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ORIGINAL ARTICLE

Bone metabolism after cinacalcet administration in patients with secondary hyperparathyroidism

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Abstract Cinacalcet, an allosteric modulator of a calcium (Ca)-sensing receptor, significantly suppresses parathyroid hormone (PTH) secretion and bone turnover rate in chronic hemodialysis (HD) patients with secondary hyperparathyroidism (SHPT). In this study, bone metabolism after cinacalcet treatment was examined, because hungry bone syndrome is sometimes experienced after parathyroidectomy in severe SHPT. We conducted a prospective observational study in 17 HD patients with SHPT. Cinacalcet was started at 25 mg/day, and the dose was increased step by step based on serum calcium level. A significant decrease in serum Ca and intact PTH concentration was found within 2 weeks. Tartrate-resistant acid phosphatase 5b, a good bone resorption marker, was significantly decreased at week 2 of the study. Serum bone alkaline phosphatase, a marker of bone formation, was increased at week 2 compared with the basal level. It became, however, gradually decreased until week 14. Only one patient whose bone turnover was considerably high had a mild numbness feeling. These results suggest that cinacalcet treatment might transiently accelerate bone formation with rapid suppression of bone resorption. This uncoupling could be involved in a mechanism by which cinacalcet decreases serum Ca level.

Keywords Cinacalcet · Bone metabolism · Hemodialysis · Secondary hyperparathyroidism · Hungry bone

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Introduction

Cinacalcet acutely inhibits parathyroid hormone (PTH) secretion through acting on a calcium-sensing receptor on the membrane of the parathyroid gland, thereby bringing great benefit to patients undergoing chronic hemodialysis (HD) therapy such as easier achievement of targeting levels of serum calcium (Ca) and phosphorus (P), reduction in the risk of parathyroidectomy (PTx), fractures, and cardiovascular hospitalization, and possible prevention of vascular calcification and bone loss [1–5]. Arterial calcification is more developed in HD patients compared with age-matched healthy subjects and is thought to be a cardiovascular risk factor in renal failure [6, 7]. Elevated serum Ca, P, and Ca × P product are also considered as cardiovascular risks in HD patients and may have a link to increased mortality [8, 9]. Cinacalcet can lead to a significant reduction in serum Ca, P, Ca × P, and PTH levels; thus, this kind of agent might be an ideal therapy for HD patients with secondary hyperparathyroidism (SHPT).

Hypocalcemia is one of the important side effects of cinacalcet. However, once this agent is started, it might need to be used for a long period because enlarged parathyroid glands cannot be easily regressed. Therefore, cinacalcet has to be carefully started for suitable cases. We

developed our original protocol and assessed the safety and effect of cinacalcet, especially on bone metabolism. In our prospective study, cinacalcet acutely suppressed bone resorption whereas it transiently accelerated bone formation. Although mechanisms of cinacalcet-induced hypocalcemia remain uncertain, it is conceivable that cinacalcet could produce a hungry bone-like effect such as is seen after PTx in patients with severe SHPT [10].

Materials and methods

Patients

Our subjects were 17 patients undergoing maintenance HD therapy with SHPT. Including criteria were persistent hyperphosphatemia, hypercalcemia, or high PTH level for at least 3 months in spite of conventional treatment. The Japanese Society for Dialysis Therapy (JSDT) guideline was used for the target range: $6.0 \geq P \geq 3.5$, $10 \geq cCa \geq 8.4$, and $180 \geq iPTH \geq 60$ [11]. The background data of the subjects are shown in Table 1. Their original disease was diabetes mellitus in 3 patients, chronic glomerular nephropathy in 9, hypertensive nephropathy in 2, and unknown in 3 patients. Maintenance HD therapy (3 sessions a week, 4 h per session) has been performed in all patients. Ca concentration in the dialysate bath was 3.0 mEq/l.

