Cinacalcet Hydrochloride Maintains Long-Term Normocalcemia in Patients with Primary Hyperparathyroidism

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Calcimimetics increase the sensitivity of parathyroid calcium-sensing receptors to extracellular calcium, thereby reducing PTH secretion. This multicenter, randomized, double-blind, placebo-controlled study assessed the ability of the oral calcimimetic cinacalcet HCl to achieve long-term reductions in serum calcium and PTH concentrations in patients with primary hyperparathyroidism (HPT). Patients (n = 78) were randomized to cinacalcet or placebo. Cinacalcet was titrated from 30–50 mg twice daily during a 12-wk dose-titration phase. Efficacy was assessed during 12-wk maintenance and 28-wk follow-up phases. The primary endpoint was the achievement of normocalcemia [serum calcium ≤ 10.3 mg/dl (2.57 mmol/liter)] with at least 0.5 mg/dl (0.12 mmol/liter) reduction from baseline. Plasma PTH, serum and urine biochemical measures of bone turnover, bone mineral density, and safety were also assessed. Seventy-three percent of cinacalcet-treated patients vs. only 5% of placebo-treated patients achieved the primary endpoint (P < 0.001). Fasting predose plasma PTH decreased 7.6% in cinacalcet patients but increased 7.7% in placebo patients (P < 0.01). Bone mineral density was unchanged by cinacalcet, but bone resorption and formation markers increased (P < 0.05). Adverse events were mild and similar between treatment groups. Cinacalcet rapidly normalizes serum calcium and reduces PTH in patients with primary HPT, and these effects are maintained with long-term treatment. Cinacalcet may be an effective, nonsurgical approach for management of primary HPT.

Primary Hyperparathyroidism (HPT) is a common disorder characterized by chronically elevated serum calcium and PTH concentrations. In the United States, many patients with primary HPT have mild, asymptomatic disease and do not meet the criteria for surgery (1). Patients with moderate to severe disease can experience worsening hypercalcemia, nephrolithiasis, loss of bone mineral density (BMD), neuromuscular weakness, and neurobehavioral symptoms including easy fatigability and impaired cognitive function (2). Parathyroidectomy is usually curative, but there are few nonsurgical treatment alternatives for patients who fail surgery, have contraindications to surgery, do not wish to have surgery, or do not meet current guidelines for surgery. Thus, there is a need for therapeutic agents that directly reduce serum calcium and PTH concentrations in patients with primary HPT.

The calcium-sensing receptor (CaR) located on cells of the parathyroid gland is the principal regulator of PTH secretion (3). Type II calcimimetics are a novel class of compounds that have direct PTH levels by binding to the CaR and increasing its sensitivity to extracellular calcium (4, 5). Calcimimetics increase the sensitivity of parathyroid calcium-sensing receptors to extracellular calcium, thereby reducing PTH secretion. This multicenter, randomized, double-blind study assessed the ability of the oral calcimimetic cinacalcet HCl to achieve long-term reductions in serum calcium and PTH concentrations in patients with primary hyperparathyroidism (HPT). Patients (n = 78) were randomized to cinacalcet or placebo. Cinacalcet was titrated from 30–50 mg twice daily during a 12-wk dose-titration phase. Efficacy was assessed during 12-wk maintenance and 28-wk follow-up phases. The primary endpoint was the achievement of normocalcemia [serum calcium ≤ 10.3 mg/dl (2.57 mmol/liter)] with at least 0.5 mg/dl (0.12 mmol/liter) reduction from baseline. Plasma PTH, serum and urine biochemical measures of bone turnover, bone mineral density, and safety were also assessed. Seventy-three percent of cinacalcet-treated patients vs. only 5% of placebo-treated patients achieved the primary endpoint (P < 0.001). Fasting predose plasma PTH decreased 7.6% in cinacalcet patients but increased 7.7% in placebo patients (P < 0.01). Bone mineral density was unchanged by cinacalcet, but bone resorption and formation markers increased (P < 0.05). Adverse events were mild and similar between treatment groups. Cinacalcet rapidly normalizes serum calcium and reduces PTH in patients with primary HPT, and these effects are maintained with long-term treatment. Cinacalcet may be an effective, nonsurgical approach for management of primary HPT.

