Pharmacodynamics of Cinacalcet Over 48 Hours in Patients With Controlled Secondary Hyperparathyroidism: Useful Data in Clinical Practice

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Context: Cinacalcet induces immediate changes in serum PTH levels, but the pharmacodynamic effect throughout the daily dosing interval in controlled patients is unknown. Also, in patients with reduced PTH, it is unknown what happens in the first 24 hours after withdrawal.

Objective: Our aim was to describe the effect over 48 hours of cinacalcet in hemodialysis patients with controlled secondary hyperparathyroidism.

Design: This was a phase 4, open-label, single-arm, single-dose, single-center clinical trial.

Setting: The study was conducted at a public hospital (Hospital Perpetuo Socorro, Alicante, Spain).

Patients: We included 10 patients on cinacalcet for 6 months or longer with intact PTH (iPTH) levels 100–400 pg/mL (8 men, mean age of 66 years (range 39–82 years)), chronically treated with 30 mg (n = 6), 60 mg (n = 3), or 90 mg (n = 1) of cinacalcet.

Intervention: A single dose (30–90 mg) was administered at baseline.

Main Outcome Measures: iPTH (Duo Kit Scantibodies and Elecsys Roche), PTH 1–84, ionized calcium, phosphorus (P), and calcitonin were determined at baseline and at 1, 3, 6, 12, 24, and 48 hours.

Results: There was a significant reduction in iPTH between 1 and 6 hours, and values returned to baseline at 24 hours [maximum mean (95% confidence interval) percent change from baseline: −50% (−34; −66) at 3 hours]. A transient increase in calcitonin and a decrease in P were also observed, with no changes in calcium. At 48 hours, there was a significant increase in iPTH [+51% (26; 76)] and P. Changes in PTH were similar with the 3 determination methods.

Conclusions: In hemodialysis patients with secondary hyperparathyroidism controlled by cinacalcet, a transient (1–6 hours) reduction in PTH and P and an increase in calcitonin are observed after each daily dose, with return to baseline at 24 hours. After calcimimetics discontinuation, PTH was significantly increased at 48 hours. The assay used to measure PTH does not influence relative changes induced by cinacalcet. (J Clin Endocrinol Metab 98: 1718–1725, 2013)
(1), which, in turn, are strong predictors of cardiovascular and all-cause mortality (2, 3). Moreover, consistent control of all bone metabolism markers is in strong association with survival in this population (4, 5).

The calcimimetic agent cinacalcet increases the sensitivity of the calcium-sensing receptor (CaR) to extracellular calcium (6), causing the inhibition of synthesis and release of PTH (7, 8). Cinacalcet has demonstrated efficacy in the simultaneous control of biochemical parameters associated with SHPT in both the extensive clinical development program and in the observational studies (9–14).

Currently in patients with chronic kidney disease stage 5, Kidney Disease: Improving Global Outcomes guidelines recommend to maintain intact PTH (iPTH) levels within 2–9 times above the upper normal limit of the assay (15). In patients with normal vitamin D levels, cinacalcet maintains PTH values close to the lower limit of the target range (10, 12, 14). Excessively suppressed PTH levels have been associated with adynamic bone disease and calcification (16–18). However, treatment with cinacalcet has demonstrated an attenuation of the progression of vascular and valvular calcification in patients on hemodialysis (19, 20) and has been associated with improved all-cause and cardiovascular survival (21).

Regarding the effect on calcium levels, it is well known that the activation of the CaR by cinacalcet stimulates calcitonin secretion and normalizes serum calcium without causing hypocalcemia (22–27). In dialysis patients, cinacalcet administration induces an increase in calcitonin levels between 2 and 6 hours, in parallel to PTH decrease, with a return to baseline levels at 24 hours (22, 24). Because calcitonin is a potent inhibitor of osteoclast activity and bone resorption, this transitory elevation could have a potentially bone-protective effect against hypercalcemia, but ongoing clinical trials will help to elucidate this question (28).

In patients who achieve SHPT control with treatment, an underlying question in the clinical practice is the daily variability in PTH levels and the effect of a missed dose on those levels (29–33). In phase I-II studies, the maximum effect of cinacalcet was achieved within 2–6 hours after administration, with a terminal half-life of 30–40 hours (30, 31). Although the pharmacodynamic effect of cinacalcet is well established in the de novo patients and in patients with elevated iPTH levels, the effect throughout the daily dosing interval in controlled patients at steady state is unknown. In addition, in patients with reduced PTH, it is unknown what happens after the withdrawal of the maintenance dose of cinacalcet.