A protocol of this study is shown in Table 2. Conventional medical treatment for SHPT, such as sevelamer hydrochloride and the vitamin D analogue Maxacalcitriol (OCT) pulse therapy, had been continued without change in the dosage for at least 1 month before and after cinacalcet administration. At the end of this study (15 weeks), dosage of cinacalcet was 50 mg (2 tablets) for 2 patients and 25 mg (1 tablet) for the other 15. Mean dosage of sevelamer hydrochloride was 2790 ± 430 mg/day. No patient was treated with $CaCO_3$ as a phosphate binder. Dosage of OCT was increased in 10 patients after 4 weeks of cinacalcet administration. Mean dosage of OCT was 12.2 μg/week at the beginning of the study and 22.6 μg/week at the end. There was no change of prescription regarding any other medication as well as dialysis condition. This study was approved by the Institutional Review Board of Shimane University. All participants gave informed consent to join this study.

Table 1 Clinical and laboratory profile in 17 patients undergoing maintenance hemodialysis (HD)

Parameter	Value	Normal range
Age (years)	57.9 ± 2.3	
Gender (male/female)	10/7	
Duration of HD (year)	15.2 ± 2.6	
OCT dose (μg/week)	12.2 ± 1.6	
Serum Ca (mg/dl)	9.7 ± 0.12	8.2–10.0
Serum cCa[a] (mg/dl)	10.1 ± 0.12	
Serum P (mg/dl)	5.62 ± 0.32	2.5–4.5
Intact PTH (pg/ml)	486 ± 42	10–65
BAP (U/l)	21.2 ± 2.1	9.6–35.4
TRACP5b (mU/dl)	747 ± 123	170–590

OCT vitamin D analogue Maxacalcitriol, *PTH* parathyroid hormone, *BAP* bone alkaline phosphatase, *TRACP5b* tartrate-resistant acid phosphatase 5b

[a] Corrected with serum Alb level with Payne's formula: cCa = Ca + (4–Alb), if serum albumin is less than 4.0 g/dl

Table 2 Protocol for cinacalcet administration in this study

Step 1: Start 1 tablet (25 mg) after dinner

Step 2: After 7 days of step 1, check cCa ≥ 8.5 mg/dl and no symptom[a]

Step 3: After 14 days of step 1 (or 4), check cCa, P, and PTH levels

Step 4: If cCa > 10 mg/dl, add 1 tablet[b] (go to step 5)

If 10 > cCa ≥ 8.0 mg/dl, continue treatment[c]

If 8.0 mg/dl > cCa, reduce by 1 tablet or stop taking

Step 5: After 7 days of step 4, check cCa ≥ 8.5 mg/dl and no symptom

Step 6: Continue steps 3–5

[a] Ask about symptoms such as numbness or tetany; instruct patient to stop taking if serious side effect occurs or when cCa is less than 7.5 mg/dl

[b] Maximum dosage of cinacalcet is 100 mg/day

[c] If P < 5.5 mg/dl, cCa < 9.0 mg/dl, and iPTH > 180 pg/ml, the dosage of intravenous vitamin D analogue may be increased

Methods

Blood samples were obtained just before the HD session to determine serum levels of Ca, albumin, P, and intact parathyroid hormone (iPTH). At least 12 h had passed after the last cinacalcet dose before blood sample collection. Bone metabolism was evaluated by serum bone alkaline phosphatase (BAP), a marker of bone formation, and tartrate-resistant acid phosphatase 5b (TRACP5b), a marker of bone resorption. Measurement of serum iPTH and BAP was performed by immunoradiometric assay (IRMA; Scantibodies) and by enzymatic immunoassay (EIA), respectively. TRACP5b, which has been reported not to be affected by renal function, was measured by novel fragments absorbed immunocapture enzymatic assay (FAICEA) using two monoclonal antibodies [12, 13]. TRACP5b activity was reported to be free from interference by TRACP5a activity [14].