**Patients and Methods**

**Patients**

The study was conducted at 18 centers in the United States. Seventy-eight adult patients, 21 men and 57 women, aged 27–83 yr, with primary HPT were enrolled in the study over 14 wk between 1999 and 2000. Eligibility requirements included serum calcium concentration greater than 10.3 mg/dl (2.57 mmol/liter) and plasma PTH concentration greater than 45 pg/ml (4.73 pmol/liter). PTH was measured on at least two occasions at least 7 d apart during the 12-month period before baseline. Exclusion criteria included pregnancy, creatinine clearance less than 50 ml/min (0.83 ml/sec) (9), treatment with bisphosphonates or fluoride in the 90 d before baseline, familial hypocalciuric hypercalcemia, or fasting urine calcium/creatinine ratio less than 0.05 (0.14). Because cinacalcet inhibits cytochrome P450 2D6 (CYP2D6), patients were excluded if they required drugs that are metabolized by this enzyme and have a narrow therapeutic index, such as flecainide, thioridazine, and many tricyclic...
antidpressants. Women on stable doses of selective estrogen receptor modulators or estrogen replacement therapy were eligible. The Institutional Review Board at each center approved the study, and written informed consent was obtained from all patients.

**Study design**

This was a multicenter, randomized, double-blind, placebo-controlled study. Patients were randomized in a 1:1 ratio to receive either cinacalcet or placebo after a 30-d screening period. The study included a 12-wk titration phase, a 12-wk maintenance phase, and an 8-wk follow-up phase to gather additional safety and efficacy information. Patients initially received 30 mg cinacalcet or placebo twice daily. The dose was increased sequentially to 40 and 50 mg twice daily at study wk 4 and 8 if patients were still hypercalcemic (serum calcium > 10.3 mg/dl). Patient visits occurred weekly during the titration phase (wk 1–12) and monthly during the maintenance phase (wk 13–24) and follow-up (wk 25–52) phases. Pharmacodynamic data were collected at wk 3, 12, and 24 after the morning dose of study drug to assess effects of study drug on serum calcium and PTH concentrations over 8 h.

The primary endpoint was the proportion of patients achieving a mean serum calcium less than or equal to 10.3 mg/dl (2.57 mmol/liter) and a reduction from baseline of at least 0.5 mg/dl (0.12 mmol/liter) during the maintenance phase. Secondary endpoints included changes over 8 h. Pharmacodynamic data were collected at wk 3, 12, and 24 for pharmacodynamic analysis. Serum calcium [coefficient of variation (CV) 12, 2, and 4 after the morning dose of study drug to assess effects of study drug on serum calcium and PTH concentrations over 8 h.

Measurements

Blood samples were collected for measurement of serum calcium and PTH at each study visit after an overnight fast and before the morning dose of study drug. Samples for serum calcium and PTH were also collected at 2, 4, and 8 h after the morning dose of study drug at wk 3, 12, and 24 for pharmacodynamic analysis. Serum calcium [coefficient of variation (CV) 1.4–1.5%] was measured by standard methods. Intact PTH (CV = 4.2–6.4%) was measured using a double-antibody immunoradiometric assay (Allegro PTH, Nichols Institute Diagnostics, San Juan Capistrano, CA).