The objective of the present study was to describe the changes in PTH over a 24-hour period after the administration of a single dose of cinacalcet in stable hemodialysis patients with controlled SHPT at steady state (i.e., chronically treated with this drug) and to describe changes in the iPTH level and other mineral metabolism parameters in the 24 hours subsequent to cinacalcet discontinuation.

Patients and Methods

This was a phase 4, open-label, single-arm, single-dose, single-center clinical trial, conducted in the Hospital Perpetuo Socorro (Alicante, Spain) from April to September 2011.

Study population

Eligible patients were between 18 and 90 years of age; on renal replacement therapy (hemodialysis 4 hours × 3 days a week, with single pool dialyzer clearance × time/volume of water in patient’s body (Kt/V) > 1.4) for at least 6 months before inclusion in the study; PTH greater than 300 pg/mL at least 6 months before; on treatment with a single dose of cinacalcet (30–90 mg/d) for at least 6 months prior to baseline; with controlled PTH levels in the last 2 months (minimum of 2 measurements between 100 and 400 pg/mL); without changes in concomitant treatments to cinacalcet, if any, for SHPT (vitamin D supplements and/or phosphate binders) in the last 2 months; without changes in the calcium content of dialysis fluid in the last 2 months; and with serum calcium levels less than 10.5 mg/dL and calcium × phosphorus (CaP) product less than 65 mg²/dL². Patients who were hospitalized or suffered surgery or immobility in the past 3 months, with a diet low in vitamin D, granulomatous diseases (tuberculosis, sarcoidosis, leprosy, Wegener disease), active infection, malignancy, liver disease, or other concomitant disease that could interfere with the results at the discretion of the investigator were excluded. Patients who were receiving drugs that could change the mineral metabolism parameters (phentyo in, phenobarbital, lithium, vitamin A, thiazides, isoniazid, rifampin), those with previous parathyroidectomy or simultaneous participation in another clinical trial, and those with any circumstance or medical condition that, in the opinion of the investigator, would not allow safe completion of the protocol (low hemoglobin levels, hemodynamic instability, anxiety, etc) were also excluded.

This study was conducted in accordance with the Helsinki Declaration and the guidelines for good clinical practice. Written approval was received from the institutional review board of the center, and informed consent was obtained before any study procedure.

Study design and treatment

To minimize selection bias, all patients who came to the clinics for hemodialysis since the start date were consecutively informed about the study and asked to participate. Patients were hospitalized on day 1 (nondialysis day) for 24 hours under homogeneous dietary conditions. The first day of the study was always on the weekend to ensure that no hemodialysis session was required during the 48-hour follow-up. Then all patients received a single baseline administration of cinacalcet orally (at the same dose that they were receiving per routine clinical practice, between 30 and 90 mg) and were prospectively followed up for 48 hours. Cinacalcet (Mimpara, Amgen Europe B.V, Breda, The Netherlands), for commercial use, was administered at approximately the same time of day (morning) to all patients, during breakfast.

A venous cannula was inserted for the extraction of blood samples. Extractions were performed at baseline (time 0,
prestudy dose, and 24 hours after the last cinacalcet dose, ie, trough level in daily dosing regimen) and after 1, 3, 6, 12, 24, and 48 hours (ie, 24 hours after the absence of the daily dose) after receiving the drug. Patients were informed that they had to return to the hospital after 48 hours.

At baseline (time 0), the following parameters were determined: iPTH [measured by 2 automated assays: the Duo PTH kit (Scantibodies Laboratory, Santee, California; normal range 14–66 pg/mL) and the Elecsys PTH test system (Roche Diagnostics, Indianapolis, Indiana; normal range 10–65 pg/mL)], PTH 1–84 [Duo PTH kit (Scantibodies Laboratory, Santee, California; normal range 5–39 pg/mL], total calcium, ionized calcium, calcitonin, phosphorus, alkaline phosphatase, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and fibroblast growth factor factor 23. At the other time points, the determined parameters were iPTH, PTH 1–84, ionized calcium, calcitonin, phosphorus, and alkaline phosphatase.

Throughout the 48-hour follow up, patients could be treated with any concomitant medications that they had been receiving previously for SHPT (vitamin D supplements and/or phosphate binders, at the same previous dose) or for other diseases. No modifications (start, interruption, or dose change) were allowed in the prescription of potent inhibitors (such as ketoconazole, itraconazole, and erythromycin) or inducers (eg, rifampin, phenytoin, phenobarbital, carbamazepine and St John’s wort) of CYP3A4.

