

Cinacalcet for the treatment of primary hyperparathyroidism

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Received 30 May 2007; accepted 2 November 2007

Abstract

Primary hyperparathyroidism (HPT) is the leading cause of hypercalcemia in the outpatient setting, and it is treated primarily by parathyroidectomy. There are few nonsurgical treatment options for patients who do not wish to have surgery, who have failed surgery, or who have contraindications to surgery. Cinacalcet increases the sensitivity of parathyroid calcium-sensing receptors to extracellular calcium, thereby reducing serum calcium levels. We conducted a retrospective chart review from 2004 to 2006 to investigate the efficacy of cinacalcet in reducing serum total calcium, ionized calcium, and parathyroid hormone (PTH) in patients with primary HPT. Patients were started on cinacalcet if they met at least one indication for parathyroidectomy, which includes T score less than -2.5 standard deviations from the mean, serum calcium 1 mg/dL above the upper limit of normal, 24-hour urine calcium above 400 mg/dL, age less than 50 years, or a creatinine clearance that is 30% below age- and sex-matched controls. The primary outcome was normalization of serum calcium. A total of 18 patients with primary HPT were started on cinacalcet: 16 men and 2 women with a mean age of 70 years. Mean baseline serum calcium was $10.60 \pm .53$ mg/dL; ionized serum calcium, $1.45 \pm .07$ mmol/L; and serum PTH, 141 ± 78 pg/mL. After treatment with cinacalcet, the mean serum calcium decreased to $9.46 \pm .34$ mg/dL, ionized calcium decreased to $1.26 \pm .06$ mmol/L, and PTH decreased to 108 ± 64.5 pg/mL. Ninety-four percent of the patients on cinacalcet had normal total serum calcium, 81% had normal serum ionized calcium, whereas only 25% had a normal serum PTH level. Cinacalcet normalizes serum calcium in most patients while only modestly reducing serum PTH levels.

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1. Introduction

Primary hyperparathyroidism (HPT) is the most common cause of hypercalcemia in the outpatient setting. It is characterized by hypercalcemia and a relative increase in serum parathyroid hormone (PTH) levels. Patients with moderate to severe disease can experience nephrolithiasis and loss in bone mineral density. Parathyroidectomy is usually curative; however, there are few nonsurgical treatment options for patients who do not wish to have surgery, who have failed surgery, or who have contraindications to surgery. In addition, 25% of patients with mild asymptomatic disease have progression of their disease over a 10-year period [1]. Estrogen therapy has been shown to improve bone mineral density in postmenopausal women with primary HPT [2]. Controlled trials using bisphosphonates have also reported an increase in bone density of

2% to 6% per year [3,4]. However, both drug treatments have a minimal effect on serum calcium levels. Small studies have reported a decrease in serum calcium with conjugated estrogens and raloxifene [5,6]. A small decrease in serum calcium was also noted with oral bisphosphonates in some studies [7,8], but other studies did not find a significant decrease in serum calcium [4,9]. Unfortunately, in some studies, oral bisphosphonate treatment was also noted to increase serum PTH levels [8].

Cinacalcet is a class II, second-generation calcimimetic that reduces serum calcium levels while causing a relatively small reduction in serum PTH levels [10–12]. It directly binds to the calcium-sensing receptor (CaR) located on the cells of the parathyroid gland and reduces PTH secretion and subsequently serum calcium by increasing the sensitivity of the CaR to extracellular calcium [13–20]. There are few studies examining the effect of cinacalcet in patients with primary HPT. Shoback et al [21] conducted a randomized, double-blind, dose-finding study in 22 patients. Normalization of the serum calcium after the second dose on day 1 persisted through day 15. Maximum decreases in serum PTH

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levels were observed 2 to 4 hours after the cinacalcet dose, and the 24-hour urine calcium to creatinine ratios were similar in the cinacalcet and placebo groups. In a 52-week, randomized, double-blind, placebo-controlled study, Peacock et al [22] investigated the long-term efficacy and safety of cinacalcet in reducing serum calcium and PTH levels in patients with mild primary HPT. In their study of 78 patients, 40 in the cinacalcet group and 38 in the placebo group, cinacalcet normalized serum calcium levels in 73% of patients, whereas the serum PTH decreased by about 8%. This effect was maintained over 52 weeks, but no clinically significant differences were observed in bone mineral density between the cinacalcet and placebo groups.

