Endocr (2011) 39:283–287
DOI 10.1007/s12020-011-9459-0

ORIGINAL ARTICLE

Cinacalcet hydrochloride in combination with alendronate normalizes hypercalcemia and improves bone mineral density in patients with primary hyperparathyroidism

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Received: 3 March 2011 / Accepted: 15 March 2011 / Published online: 29 March 2011

Abstract Cinacalcet is effective in controlling the biochemical abnormalities in patients with primary hyperparathyroidism (PHPT) but it seems to be less effective on bone mineral density (BMD). In the same patients, bisphosphonates are reported to be effective on bone resorption but less effective on calcium and PTH excess. In this study, the efficacy of cinacalcet in combination with alendronate has been retrospectively evaluated in patients with PHPT. Twenty-three patients with PHPT who had not been operated were retrospectively investigated. Cinacalcet was evaluated in combination with alendronate in 10 of the 23 patients, and in monotherapy in 13 other patients. Serum calcium, phosphorus and PTH, 24 h urine calcium and phosphorus as well as BMD, evaluated by DXA and expressed as *T*-score, were measured before and after treatment. In all patients serum calcium and phosphorus and urinary calcium excretion were effectively and stably controlled and PTH was significantly decreased after treatment. There was no difference in the rate of serum calcium and PTH decrease between subjects treated with cinacalcet plus alendronate and those treated with cinacalcet alone. *T*-score increased by 9.6% at lumbar spine and 3.9% at femur level in the cinacalcet plus alendronate subgroup and was unchanged in the cinacalcet subgroup ($P < 0.01$). In patients with PHPT, the biochemical abnormalities are rapidly improved by cinacalcet regardless from the administration in monotherapy or in combination with alendronate. BMD is significantly improved in patients receiving cinacalcet plus alendronate and stable in those receiving cinacalcet in monotherapy.

Keywords Alendronate · Bone mineral density · Cinacalcet · Hypercalcemia · Primary hyperparathyroidism

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Introduction

Primary hyperparathyroidism (PHPT) is one of the commonest endocrine disorder with an incidence of about 25–50 new cases per year per 100,000 and a prevalence of 3 per 1,000 individuals in the general population, which raises to 21 per 1,000 among women aged 55–75 years [1]. In 95% of cases it is caused by a sporadic adenoma in one of the parathyroid glands. In patients with moderate or severe disease, PHPT results clinically in nephrolithiasis, osteoporosis, muscle weakness, cardiac and psychiatric abnormalities. Survival is also impacted in case of patients with long-time uncontrolled PHPT who develop renal insufficiency. The surgical removal of the parathyroid adenoma is the only definitive treatment for PHPT [2, 3]. However, many patients with sporadic PHPT have a mild or asymptomatic disease and do not meet the criteria for

surgery [4]. In addition, some patients fail surgery, some patients have contraindications to surgery and some other patients do not wish to have surgery.

If surgery is a well-established therapeutic strategy for PHPT since long time, what is changed in the last years is the availability of a new class of biotherapeutic agents, the calciomimetics, acting on calcium receptors. Recently, cinacalcet hydrochloride has been demonstrated to be highly effective in controlling hypercalcemia and PTH hypersecretion in patients with sporadic PHPT [5–8]. Bisphosphonates have been reported to induce only a slight and not durable decrease of serum calcium concentrations in patients with PHPT [9–11]. However, bisphosphonates are indicated in case of osteoporosis and in this attempt an improvement of bone mineral density (BMD) has been observed also in patients with PHPT.

In this study, effectiveness of cinacalcet hydrochloride in combination with alendronate or in monotherapy has been evaluated in patients with PHPT.