Study end points and assessments

The primary efficacy end point was the change in iPTH levels (Scantibodies Laboratory) over the first 24 hours after the administration of cinacalcet in patients at steady state. Secondary efficacy end points were a mean change from baseline in iPTH levels at 24 hours and 48 hours according to the different determination methods and a change over 48 hours in ionized calcium, calcitonin, phosphorus, and alkaline phosphatase. Adverse events were also collected.

Statistical analysis

Categorical variables were summarized using frequencies and percentages, and continuous variables were summarized using means, SD, SE, and 95% confidence intervals (CIs). The efficacy analysis set consisted of all enrolled patients who completed the study without major protocol deviations, and the safety analysis set consisted of all patients who had taken the dose of cinacalcet. Changes in biochemistry levels over the first 24 hours were analyzed using 95% CIs for the mean of individual differences. Statistical analyses were performed with the SAS package, version 8.2. (SAS Institute, Cary, North Carolina).

Results

Population characteristics and drug exposure

The study enrolled 10 patients who were included in both the efficacy and the safety analysis set. All of them received cinacalcet at baseline and completed the study according to the protocol.

Patients were 8 men and 2 women with a median age of 66.0 years (range 39.4–82.0 years). Median body mass index was 27.4 kg/m² (range 21.2–33.4 kg/m²). The median time since diagnosis of SHPT was 4.5 years (range 2.0–31.0 years), and the median time on hemodialysis was 5.0 years (range 2.0–31.0 years). All patients were on conventional hemodialysis, and the dialysate contained 1.5 mmol/L calcium. All patients had endotoxin filter, and vascular access was an arteriovenous fistula in 7 patients and a tunneled catheter in 3 patients. Mean (SD) iPTH level at the time of SHPT diagnosis was 624.4 pg/mL (range 210.3 pg/mL) and at the time of cinacalcet initiation was 1069.2 (671.9) pg/mL (range 611.8–2459.0 pg/mL). Mean (SD) levels of iPTH, calcium, and phosphorus in the 2 months prior to inclusion were 252.9 (80.5) pg/mL (range 152.3–396.1 pg/mL), 8.7 (0.6) mg/dL (range 7.8–9.5 mg/dL), and 4.9 (0.9) mg/dL (range 3.2–6.1 mg/dL), respectively.

At baseline (before the cinacalcet dose), the mean (SD) laboratory values were as follows: iPTH (Scantibodies Laboratory), 163.6 (97.6) pg/mL; iPTH (Roche Diagnostics), 218.9 (112.3) pg/mL; PTH 1–84 (Scantibodies Laboratory), 90.4 (58.4) pg/mL; total calcium, 8.8 (0.4) mg/dL; ionized calcium, 5.0 (0.4) mg/dL; phosphorus, 4.5 (0.6) mg/dL; calcitonin, 15.0 (14.1) pg/mL; alkaline phosphatase, 52.7 (15.1) U/L; 25-hydroxyvitamin D, 52.6 (13.5) ng/mL; 1,25-dihydroxyvitamin D, 18.8 (14.5) pg/mL; and fibroblast growth factor 23, 23, 1400 (961) pg/mL.

The concomitant treatments for SHPT were as follows: 7 patients were receiving both vitamin D sterols (calcidiol, combined with colecalciferol in 1 patient and with alfalcacidol in another one) and phosphate binders (2 received lanthanum carbonate, 2 lanthanum carbonate + calcium acetate, 1 calcium acetate, 1 calcium carbonate, and 1 sevelamer carbonate); 2 patients received only phosphate binders (1 lanthanum carbonate and 1 lanthanum carbonate + calcium acetate + polystyrene sulfonate resin); and 1 patient did not receive any other drug besides cinacalcet.

At the baseline time point, 6 patients received 30 mg cinacalcet, 3 received 60 mg, and 1 received 90 mg. The mean time since the cinacalcet initiation was 3.1 (1.2) years (range 1.9–5.8 years).

Change in iPTH over the first 24 hours

During the first 24 hours after the administration of cinacalcet, there were modifications of iPTH levels (measured using Duo PTH Kit from Scantibodies Laboratory) (Figure 1, A and B, and Table 1). PTH values decreased between 1 and 6 hours, with a slight rebound at 12 hours, and finally returning to baseline at 24 hours (P = .014, repeated measures ANOVA).