To date, there are no reports of cinacalcet therapy for primary HPT in a clinical practice setting. For cinacalcet to be used in practice, data on its use in a clinical practice setting, as opposed to a controlled research study, should be helpful to clinicians in practice. We report our experience with cinacalcet therapy for primary HPT in a Veterans Administration endocrine clinic.

2. Patients and methods

2.1. Patients and study design

We conducted a retrospective review from 2004 to 2006 to investigate the efficacy of cinacalcet in reducing serum calcium and PTH levels in patients with mild to moderate primary HPT. Patients included in this study met at least one indication for parathyroidectomy, which includes T score less than -2.5 standard deviations from the mean, serum calcium 1 mg/dL above the upper limit of normal, 24-hour urine calcium above 400 mg/dL, age less than 50 years, or a creatinine clearance that is 30% below age- and sex-matched controls. However, the patients refused surgery, had multiple medical problems precluding surgery, or failed surgery. Serum PTH, total calcium, and ionized calcium were measured multiple times before and during treatment.

Patients were started on cinacalcet 30 mg/d, and the dose was adjusted every 2 weeks based on serum ionized calcium levels measured usually 2 to 4 hours after the morning cinacalcet dose. The primary end point was normalization of serum ionized calcium. The serum ionized calcium is not influenced by serum albumin; therefore, it was used in preference to the total serum calcium. Cinacalcet inhibits cytochrome P450 isoenzyme 3A4 and can increase the levels of drugs that are metabolized by this enzyme, such as flecainide, thioridazine, ketoconazole, and many tricyclic antidepressants. None of the patients included in this study were receiving these drugs. The patients were queried about symptoms related to hypercalcemia such as fatigue, nausea, depression, polyuria, and abdominal pain. Blood specimens were performed the morning of the patient's visit after their morning cinacalcet dose. The study was approved by the Human Subject Committee of the Veterans Administration Greater Los Angeles Healthcare System.

2.2. Laboratory determinations

Total serum calcium (reference range, 8.4–10.2 mg/dL) was measured using the SYNCHRON LX system (Beckman Instruments, Brea, CA) that determines total calcium concentration by indirect potentiometry using a calcium ion selective electrode in conjunction with a sodium reference electrode. Intact serum PTH concentrations (reference range, 14–72 pg/mL) were determined by direct chemiluminescence assay using the ADVIA Centaur System (Siemens Co, Tarrytown, NY). Serum ionized calcium (reference range, 1.15–1.29 mmol/L) was measured using a polyvinyl chloride membrane containing calcium ion exchanger.

2.3. Statistical analysis

Statistical testing was conducted using the paired *t* test. A *P* value of $< .05$ was considered statistically significant. Values reported are mean \pm SD.

3. Results

A total of 18 patients with primary HPT were started on cinacalcet. The study included 16 men and 2 women with a mean age of 70 years (range, 43–90 years). Two patients, one male and one female, stopped treatment because of nausea with one dose of cinacalcet in one and light-headedness with diarrhea after 3 doses of cinacalcet in the other. Sixteen patients (89%) took cinacalcet for an average of 8 months (range, 1–19 months) without any adverse effects. The individual calcium and PTH mean values of each patient are presented in Table 1 before and during treatment with cinacalcet.

Mean baseline serum calcium was 10.60 ± 0.53 mg/dL, with a serum PTH of 141 ± 78 pg/mL and an ionized serum

Table 1
Summary of patients

Patient	Age/sex	Mean pretreatment serum calcium/PTH	Mean during treatment serum calcium/PTH	Cinacalcet dose	Creatinine
1	68/M	10.7/130	9.8/52	30 qd	0.9
2	73/M	10.6/184	9.8/173	30 bid	1
3	90/M	10.6/353	9.4/305	30 bid	1.2
4	58/F	10.4/71	9.6/58	30 bid	0.9
5	56/M	10.4/252	10/137	30 bid	0.9
6	55/M	11/112	9.1/99	45 bid	0.8
7	43/M	10.8/214	8.7/104	30 bid	1
8	71/M	9.96/80	9.4/125	30 qd	0.8
9	70/M	10.8/179	9.5/134	45 bid	1.1
10	65/M	10.4/100	9.8/113	30 qd	1.1
11	65/M	10.7/64	9.1/31.8	30 bid	0.9
12	90/F	10.7/111	9.6/68	30 bid	0.7
13	59/M	10.0/76	9.6/76	30 bid	0.9
14	86/M	10.6/114	9.1/78	30 bid	1
15	78/M	10.5/127	9.3/116	30 bid	1.2
16	75/M	12.2/85	9.6/59	30 bid	1
Mean		10.6/141	9.5/108		