Patients and methods

Patients

Among 57 patients with sporadic PHPT diagnosed and followed-up at the Department of Endocrinology of the "Federico II" University of Naples from February 2008, all patients who had been not operated and were under treatment with cinacalcet were retrospectively investigated. In order to have a homogeneous study population and to limit the effects of age on BMD, one woman in premenopausal age and two men younger than 50 years of age were excluded. Twenty-three patients were finally considered for this study. The study population included 8 patients who did not meet current guidelines for surgery and 15 patients with PHPT-related symptoms or fulfilling at least one criterion of the NIH guidelines for parathyroid surgery who had contraindications to surgery (5 patients) or refused to be operated (10 patients).

Mean age was 63.9 ± 2.0 years (range 49–86), males were 10 and females were 13 (male:female ratio 0.77) (Table 1). At the time of diagnosis, all patients had hypercalcemia, hypophosphatemia, high serum concentrations of PTH. At the color-Doppler ultrasonography a parathyroid enlargement was detected in all patients, ranging 8–23 mm (mean ± SEM 15.4 ± 0.75 mm). There was a history of bone abnormalities in 78% of patients (osteopenia in 13, osteoporosis in 5, vertebral fractures in 3), a history of kidney stones in 52% (nephrolithiasis in 6, microlithiasis in 6). All patients had normal renal function as expressed by creatinine clearance.

All patients were under treatment with cinacalcet: 10 of them in combination with alendronate, while 13 of them received cinacalcet alone. The patients in treatment with cinacalcet plus alendronate were all affected with osteoporosis/osteopenia (100%) associated with bone symptoms, while those in treatment with cinacalcet alone had osteoporosis/osteopenia in 61% and no symptoms. Treatment subgroups did not differ in terms of demographic and biochemical characteristics (Table 1). At the time of the study, the treatment follow-up was 12 months in all patients, 18 months in 19 patients, and 24 months in 14 patients. The study was approved by the institutional ethics committee and was conducted in accordance with the Declaration of Helsinki.

Biochemistry

At baseline and at each study visit, serum calcium, phosphorus and PTH were measured on blood samples and urinary calcium excretion was measured on urine samples collected over 24 h after an overnight fast. The 24-h urine calcium excretion was factored by creatinine excretion. The 25-hydroxy-vitamin-D was also assessed basally and then at the time of the achievement of normocalcemia.

Imaging

A color-Doppler neck ultrasonography was performed at the diagnosis of PHPT and every 6 months during the follow-up. BMD was evaluated by dual-energy X-ray absorptiometry technique (DXA) at the lumbar spine and total femur. BMD was expressed as a *T*-score. Vertebral fractures were evaluated by anteroposterior and lateral X-ray examinations of the thoracic and lumbar spine. Vertebral fractures were diagnosed on visual inspection using the semiquantitative visual assessment (SQ), previously described by Genant et al. [12]. Both DXA and spine radiography were evaluated at baseline and at 1 year follow-up.

Treatment

Cinacalcet hydrochloride was started at the dose of 30 mg a day per os. The dose of cinacalcet was then increased to 30 mg at each assessment until obtaining normocalcemia. The maximal dose administered was 90 mg a day. Alendronate was administered at the dose of 70 mg a week per os.

At the time of the achievement of normocalcemia, a replacement therapy with colecalciferol was started in case of 25-hydroxy-vitamin-D insufficiency, as expressed by serum concentrations of 25-hydroxy-vitamin-D <20 ng/ml