Serum phosphorus (CV = 2.2–2.4%), creatinine (CV = 1.6–13.5%), 1,25-dihydroxyvitamin D (CV = 9.1–20.3%), bone-specific alkaline phosphatase (BALP) (CV = 9.9–11.4%), and NTX (CV = 6.4–9.5%) were measured at baseline and at wk 24 and 52. Serum 1,25-dihydroxyvitamin D was measured by radioreceptor assay (Endocrine Sciences, Calabasas Hills, CA). Serum NTX levels were determined by ELISA (Osteomark NTx assay, Ostex International, Seattle, WA). Urine was collected over 24 h and after an overnight fast at baseline and at wk 24 and 52 for the measurement of calcium (CV = 3.4–4.9%), phosphorus (CV = 1.7–1.9%), NTX (CV = 5.1–11.3%), and deoxypyridinoline (DPD) (CV = 8.6–17.1%), which were expressed as a ratio with urine creatinine. Urine calcium, phosphorus, creatinine, and urine-free DPD were measured by Covance Central Laboratories (Indianapolis, IN). Tubular reabsorption of calcium (TmCa) = [total plasma calcium × 0.59 – urine calcium × plasma creatinine/urine calcium] / 1 – 0.08 loge [total plasma calcium] and fractional urinary excretion of calcium (FeCa) = 1 – TmCa were calculated from the calcium and phosphate (in milligrams) values in the respective fasting blood and urine samples using the indicated formulas (19).

BMD of the lumbar spine, total femur, and 1/3 distal radius was measured by dual-energy x-ray absorptiometry at baseline and at wk 24 and 52 using a Hologic densitometer (Hologic, Waltham, MA) (n = 27, cinacalcet; n = 26, placebo) or a Lunar densitometer (Lunar Inc., Madison, WI) (n = 13, cinacalcet; n = 12, placebo). For each patient, BMD was measured on the same densitometer throughout the study. To combine measurements in men and women over a wide age range made on either Hologic or Lunar machines, BMD was expressed as a Z score. To examine for longitudinal changes, the changes in Z score for each individual were calculated, and the mean changes for the placebo and cinacalcet groups were presented as mean change in Z score.

**Statistical analysis**

The proportion of patients achieving a serum calcium less than or equal to 10.3 mg/dl (2.57 mmol/liter) and a reduction in serum calcium of at least 0.5 mg/dl (0.12 mmol/liter) from baseline was determined using mean values for each patient derived from up to three measurements obtained during the maintenance phase. The difference in the proportion of patients achieving the primary endpoint in the cinacalcet and placebo groups was determined using logistic regression and included all randomized patients. For this analysis, patients leaving the study before the maintenance phase were considered not to have achieved the primary endpoint, regardless of serum calcium values at the time of withdrawal. An additional analysis was performed using the last on-study serum calcium value for patients who withdrew before the maintenance phase. Biochemical and BMD variables were compared between placebo and cinacalcet groups at wk 24 and 52 using one-way ANOVA. Adverse events were tabulated by treatment group and analyzed using descriptive statistics.

**Results**

A total of 78 patients with primary HPT were randomized (40 cinacalcet, 38 placebo). One patient who was randomized to placebo withdrew before receiving the study drug. The mean age was 62 yr in both groups (range, 27–83 yr), and the majority of patients were women (70% cinacalcet, 76% placebo). Nine patients in each group had a prior history of parathyroidectomy. Twenty-eight of 40 patients (70%) in the cinacalcet group and 28 of 38 patients (74%) in the placebo group completed the 52-wk study.

Mean baseline biochemical values were similar between treatment groups and characteristic of patients with mild to moderate primary HPT (Table 1). In the cinacalcet group, the mean baseline serum calcium level was 10.7 ± 0.5 mg/dl (2.67 ± 0.12 mmol/liter), and the mean PTH level was 105 ± 36 pg/ml (11.0 ± 3.78 pmol/liter) compared with 10.7 ± 0.4 mg/dl (2.67 ± 0.10 mmol/liter) and 120 ± 54 pg/ml (12.6 ± 5.68 pmol/liter), respectively, in placebo-treated patients.

Mean (SD) baseline Z scores for cinacalcet were 0.15 (2.20) at the lumbar spine, −0.31 (0.91) at the total femur, and −0.46 (1.41) at the 1/3 distal radius. For placebo patients, the baseline Z scores were −0.10 (2.27) at the lumbar spine, −0.33 (0.96) at the total femur, and −0.31 (1.38) at the 1/3 distal radius. Mean (SD) baseline T scores for the cinacalcet group were −0.90 (1.55) at the lumbar spine, −1.20 (1.02) at the total femur, and −1.61 (1.58) at the 1/3 distal radius. For placebo patients, the baseline T scores were −1.22 (1.57) at the lumbar spine, −1.32 (1.07) at the total femur, and −1.79 (1.62) at the 1/3 distal radius.