Statistics

All data are shown as mean ± standard error of the mean. A paired *t* test was performed for comparison between two

time points. A single regression analysis was performed for correlations among the variables. A multiple comparison was conducted by analysis of variance (ANOVA) with Fisher's protected least squares difference (PLSD) or the Kruskal–Wallis test. A chi-square test was also performed to determine the statistical significance. A P value <0.05 was considered statistically significant.

Results

Effect on serum Ca and P levels and on PTH secretion

Cinacalcet administration led to a significant decrease in serum Ca level and a Ca × P product at week 2 (Fig. 1). A significant decrease in serum P level was also shown within 4 weeks. Serum iPTH level was significantly decreased at week 2 (Fig. 1). However, gradual increases in Ca, P, and Ca × P accompanied by sustained inhibition of iPTH levels after 4 weeks could be best explained by the co-administration of OCT. Maximal suppression was found at the end of the study (51.3% ± 7.1% reduction from baseline).

Achievement of the target range

If the Japanese Society for Dialysis Therapy (JSDT) guideline is adapted, 4 patients (24%) reached the target range at the end of the study: $6.0 \geq P \geq 3.5$, $10 \geq cCa \geq 8.4$, and $180 \geq iPTH \geq 60$ [11]. Five patients (29%) achieved the target of all components of the K/DOQI guideline at week 14, although no one achieved it at the beginning of the study [15]. This finding suggests that the target range could be achieved by a combination therapy of cinacalcet and OCT, even if it could not be achieved by conventional therapy.

Effect on bone metabolism

A time-dependent decrease in serum TRACP5b level was observed (Fig. 2). Interestingly, serum level of BAP, a marker of bone formation, was increased at week 2 compared with the basal level (Fig. 2). These early changes in TRACP5b and BAP levels were most likely the result of cinacalcet treatment because OCT dosages were not changed at week 2. The elevated BAP level, however, gradually decreased, and at week 14 it was significantly lower than the baseline level, suggesting that extensive management of SHPT with cinacalcet and OCT induced a significant reduction of serum PTH level and bone turnover rate.

Because there was a tendency to positive correlation between percent changes in iPTH from the baseline and percent changes in TRACP5b from the baseline at week 2 ($P = 0.062$) as well as at week 8 ($P = 0.067$),