Table 1 Baseline demographic, biochemical, clinical, and instrumental data

	Whole population $n = 23$	Cinacalcet + Alendronate $n = 10$	Cinacalcet $n = 13$	Reference range
Age (years)	63.9 ± 2.0	67.6 ± 3.7	61.1 ± 2.1	–
Women/men (no.)	13/10	6/4	7/6	–
Serum calcium (mg/dl)	11.1 ± 0.13	11.1 ± 0.18	11.0 ± 0.20	8.5–10.5
Serum PTH (pg/ml)	132 ± 13.1	145 ± 24	122 ± 14	10–65
Serum phosphorus (mg/dl)	3.0 ± 0.13	3.0 ± 0.23	2.9 ± 0.15	2.5–5.0
Bone alkaline phosphatase (U/L)	27.7 ± 1.2	26.8 ± 2.4	28.2 ± 1.8	10–25
Serum 25OH-vitamin D (ng/ml)	20.3 ± 1.7	19.5 ± 2.2	20.9 ± 2.2	>20
24-h urine calcium (mg/die)	357 ± 28	342 ± 38	368 ± 41	<250
24-h urine calcium to creatinine ratio	0.33 ± 0.03	0.31 ± 0.04	0.35 ± 0.05	0.07-0.29
Lumbar spine (*T*-score)	−2.07 ± 0.17	−2.15 ± 0.30	−2.02 ± 0.31	>−1.0
Total femur (*T*-score)	−2.17 ± 0.19	−2.25 ± 0.30	−2.10 ± 0.25	>−1.0
Osteopenia/osteoporosis/vertebral fracture (no.)	13/5/3	7/3/3	6/1/0	–
Nephrolitiasis/microlithiasis (no.)	6/6	3/2	3/4	–
Parathyroid adenoma (mm)	15.4 ± 0.75	16.5 ± 1.3	14.6 ± 0.9	–

Data are presented as Mean ± SEM

[13]. No other medical treatment for PHPT had been administered.

Statistical analysis

The statistical analysis was performed by SPSS for Windows version 10 (SPSS, Inc., Chicago, IL). The comparison between the numerical data was performed by unpaired *t-test* and ANOVA for repeated measures where appropriate. Data are reported as mean ± SEM. The significance was set at 5%.

Results

Effects of cinacalcet in the whole PHPT population

During treatment with cinacalcet, a rate of 35% of patients required to increase the dose to 60 mg a day at 3–6 month follow-up and 9% of them required a further dose increase to 90 mg a day at 6–9 month follow-up. Before therapy with cinacalcet, all patients had hypercalcemia and high serum PTH concentrations. After the introduction of cinacalcet, serum calcium rapidly decreased in all patients. After 3 months of therapy, serum calcium was significantly decreased while serum phosphorus was significantly increased when compared to baseline ($P < 0.001$). No significant change occurred in serum PTH within 3 months. After 6 months of therapy with cinacalcet, no further variation was observed in serum calcium and phosphorus as compared to 3 month follow-up, while serum PTH was significantly decreased as compared to baseline ($P < 0.001$). These results were maintained after 12 and 24 months of therapy with cinacalcet (Fig. 1). The 24-h urine calcium excretion and the 24-h urine calcium to creatinine ratio significantly decreased from baseline ($P < 0.001$). Bone alkaline phosphatase levels were elevated at baseline and significantly decreased 6 months after therapy ($P < 0.05$).

At month 12 follow-up, serum calcium and PTH concentrations were within the normal range in 100% and 43% of patients, respectively. At the last follow-up evaluation (24 months), serum calcium persisted in the normal range in all patients while PTH was normal in 48%.

Sixteen subjects (65%) showed an insufficiency of 25-hydroxy-vitamin-D (<20 ng/ml) at baseline which persisted in 10 (43%) at the achievement of normocalcemia (12 month follow-up). These subjects received a replacement treatment with colecalciferol. *T*-score was mildly but not significantly increased at lumbar spine and unchanged at femur level 12 months after cinacalcet. No further vertebral fracture was observed in any patient after cinacalcet as compared to baseline. No episode of renal colic was observed during therapy with cinacalcet. Cinacalcet was safe and well tolerated.

Cinacalcet plus alendronate versus cinacalcet in monotherapy

By considering separately the subgroup of patients receiving cinacalcet in combination with alendronate and that receiving cinacalcet in monotherapy, both subgroups obtained similar results 1 year after cinacalcet in terms of decrease in serum calcium and PTH concentrations, without significant differences (Table 2).