During the maintenance phase, 73% of patients in the cinacalcet group achieved the primary endpoint [predose serum calcium ≤ 10.3 mg/dl (2.57 mmol/liter) and a decrease from baseline of ≥0.5 mg/dl (0.12 mmol/liter)] compared with 5% of the placebo group (P < 0.001). When serum calcium values from patients who withdrew during the dose- titration phase were included in the analysis, 88% of the cinacalcet group achieved the primary endpoint, compared with 5% of the placebo group (P < 0.001). Mean serum calcium levels were reduced to the normal range within the first 2 wk of treatment with cinacalcet (Fig. 1) and remained normal throughout the 52 wk of the study. In the placebo group, the mean serum calcium levels did not change significantly from baseline levels throughout the study.

Corresponding modest but significant reductions in fast-
ing plasma PTH (measured ~12 h after administration of study drug) were observed in the cinacalcet group. Mean plasma predose PTH decreased by 7.6% from 105 ± 36 pg/ml (11.0 ± 3.78 pmol/liter) to 95 ± 34 pg/ml (10.0 ± 3.55 pmol/liter) during the maintenance phase compared with a 7.7% increase from 120 ± 54 to 127 ± 53 pg/ml (12.6 ± 5.69 to 13.3 ± 5.52 pmol/liter) in the placebo group (P < 0.01; Fig. 2). In the cinacalcet group, predose plasma PTH reductions were maintained throughout the follow-up period.

Pharmacodynamic data collected at wk 24 demonstrated that the serum calcium concentrations remained unchanged after the morning dose of cinacalcet, whereas the corresponding plasma PTH concentrations underwent cyclic changes with dosing. At wk 24, mean serum calcium was normal, whereas mean plasma PTH remained elevated at the predose measurement. After the morning dose of cinacalcet, serum calcium was unchanged at all time points measured (Fig. 3A), whereas PTH decreased by 37% into the normal range at 2 h after dose (P < 0.0001) and gradually returned toward predose levels by 8 h (Fig. 3B). In the placebo group, no changes in calcium or PTH concentrations were observed over the corresponding time period. Results were similar at wk 3 and 12 (data not shown), indicating that no changes in serum calcium occurred once steady state had been achieved, but plasma PTH continued to undergo pharmacodynamic changes with dosing.

Mean fasting predose biochemistries at baseline and at wk 24 and 52 are shown in Table 1. Serum phosphorus increased in the cinacalcet group and at wk 52 was higher (P < 0.001) than in the placebo group. The fasting urine calcium-creatinine ratio and the 24-h urine calcium-creatinine ratio decreased in the cinacalcet group, although the difference between treatment groups was statistically significant only for the fasting calcium-creatinine ratio (P < 0.001). At wk 52, tubular reabsorption of calcium decreased (P < 0.001) and phosphorus reabsorption increased (P < 0.001) from baseline in the cinacalcet group, whereas there were no changes in the placebo group. Serum 1,25-dihydroxyvitamin D concentrations were similar in both groups at wk 52 and unchanged from baseline. Serum creatinine and 24-h urine creatinine remained relatively constant and similar in both groups throughout the study.

Some markers of bone turnover—serum BALP, serum NTx, and the urine NTx-creatinine ratio—were increased (P < 0.05) at wk 52 in the cinacalcet group compared with placebo, but remained in the normal range. The urine DPD-creatinine ratio increased in the cinacalcet group, but at wk 52, it was not significantly higher than in the placebo group. In the placebo group, there was no significant change in any of the biochemical markers of bone turnover during the study.

BMD was measured at baseline and at wk 24 and 52 and expressed as a Z score. In general, few differences in mean change in Z score occurred between the cinacalcet and placebo groups after 24 or 52 wk of treatment. At wk 24, the mean change in Z score at the lumbar spine was significantly lower in the cinacalcet group compared with the placebo group (P < 0.05) (Table 2); however, no difference between groups was observed at wk 52. No other significant differences for the lumbar spine, total femur, or 1/3 distal radius
at wk 24 or 52 were observed between treatment groups (Table 2).