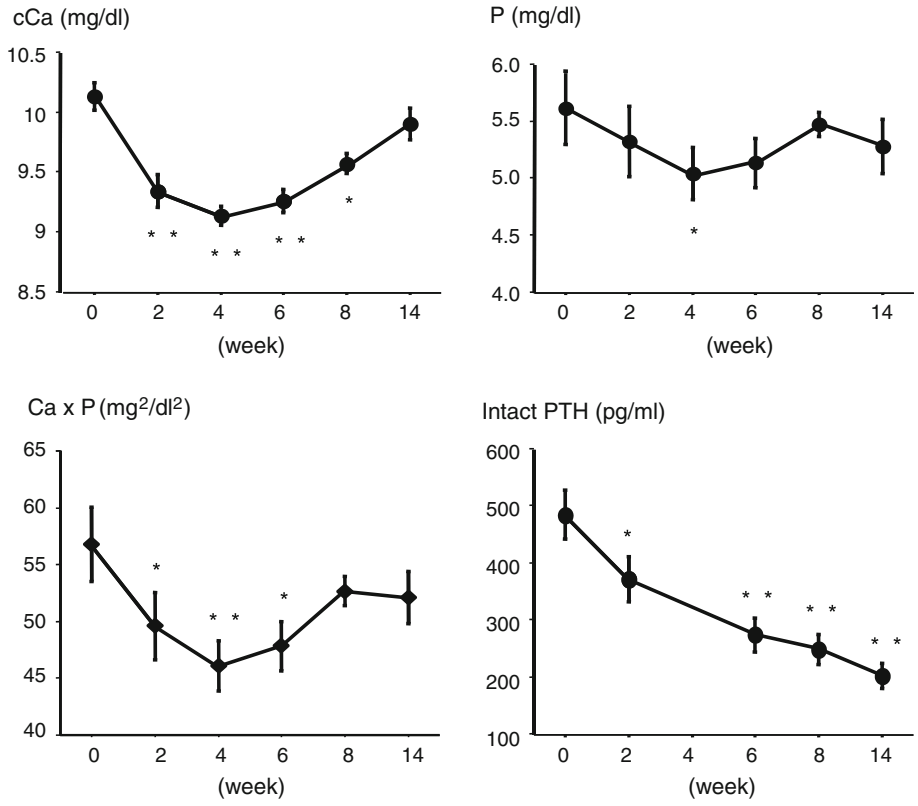

Fig. 1 Effect of cinacalcet on serum Ca, P, Ca × P, and intact parathyroid hormone (PTH) levels in 17 hemodialysis (HD) patients. Serum corrected Ca (cCa), Ca × P product, and intact PTH levels were significantly decreased 2 weeks after Cinacalcet (25 mg/day) therapy. Serum P was also decreased at week 4. These changes in serum markers after 4 weeks could be affected not only by cinacalcet but also by the co-administration of the vitamin D analogue Maxacalcitriol (OCT). *$P < 0.05$; **$P < 0.001$

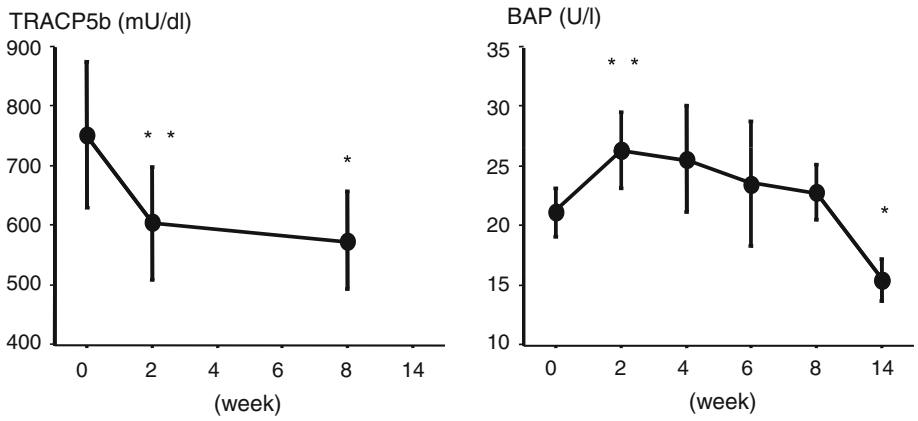

Fig. 2 Effect of cinacalcet on bone resorption and formation. Serum TRACP5b, a bone resorption marker, was significantly decreased at weeks 2 and 8, whereas serum bone alkaline phosphatase (BAP), a bone formation marker, was significantly increased at week 2 and gradually decreased thereafter. $*P < 0.05$; $**P < 0.01$

cinacalcet-induced suppression of bone resorption could be mediated through remarkable suppression of PTH secretion. On the other hand, no correlation was found between percent changes in iPTH from the baseline and percent changes in BAP from the baseline at week 2 ($P = 0.71$) as well as at week 8 ($P = 0.67$).

Safety

As for side effects of cinacalcet, one woman felt numbness in her extremities in the night 3 days after cinacalcet treatment. Her basal levels of serum cCa, P, iPTH, BAP, and TRACP5b were 10.0 mg/dl, 5.8 mg/dl, 513 pg/ml, 32.2 U/l, and 1470 mU/dl, respectively. The numbness had disappeared when she came to the clinic next morning. Serum cCa level was 9.0 mg/dl before HD, although it was expected to be lower with the presence of this symptom. After a couple of days of cessation of cinacalcet, she was able to restart the medicine, and no side effects occurred thereafter. A gastrointestinal side effect, which occurred most frequently in cinacalcet treatment, was not experienced. We did not observe any other complications throughout this study period.

