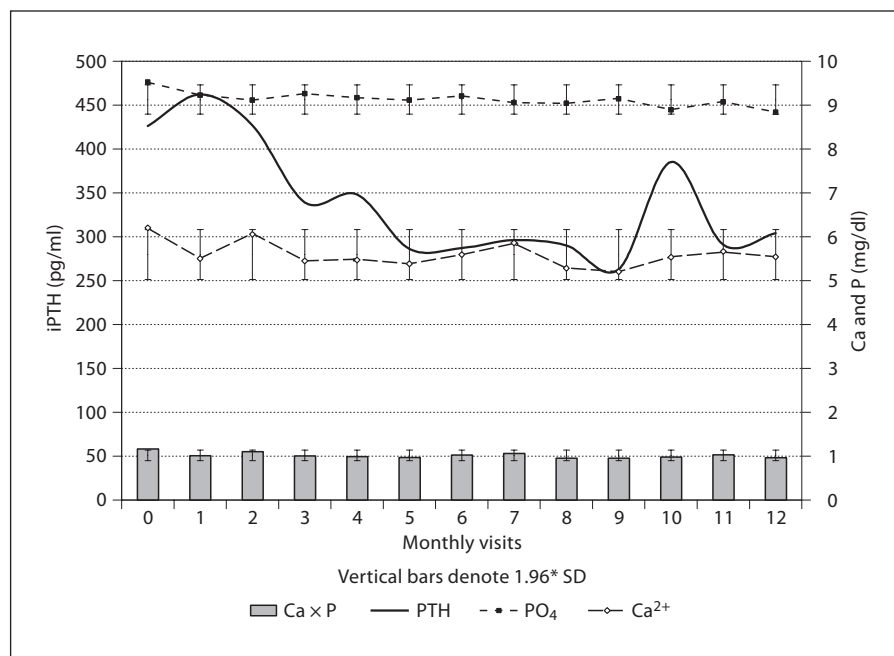
to the K/DOQI guidelines: iPTH 150–300 pg/ml, Ca 8.4–9.5 mg/dl, P 3.5–5.5 mg/dl, Ca × P product <55. All patients started cinacalcet at a daily dose of 30 mg and, regardless of dose, were instructed to take cinacalcet once daily with the evening meal. Paricalcitol was administered intravenously three times weekly at scheduled hemodialysis sessions. Serum Ca was measured at baseline and levels were monitored at two weeks after initiating cinacalcet therapy and at 2 weeks after any dose adjustment. Serum Ca drawn every second week of each month (4 weeks after initiating cinacalcet therapy or changing of the dose) was used for all comparisons. All other bone metabolism and disease parameters (P, iPTH, alkaline phosphatase) were repeated monthly. If iPTH remained >300 pg/ml and all other parameters were within K/DOQI targets, further medication adjustments followed the algorithm (fig. 1). If patients developed symptomatic hypocalcemia cinacalcet was discontinued. When symptomatic hypocalcemia resolved, and Ca was greater than 8.0 mg/dl cinacalcet was restarted at the next lower dose. Intact PTH was measured using

an electrochemiluminescence immunoassay (Roche™), normal range 15–75 pg/ml. Statistical analysis methods for paired observations (Student's t test) were applied using standard software (Stata Corp. 2003, Stata Statistical Software, Release 8.0, College Station, Tex., USA) and performed retrospectively. A z statistic test was used to compare proportions from a single population based on paired observations. Results are reported in means, standard deviations and 95% confidence intervals, as appropriate. Study protocol was approved by the University of Chicago Institutional Review Board.

## Results

Thirty-five African American HD patients (11 men, 24 women), average age 58 years and average dialysis duration 36 months, were initiated on a combined cinacalcet and paricalcitol treatment for SHPT. After 12 months of therapy Ca decreased from 9.5 to 8.8 mg/dl (p = 0.003, 95% CI 0.34–1.04), P from 6.2 to 5.5 mg/dl (p = 0.047, 95% CI 0.01–1.34) and Ca × P from 58 to 48 (p = 0.001, 95% CI 4.2–15.7). Intact PTH levels decreased by 29% (from 426 to 300, p = 0.03, 95% CI 19.3–401.7) (fig. 2).

Sixty six percent of patients achieved target iPTH and 58% of patients had a 30% or greater decrease in iPTH (table 1). More than 70% of all patients had reached Ca × P <55. All patients with severe SHPT (iPTH >800), a group routinely referred for parathyroidectomy, achieved a 30% or more reduction in iPTH.



**Fig. 2.** Average bone and mineral metabolism parameters.

Number of patients on paricalcitol therapy increased from 40 to 63% (from 14 to 22 patients) and average weekly paricalcitol dose was essentially unchanged (17 vs. 19  $\mu\text{g}$ ).