Nine patients in each treatment group (23% of the study population) had previously undergone unsuccessful parathyroidectomy. Seven of these patients in the cinacalcet group normalized their serum calcium and achieved the primary outcome, compared with one patient in the placebo group. In the cinacalcet group, mean serum calcium decreased from 10.8 mg/dl (2.70 mmol/liter) at baseline to 9.5 mg/dl (2.38 mmol/liter) at wk 52. In placebo-treated patients who had previous parathyroidectomy, serum calcium remained at baseline levels [11.1 mg/dl (2.78 mmol/liter)] throughout the study. PTH levels decreased by 10.5% in cinacalcet-treated patients with a previous parathyroidectomy and increased 3.1% in placebo-treated patients with previous parathyroidectomy. When BMD data were analyzed separately for these patients, the data were not different from the treatment groups as a whole (data not shown).

Cinacalcet was well tolerated in this study, and occurrence of adverse events was similar between treatment groups. The two most common adverse events were nausea (28% cinacalcet, 16% placebo) and headache (23% cinacalcet, 41% placebo). Similar numbers of patients in each group withdrew from the study because of adverse events (eight cinacalcet, six placebo). Three of these patients from the cinacalcet group experienced serum calcium levels less than 8.0 mg/dl (2.00 mmol/liter) while receiving the lowest dose of study drug and, in accordance with the study protocol, were withdrawn from the study. Two cinacalcet-treated patients experienced mild paresthesias that were considered treatment related. Serum calcium values were 7.9 mg/dl (1.98 mmol/liter) in the three patients who withdrew because of asymptomatic...
shaded areas (8.4–10.3 mg/dl) and plasma PTH (10–65 pg/ml) are indicated by the data. Data were collected at wk 24. The normal ranges for serum calcium 8 h after the morning dose for serum calcium (A) and plasma PTH (B).

Fig. 3. Response to cinacalcet or placebo before (0), and at 2, 4, and 8 h after the morning dose for serum calcium (A) and plasma PTH (B). Data are collected at wk 24. The normal ranges for serum calcium (8.4–10.3 mg/dl) and plasma PTH (10–65 pg/ml) are indicated by the shaded areas. BL, Baseline value. Data are presented as mean ± SE.

hypocalcemia and 7.8 mg/dl (1.95 mmol/liter) and 8.1 mg/dl (2.02 mmol/liter) in the patients who experienced paresthesias.

**Discussion**

In this study, cinacalcet administered twice daily rapidly normalized predose serum calcium in the majority of patients and caused modest reductions in predose PTH concentrations in patients with mild to moderate primary HPT. The effect of cinacalcet was sustained over 52 wk with no evidence of fluctuations in serum calcium concentration after individual doses once steady state had been established. These results confirm and extend the findings of our previous short-term study (15 d plus a 7-d follow-up) that showed cinacalcet is effective in reducing serum calcium in patients with primary HPT (8). During the maintenance phase, 73% of cinacalcet-treated patients achieved normocalcemia with a decrease of at least 0.5 mg/ml (0.12 mmol/liter) from baseline, whereas only 5% of placebo-treated patients achieved this target. The proportion increased to 88% in the cinacalcet group compared with 5% in the placebo group when serum calcium values for patients who withdrew before the maintenance phase were included. In 90% of patients, the lowest dose of cinacalcet, 30 mg twice daily, was sufficient to induce normocalcemia, and no patients required titration to the maximum permitted dose of 50 mg twice daily.