Table 2

Serum calcium, PTH, and ionized calcium baseline and during treatment (mean \pm SD)

	Serum calcium (mg/dL) n = 16	Serum PTH (pg/mL) n = 16	Serum ionized calcium (mmol/L) n = 16
Baseline	10.60 \pm 0.53 (9.96–12.20)	141 \pm 78 (64–353)	1.45 \pm .07 (1.39–1.66)
Cinacalcet	9.46 \pm 0.34 (8.70–10.30)	108 \pm 64.5 (52–305)	1.26 \pm .06 (1.18–1.39)
P value	<.001	.007	<.001

Values in parentheses are ranges.

calcium of $1.45 \pm .07$ mmol/L (Table 2). The average baseline 24-hour urine calcium was 279 ± 202 mg/d. After a cinacalcet dose of 30 mg daily ($n = 3$), 30 mg twice daily ($n = 11$), and 45 mg twice daily ($n = 2$), the mean serum calcium decreased to 9.46 ± 0.34 mg/dL ($P < .001$), with a serum PTH of 108 ± 64.5 pg/mL ($P = .007$) and a serum ionized calcium of $1.26 \pm .06$ mmol/L ($P < .001$). Fig. 1 shows the serum ionized calcium before and during cinacalcet therapy in each patient. The mean 24-hour urine calcium decreased from 279 ± 202 to 244 ± 111 mg/d ($n = 5$, not significant). With treatment, the serum calcium decreased by 11%, the serum PTH decreased by 23%, and the serum ionized calcium decreased by 13%. The decreases in serum PTH, total calcium, and ionized calcium were statistically significant.

Fifteen (94%) of the 16 patients who remained on cinacalcet treatment had a normal serum total calcium, 13 (81%) of the 16 patients had a normal serum ionized

calcium, whereas only 4 (25%) of the 16 patients had a normal serum PTH level. Of the 3 patients who did not have a normal serum ionized calcium, one was on 30 mg/d of cinacalcet, whereas the other 2 patients were on 30 mg twice daily.

Of the 16 patients, only 3 patients reported subjective improvement in mood; one patient (patient 16) had dramatic improvement in both mood and energy when serum total calcium decreased from an average of 12.2 to 9.6 mg/dL with cinacalcet treatment.

4. Discussion

Cinacalcet offers a nonsurgical treatment option for patients who refuse surgery or who have failed surgery. In our study, cinacalcet normalized serum total and serum ionized calcium in 94% and 81% of patients, respectively. In the 3 patients whose serum ionized calcium did not normalize, a higher dose of cinacalcet might have resulted in its normalization. Because compliance was not measured by pill counting, persistently elevated serum calcium levels may have resulted from noncompliance with therapy. Serum PTH normalized in only 25% of patients, although the serum PTH level decreased by 23%. Peacock et al [22] reported a decrease in serum PTH of 37% 2 hours after the morning dose of cinacalcet. In our study, the serum PTH values were not drawn at exactly 2 hours after the cinacalcet dose, which may explain the discrepancy.

In the previous studies, cinacalcet was used predominantly in women with a mean age of 60 to 62 years