The mean (95% CI) percentage change from baseline in iPTH was as follows: −42% (−19 to −64) at 1 hour;
Changes in iPTH at 48 hours after the administration of calcimimetics

All the individuals experienced an increase in iPTH levels between 24 and 48 hours (Figure 2A). Consequently, the mean iPTH level was significantly increased as compared with baseline, with a mean (95% CI) percent change of 51% (26–76) (Figure 2B).

Calcitonin, total calcium, ionized calcium, phosphorus, and phosphatase alkaline

Figure 3 shows the change in mean serum concentration of calcitonin, total calcium, ionized calcium, phosphorus, and phosphatase alkaline levels over the 48-hour follow-up.

In parallel to the reduction in serum PTH levels, an increase in calcitonin was observed between 1 and 6 hours, with a return to baseline values at 24 hours, and stabilization between 24 and 48 hours ($P = .015$, repeated measures ANOVA). Serum phosphorus decreased between 1 and 12 hours, returned to baseline at 24 hours, and increased at 48 hours ($P = .032$).

No significant changes were observed in ionized calcium levels during the 24-hour dosing interval or at 48 hours ($P = .108$) (intrapatient variability of 4.9–18.6%, range of values: 4.3–5.9 mg/dL). No changes in total calcium or alkaline phosphatase were observed, either.

Concordance between change in iPTH (Scantibodies Laboratory and Roche Diagnostics) and PTH 1–84

The mean percent change from baseline in PTH levels did not differ significantly between the 3 methods of quantification used in the study (Figure 4 and Table 1).

| Table 1. Mean PTH Values at Each Time Point According to the 3 Determination Methods Used in the Study (iPTH, Scantibodies Laboratory; iPTH, Roche Diagnostics; PTH 1–84, Scantibodies Laboratory) |
|---------------------------------|--------|--------|--------|--------|--------|--------|--------|
| Time After Dose, h              | 0      | 1      | 3      | 6      | 12     | 24     | 48     |
| iPTH (Scantibodies Laboratory)  | 163.6 (97.6) | 87.2 (41.6) | 73.9 (35.3) | 141.5 (100.3) | 218.0 (156.7) | 193.3 (125.6) | 239.4 (128.9) |
| iPTH (Roche Diagnostics)        | 218.9 (112.3) | 117.3 (56.6) | 98.5 (46.9) | 153.1 (114.8) | 255.6 (129.3) | 229.3 (108.4) | 298.1 (94.4) |
| PTH 1–84 (Scantibodies Laboratory) | 90.4 (58.4) | 47.3 (28.3) | 38.6 (17.9) | 69.6 (42.6) | 111.3 (76.5) | 102.5 (64.7) | 124.4 (66.9) |

Values are mean (SD) picograms per milliliter.
Safety

There were no adverse events during the study. No changes in the heart rate or in systolic or diastolic blood pressure levels were observed; also, no abnormalities in physical examination at 24 and 48 hours were found.

Discussion

The present exploratory study allows us to describe for the first time the pharmacodynamic effect over 48 hours of a single dose of cinacalcet in patients with PTH levels controlled with the long-term administration of calcimimetics. A transitory decrease in iPTH levels was found in all patients hours after the administration of calcimimetic. The maximum suppression (≈ 50% of baseline value) occurred between 1 and 6 hours after the dose, with a progressive return to the initial values between 6 and 24 hours. These results are in agreement with previous pharmacodynamic evaluations in de novo or uncontrolled patients, with a similar degree and timing of the PTH reduction (22, 30, 31). Thus, regardless of the baseline levels and previous exposure to cinacalcet or to other SHPT drugs, the present study shows that a dose of cinacalcet induces a reliable and predictable degree of reduction in PTH.

In parallel to the reduction in PTH levels, transitory changes in calcitonin and serum phosphorus levels (increase and decrease, respectively) were observed, without noticeable effects on total calcium, ionized calcium, or alkaline phosphatase. Previous studies had observed similar effects of cinacalcet in normocalcemic patients (22, 30, 31). A significant change in serum calcium should be expected if patients had initiated treatment recently, but this was not the case because all patients had been treated for more than 1 year, and their calcium level had stabilized after a few months on cinacalcet (data not shown). During the first month after calcimimetic initiation, there is rapid incorporation of calcium to the bone, a hungry bone phenomenon similar to that observed after a parathyroidectomy, which causes a reduction in total calcium levels. After a few months on cinacalcet, the parathyroid glands maintain less PTH secretion with lower serum calcium; thus, calcimimetics make the parathyroid cell more sensitive to extracellular calcium. A new steady state is generated. With less PTH the bone turnover decreases, with both less calcium influx to the bone and less calcium efflux from the bone.