During the maintenance phase, predose plasma PTH concentrations were reduced by approximately 8% with cinacalcet treatment. It should be noted that this value, which reflects hormone concentration before the morning dose of cinacalcet, underestimates PTH reduction over 24 h. At wk 24, pharmacodynamic data demonstrated that plasma PTH concentration 2 h after dosing decreased into the normal range (Fig. 3B), corresponding to a 60% reduction from baseline. Assuming that the decrease in PTH after the evening dose was similar to that after the morning dose, the area under the curve indicates that there was an approximately 20% reduction in plasma PTH over each 24-h cycle. Furthermore, there was no indication from the pharmacodynamic data that this response changed with length of time on drug. In contrast to the cyclic change seen in PTH, serum calcium remained unchanged over the 8-h sampling period after the morning dose of cinacalcet. These serum calcium results indicate that once steady state has been achieved, no sharp declines in serum calcium occur after individual doses; thus, the risk of acute hypocalcemia and accompanying symptoms appears to be avoided with twice-daily dosing with cinacalcet in patients with primary HPT.

Drugs to manage the hypercalcemia of primary HPT, such as estrogens, selective estrogen receptor modulators, and bisphosphonates, have shown a limited ability to treat the disorder (11–14). These agents act primarily by inhibiting bone resorption, although their effects on serum calcium are relatively small. Cinacalcet treatment was highly effective in reducing serum calcium levels in this study, and suppression was maintained during 1 yr of treatment, suggesting that cinacalcet may be an important therapeutic agent for managing primary HPT, particularly when parathyroidectomy is not a viable option. Indeed, nine patients in each group (23% of the study population) had previously undergone unsuccessful parathyroidectomy. Seven of these patients in the cinacalcet group normalized their serum calcium and achieved the primary outcome, compared with one patient in the placebo group. Although this study did not include patients with severe primary HPT or parathyroid carcinoma, our preliminary reports indicate that cinacalcet may also successfully reduce serum calcium in these patients (15, 16).

In addition to normalizing serum calcium, cinacalcet treatment increased serum phosphorus. By wk 12, serum phosphorus levels and tubular reabsorption of phosphorus had increased, and the fasting urine calcium-creatinine ratio and tubular reabsorption of calcium had decreased in the cina-

![Table 2](image-url)
Calcium follow-up, with no apparent symptoms is currently managed by regular normalization of serum calcium. Although mild primary HPT failed parathyroidectomy, to asymptomatic. In patients who asymptomatic, with 18 of the 79 patients having previously had a parathyroidectomy. Disease severity in this study ranged from symptomatic and biochemical markers of bone turnover, there is a pressing need for biochemistry and symptoms, and additional studies will be needed in this area.

In our patients, spine BMD was normal, but hip and forearm BMDs were in the osteopenic range, as expected in patients with this degree of primary hyperparathyroidism. Over the 52 wk of the study, no clinically significant differences in change in BMD were observed between the cinacalcet and placebo groups.

Cinacalcet was well tolerated in this study. Occurrences of adverse events and treatment-related adverse events were similar between the placebo and cinacalcet groups. Adverse events reported during the study were generally mild or moderate and resulted in only a small number of withdrawals.

The comparative utility and cost-benefit between cinacalcet and parathyroidectomy as treatment modalities for primary HPT have yet to be established. Although parathyroidectomy is usually curative and reverses abnormal biochemistry and symptoms, there is a pressing need for medical therapy to normalize serum calcium in patients who have either a contraindication to or have failed parathyroidectomy. Disease severity in this study ranged from symptomatic, with 18 of the 79 patients having previously had a failed parathyroidectomy, to asymptomatic. In patients who had symptoms, had a failed parathyroidectomy, or who were apparently asymptomatic, cinacalcet was equally effective in normalizing serum calcium. Although mild primary HPT with no apparent symptoms is currently managed by regular medical follow-up, i.e. watchful waiting, the long-term effects of mild hyperparathyroidism (18, 19) and hypercalcemia (20) on increasing premature cardiovascular death is of concern. Whether therapy should be considered for other-wise asymptomatic mild hypercalcemia, and what the choice of such therapy should be, require additional study before a change from the current management of watchful waiting can be recommended.

In conclusion, in these patients with primary HPT, cinacalcet was highly effective in normalizing serum calcium levels and reducing PTH, and this effect was maintained over long-term administration. The drug was well tolerated and may provide a valuable and effective management option for patients with primary HPT.

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