At the end of observation period, 6% more patients were on calcium-based binders, while the proportion of patients on sevelamer decreased by 29%. Lanthanum carbonate was introduced during the study period, and 20% of all patients were using it at 12 months. Average calcium-based binder dose increased from 4 tablets to 4.3 tablets per meal and sevelamer dose remained stable. Six patients at baseline (versus nine at the end of observation period) were taking more than 1,500 mg of elemental Ca a day. Their average serum Ca decreased, however, from 9.5 (range 8.3–11.2) to 8.7 (range 7.4–10.3) mg/dl. Average cinacalcet dose was 69 mg (median 60 mg). Four episodes of asymptomatic hypocalcemia ( $\text{Ca} < 7.5$  mg/dl) occurred. Cinacalcet dose was held in two patients and their corrected Ca was greater than 8 mg/dl 1 month later. One of them restarted cinacalcet at the next lower dose and another patient resumed 30 mg daily dose. The remaining 2 patients were not receiving paricalcitol therapy at the time. They were started on paricalcitol and hypocalcemia resolved the following month.

Alkaline phosphatase increased from an average 141 to 162 IU/l ( $p = 0.05$ , 95% CI -41.9 to 0.43) and remained elevated over 12 months. Almost 60% of patients had a rise in alkaline phosphatase.

## Discussion

Therapy with cinacalcet and paricalcitol utilizing a combined titration protocol is an effective long-term approach and helps achieve K/DOQI targets for bone metabolism and disease in patients failing conventional therapies with phosphate binders and paricalcitol.

Since its approval by the FDA, the role of cinacalcet in the treatment of SHPT has been debated: in some instances, target iPTH can be achieved with active vitamin D and its analogs, and in other instances – with cinacalcet as single therapies [8]. Some suggest instituting cinacalcet if iPTH remains between 300 and 800 pg/ml despite traditional therapy [9]. Combination therapy, from both a pathophysiological and clinical perspective, may be more advantageous, utilizing several different mechanisms in treating resistant disease [10]. Active vitamin D acts directly on the parathyroid gland to decrease PTH synthesis, and calcimimetics increase the CaSR sensitivity which lowers the threshold for extracellular Ca and decreases PTH secretion [11]. These agents also act synergistically as vitamin D increases CaSR mRNA transcription [12].

The impact of cinacalcet on the concomitant active vitamin D or its analog dosing has not been well studied. In a two-year extension of a phase II cinacalcet study the number of patients on vitamin D decreased from 71% at the beginning of the study to 58% at week 100 [13]. An-

other trial started cinacalcet in patients with controlled SHPT and elevated Ca  $\times$  P, simultaneously decreasing paricalcitol to 'physiologic' doses (2  $\mu$ g with each HD). At the end of the study paricalcitol was discontinued in 21% of the patients, and the mean dose decreased by 49% [8].

Our approach allows for more patients to safely receive vitamin D analog paricalcitol in the course of SHPT treatment. The clinical implication here may be quite important, as dialysis patients treated with injectable active vitamin D may have a survival benefit compared to the patients who received no vitamin D therapy at all [18]. Interestingly, HD patients receiving alfacalcidol compared to those not receiving active vitamin D had a lower risk of cardiovascular death which has led to advocacy to prescribe active vitamin D regardless of Ca or P levels [19].

Low nutritional vitamin D levels have been linked to cardiovascular disease [14], the number one cause of death among ESRD patients [17]. Decreased nutritional vitamin D levels are associated not only with bone disease, but also with infection, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and other chronic illnesses [14, 15]. Malignancies such as prostate, breast, colorectal, gastric, esophageal, pancreatic, and bladder cancer have been found in patients with low vitamin D levels and cellular immunity improves with 1 $\alpha$ -hydroxyvitamin D<sub>3</sub> [16]. Unfortunately, screening for nutritional vitamin D deficiencies in dialysis patients is not yet recommended by the K/DOQI and thus, it is not a part of standard dialysis laboratory testing.

Calcium-based phosphate binder use and the average dose increased in our study, but serum Ca decreased, consistent with a previous observation [9]. In the phase III cinacalcet trials, more patients on cinacalcet were started on calcium-based binders, but their mean dose was unchanged [5–7].

We noted a trend of rising alkaline phosphatase. There is little information about the impact of cinacalcet alone or in combination with active vitamin D or its analogs on bone histology. Several studies have documented improvements in bone-specific alkaline phosphatase [7, 20] and an animal model showed a reduction in peritrabecular fibrosis and improvement in osteitis fibrosa with calcimimetic therapy [21]. Studies in humans have demonstrated a decreased relative risk for fractures and increases in bone mineral density by DEXA scanning in HD patients on cinacalcet [20]. The increase in alkaline phosphatase may indeed represent an increase in bone formation. SHPT causes an increased bone resorption and bone formation, with osteoclast activity exceeding that of osteoblasts [22]. A decrease in PTH, coupled with the preservation of the physiological 'pulsatile' manner of PTH secretion, as occurs with calcimimetic therapy, could result in a decreased bone resorption and may allow for unimpeded osteoblast activity. With ongoing mineralization, serum Ca and P would fall due to increased uptake by bone, and alkaline phosphatase would rise, as was seen in our patients.

There are obvious limitations to our study. Intervention was based on intent-to-treat, did not account for possible nonadherence to medications and data was analyzed retrospectively. We did not have a control group, and the number of patients treated with cinacalcet was limited. In addition, we did not use bone-specific markers to characterize bone turnover. Despite these shortcomings our proposed titration protocol for cinacalcet and paricalcitol allows for wider active vitamin D analog use in SHPT therapy. It enables patients failing traditional therapy to achieve K/DOQI Practice Guidelines for bone metabolism and disease and allows us to simultaneously treat active vitamin D deficiency.

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