T-score change after therapy was significantly higher in the subgroup of patients in therapy with cinacalcet plus

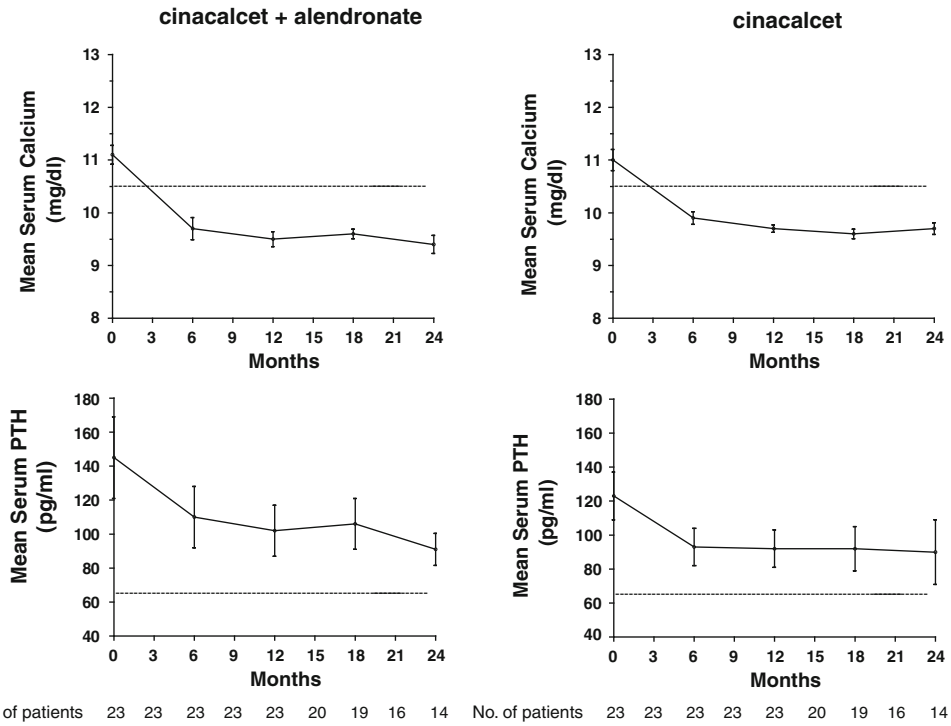

Fig. 1 Serum concentrations of calcium and PTH before and after the beginning of cinacalcet according to treatment. Data are presented as mean ± SEM. The *dashed line* indicates the upper limit of the normal range

Table 2 Percent change of biochemistry and bone mineral density from baseline to month 12 according to treatment subgroup

	Cinacalcet + alendronate $n = 10$	Cinacalcet $n = 13$
Serum calcium (mg/dl)	−14 ± 1.4	−12 ± 1.3
Serum PTH (pg/ml)	−29 ± 8.4	−25 ± 5.9
Bone alkaline phosphatase (U/L)	−41 ± 9.5[a]	−16 ± 4.8
Serum 25OH-Vitamin D (ng/ml)	+18 ± 4.8	+17 ± 4.0
24-h urine calcium (mg/die)	−29 ± 8.7	−25 ± 7.7
24-h urine calcium to creatinine ratio	−23 ± 7.6	−18 ± 5.5
Lumbar spine (*T*-score)	+9.6 ± 1.4[b]	+1.3 ± 0.9
Total femur (*T*-score)	+3.9 ± 1.0[a]	+1.1 ± 0.8

Data are presented as Mean ± SEM

[a] $P < 0.05$ compared with values in cinacalcet subgroup

[b] $P < 0.01$ compared with values in cinacalcet subgroup

alendronate than in the subgroup of patients under cinacalcet in monotherapy ($P < 0.01$) (Table 2). In parallel, the decrease in bone alkaline phosphatase levels was significantly higher in the subgroup receiving the combined treatment than in that receiving cinacalcet in monotherapy ($P < 0.05$) (Table 2).

At the ultrasonographic examination, size of parathyroid adenomas was unchanged after cinacalcet in both subgroups.