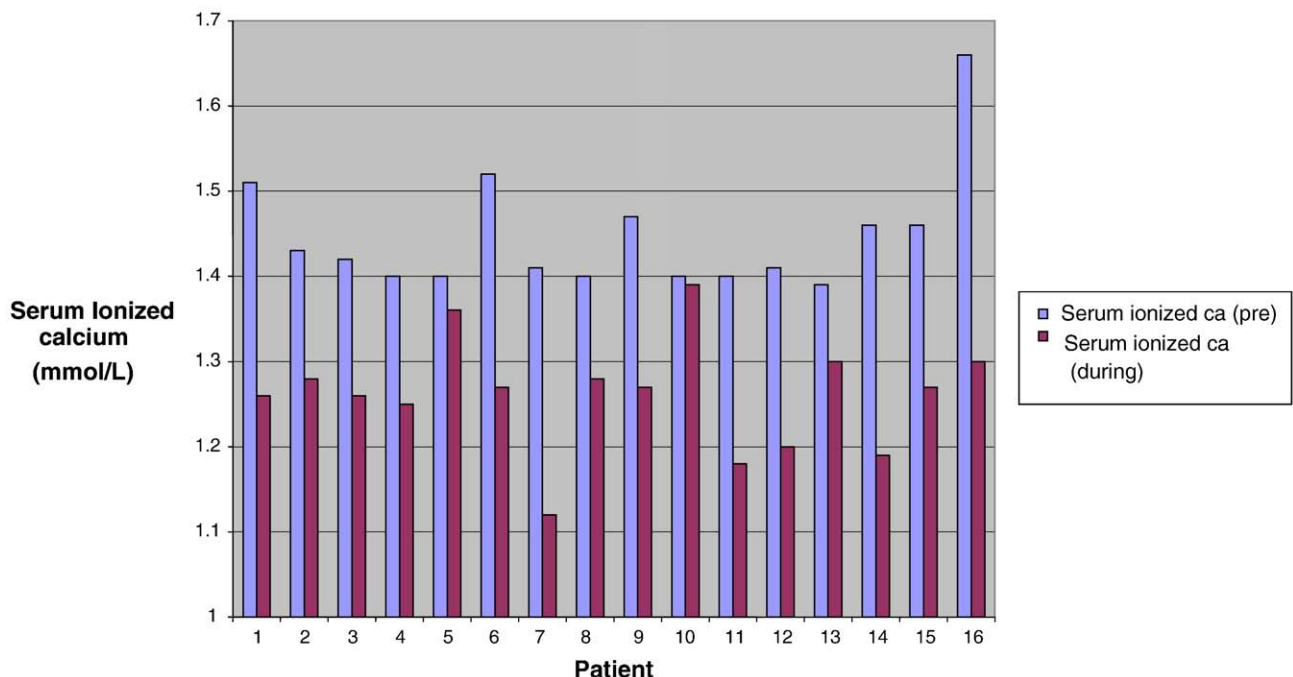


Fig. 1. Serum ionized calcium (in millimoles per liter) before and during cinacalcet therapy in each patient.

[21,22]. Our study population consisted mostly of older men. The combined results indicate that cinacalcet normalizes serum calcium levels in both men and women regardless of age.

Cinacalcet was well tolerated in this study. Only 2 patients stopped the medication because of adverse effects. The other 16 patients had no adverse effects related to cinacalcet.

Twenty-four-hour urine calcium levels did not decrease significantly. This result is consistent with the study of Shoback et al [21] that reported no difference in fasting and 24-hour urine calcium to creatinine ratios between the cinacalcet and placebo groups. Peacock et al [22] also reported no significant decrease in the 24-hour urine calcium; however, they did find a statistically significant decrease in fasting urine calcium to creatinine ratios. There are several explanations for the lack of decrease in the 24-hour urine calcium. Renal tubular cells have receptors for both PTH and calcium. Activation of the calcium receptors results in decreased calcium reabsorption, whereas activation of the PTH receptors results in increased calcium reabsorption from the distal tubule. In patients with primary HPT, the PTH effect seems to predominate. In patients treated with cinacalcet, the PTH levels are lower. This results in decreased reabsorption of calcium from the renal distal tubule, resulting in excretion of calcium in the urine. In addition, CaRs are found in the kidney, with the highest concentration in the thick ascending limb. Cinacalcet increases the sensitivity of these receptors, thereby resulting in increased excretion of calcium [23].

Cinacalcet was approved by the Food and Drug Administration in 2004 for secondary HPT related to renal insufficiency and parathyroid cancer, and it is not yet approved for primary HPT. Parathyroidectomy remains the treatment of choice for patients with primary HPT [24]. After successful parathyroidectomy, most patients notice an improvement in symptoms [25], bone mineral density increases at all skeletal sites [26], and serum calcium and serum PTH levels normalize. Bisphosphonates remain a treatment option in individuals with a low bone density who decline surgery. Alendronate therapy increases bone density in the lumbar spine and the femoral neck by about 3% [4]. In our study, bone mineral density was not routinely measured because the study needed to be longer to assess the effect of cinacalcet on bone density. Peacock et al [22] reported no increase in bone density with cinacalcet. The effects of bisphosphonates on serum calcium are minimal; and in some studies, the serum PTH level increased.

In summary, cinacalcet normalizes serum total and ionized calcium in most patients with primary HPT; and it is well tolerated. The PTH levels decrease but do not normalize in most patients. In our study, only 3 of 16 patients reported symptomatic improvement. Our study was not designed to determine if quality of life was improved by normalizing serum calcium. A prospective, randomized,

double blind, placebo-controlled study should be conducted to determine the effect of cinacalcet on the quality of life and to further elucidate its role in the treatment of presumably asymptomatic patients who refuse surgery, have failed surgery, or have multiple medical problems precluding surgery.

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