Once the equilibrium steady state is reached, PTH levels remain stable without further reduction. After a single dose of calcimimetics, there is a transitory decrease in the PTH level, which is paralleled by an acute increase in calcitonin. The increase in calcitonin is explained by the action of calcimimetic on the calcium-sensing receptors located in the C cells of the thyroid. Similarly, the calcimimetics act on the parathyroid glands to produce a transient decrease in PTH (due to the short half-life of the calcimimetic). There is no change in total calcium or ionized calcium, which can be explained by the opposing ef-
flicts of PTH and calcitonin on serum calcium levels. Also, it must be taken into account that the transient decrease in PTH levels observed after a single administration of the calcimimetic is very modest as compared with the large decrease in PTH during the first weeks to months after the initiation of therapy. The amount of calcium given to patients treated with calcimimetics should not be greater than 1 g/d. This is because, in the absence of residual diuresis, too much calcium intake could produce an excessively high calcium balance. Thus, calcium levels should not be corrected using exogenous calcium administration, even in the early stages of the disease, and the use of vitamin D is restricted to those patients who are deficient. Patients with advanced secondary hyperparathyroidism who fail to respond to medical therapy may need parathyroidectomy. Patients with partial parathyroidectomy receive calcium and vitamin D as long as they need to prevent severe hypocalcemia, but usually the calcium becomes stable at a lower level than they had previously, remaining constant thereafter.

The rise in calcitonin levels is explained by the activation of the CaR present in thyroid C cells, in which it regulates calcitonin secretion (34). Calcitonin opposes the effects of PTH and lowers serum calcium levels by inhibiting osteoclast activity in bones and absorption/reabsorption by intestines and renal tubules (35). The clinical significance of calcitonin stimulation on bone remodeling remains to be further investigated, and the recently concluded BONAFIDE (Bone Histomorphometry Assessment For Dialysis Patients With Secondary Hyperparathyroidism of End Stage Renal Disease) trial may provide useful information in this regard (28). A previous study in hypercalcemic SHPT patients after kidney transplantation suggests that, although cinacalcet can be associated with decreased bone formation, it seems to increase bone density in some locations without changing bone volume (25).

The present study also allows us to describe the changes that occur in bone mineral parameters just 2 days after the last dose of cinacalcet. The iPTH levels rose in all patients, with a mean increase of 50% of baseline values. Despite this quick increase, the levels achieved at 48 hours did not reach the high values that the patients had before cinacalcet initiation. We do not know what would have happened after a longer period without cinacalcet. Serum phosphorus also increased quickly, ending up with mean levels (5.3 mg/dL) outside the recommended target (15). These findings provide useful information for the clinical practice, suggesting that, in patients with theoretically controlled SHPT, any change in prescribed drugs should be undertaken cautiously and should be accompanied with a close biochemical monitoring.

One important issue for clinicians is when therapy (cinacalcet) should be discontinued due to the low PTH levels that carry the risk of low bone turnover (16, 17). In our

Values are mean ± SE.

**Figure 3.** Changes in mean iPTH, calcitonin, total calcium, ionized calcium, phosphorus, and alkaline phosphatase levels over the first 48 hours after the dose after a single administration of cinacalcet (30–90 mg).

**Figure 4.** Mean percentage change from baseline at 24 and 48 hours in iPTH levels based on the 3 determination methods used in the study (iPTH, Scantibodies Laboratory; iPTH, Roche Diagnostics; PTH 1–84, Scantibodies Laboratory).
The present study was designed to explore the effect of cinacalcet under clinical practice conditions, with a diversity of patients and treatments.

In conclusion, in hemodialysis patients with SHPT controlled by cinacalcet, a similar pharmacodynamic effect to that observed de novo and uncontrolled patients is produced during the 24-hour dosing interval, with predictable and transient reductions in PTH and serum phosphorus and an increase in calcitonin. Our results also suggest that the loss of 1 dose of cinacalcet in patients at steady state results in a significant and rapid increase in PTH and phosphorus within the subsequent 24 hours. Finally, the assay used to measure PTH does not influence the measurement of relative changes induced by cinacalcet treatment, provided that the sample is taken at least 12 hours apart from the last dose. Therapeutic decisions may be made based on serial monitoring with the same assay.

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