Discussion

In this study, cinacalcet hydrochloride effectively controlled biochemical abnormalities in patients with PHPT, without significant differences between monotherapy and combination therapy with alendronate. Both treatment subgroups experienced a rapid decrease of hypercalcemia and hypercalciuria, with normalization of hypercalcemia in 100% of cases, decrease of serum PTH at a similar extent and stabilization of these results at 24 month follow-up. Alendronate did not exhibit a synergistic activity when combined with cinacalcet. This is in line with previous observations highlighting that bisphosphonates are lowly effective on the biochemical abnormalities of PHPT [9–11].

As previously demonstrated, cinacalcet is effective on serum calcium, phosphorus, and PTH abnormalities of PHPT patients [5–8]. These effects are related to the activity of cinacalcet on the calcium sensing receptor. Cinacalcet also is known to induce a decrease in the renal resorption of calcium, however, urine calcium excretion in PHPT patients treated with this agent is decreased or at least not worsened [5–8] and this is likely in relation with

the decrease of serum calcium load to renal filtration. All biochemical effects of cinacalcet are long lasting maintained as it could be observed in a subgroup of patients followed-up for 24 months.

Concerning the dose of cinacalcet, this study suggests that a dose of 30 mg once a day is effective in normalizing serum calcium concentrations in most of the patients and only one third of them requires an increase to 30 mg twice a day or more. This is in line with data reported by Falchetti et al. [14] in one patient with MEN1 PHPT followed for 1 year and seems to suggest that 30 mg once a day may be the starting dose of cinacalcet in patients with PHPT. This dosage is particularly well tolerated without any patient complaining significant side effects or requiring drug discontinuation.

A relevant difference concerns indeed BMD which was improved in the subgroup in combination therapy but not in that in monotherapy. Bisphosphonates are known to be effective in decreasing bone turnover in patients with PHPT and improving BMD [10, 11, 15]. On the other hand, cinacalcet has shown no significant effects on BMD as evaluated by DXA at spine, hip, and wrist [16]. However, it would be more appropriate to say that the bone damage is not restored by cinacalcet in PHPT patients while a further damage did not develop during therapy with cinacalcet. In other words, cinacalcet seems to arrest the decrease of BMD and the impairment of bone tissue in PHPT, as seen in the current study and in all others evaluating the BMD in these patients [6, 14, 16]. In parallel, alkaline phosphatase slightly varies in PHPT patients treated with cinacalcet [5–8, 14, 16]. For this reason, the much greater decrease of alkaline phosphatase observed in the current study in patients treated with cinacalcet in combination with alendronate (41%) than in those treated with cinacalcet alone (16%) has to be related to the activity of alendronate in blocking bone resorption. This was associated with an increase in BMD at lumbar spine of 9.6% after cinacalcet plus alendronate and no change after cinacalcet alone. An improvement of BMD might subsequently occur even in the subgroup of patients in monotherapy with cinacalcet, due to the administration of colecalciferol replacement in those patients who still had hypovitaminosis D after the achievement of normal serum calcium concentrations.

Thus, cinacalcet is a helpful alternative to parathyroidectomy among PHPT patients for whom surgery is contraindicated or refused and in those patients with PHPT relapsing after surgery. On the other hand, cinacalcet plus alendronate, with the adjunction of colecalciferol where appropriate, may be an effective therapeutic approach in those PHPT patients who are also affected by low BMD.

In summary, in patients with PHPT, the biochemical abnormalities are rapidly improved by cinacalcet, resulting in normocalcemia and decrease of serum PTH and urinary calcium concentrations. These results are stably maintained during a 24 month follow-up. Cinacalcet is equally effective on calcium and PTH serum abnormalities either when used in monotherapy or in combination with alendronate. BMD is unchanged in patients receiving cinacalcet in monotherapy and improved in those receiving a combined therapy with cinacalcet and alendronate.

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