Discussion

In this study, we found that serum BAP level was transiently elevated after administration of cinacalcet whereas serum TRACP5b level was rapidly suppressed. Chronic suppression of bone turnover by cinacalcet has been previously reported [1, 4]. Shigematsu et al. [16] have recently shown a transient increase in serum BAP level and a rapid decrease in TRACP level during long-term cinacalcet treatment in 200 HD patients. In their study, serum BAP level was elevated 4 weeks after cinacalcet treatment and gradually decreased thereafter, whereas serum levels of the bone resorption markers TRACP and NTx (amino-terminal telopeptide of type I collagen) were markedly reduced at 4 weeks. These findings are very consistent to our results. In the present study, we detected these changes in bone markers at as early as 2 weeks of cinacalcet administration. Thus, these findings indicate that bone changes could occur much earlier than we expected.

Cinacalcet, which allosterically acts on the Ca-sensing receptor on the parathyroid cells, promptly suppresses PTH secretion, followed by a decrease in serum Ca and P [17–19]. Because this medicine mimics extracellular Ca action, it is called a calcimimetic. Previous reports demonstrated that NPS R-568, a first generation of calcimimetic agents, acutely suppresses PTH secretion within 1 h in postmenopausal women with mild primary hyperparathyroidism [20]. This action resulted in a significant reduction in serum Ca to reach nadir 2–6 h after administration. The mechanism of this phenomenon has not been elucidated.

Because the Ca-sensing receptor is expressed on bone tissue, possibilities of direct effect of cinacalcet on bone cells cannot be excluded [18, 21]. According to previous in vitro studies, activating the Ca-sensing receptor in osteoblasts or the precursors resulted in the stimulation of their proliferation and differentiation whereas activating the Ca-sensing receptor in osteoclasts or the precursors led to apoptosis and to the inhibition of their activity and differentiation [22–27]. However, because the Ca-sensing receptor expression level in bone is much less than that in the parathyroid gland, a PTH-mediated hungry bone-like phenomenon would be plausible as the main mechanism of calcimimetics-induced hypocalcemia.

Yajima et al. [28] demonstrated bone histomorphometric data after PTx in SHPT, where osteoclast surface was disappeared within 4 weeks after PTx and osteoblast surface transiently increased at 1 week, followed by a reduction at 4 weeks. These bone biopsy data well explained our findings reported previously, where decreased bone mineral density (BMD) was significantly regained as soon as 1 month after PTx, and the impact of the recovery was associated with serum PTH level just before PTx [10]. Lazar and Stankus [29] presented a case with cinacalcet-induced

symptomatic and persistent hypocalcemia closely resembling the PTx-induced hungry bone syndrome. More recently, effects of cinacalcet on bone histology were demonstrated in patients with SHPT [30]. According to the report, parameters of bone formation and resorption were decreased with a concomitant increase in mineralized bone volume after 52 weeks of treatment with cinacalcet and low-dose vitamin D sterol.

Cinacalcet also leads to P reduction in patients with SHPT. In the present study, greater reduction of serum PTH level was obtained in patients whose serum P levels were well controlled and OCT dosages were raised. Recent findings indicate that calcimimetics might lead to an increased vitamin D receptor (VDR) expression in the parathyroid cells [31]. On the other hand, the vitamin D analogue OCT induced upregulation of Ca-sensing receptor and VDR was reduced in uremic rats when it was directly administered in the parathyroid gland [32], suggesting that a combination of cinacalcet and vitamin D or its analogue might be reasonable therapy for SHPT [33, 34]. In addition, cinacalcet could cancel out the negative effects of vitamin D such as hypercalcemia and hyperphosphatemia.

We experienced a side effect of cinacalcet in only 1 woman among 17 HD patients. Probably because her bone turnover rate was high, it was conceivable that cinacalcet could induce hungry bone status. Her serum BAP levels were 32.2 U/l, 54.9 U/l, and 45.4 U/l at week 0, 2, and 8, respectively. The ratio of BAP level at week 2 divided by week 0 showed 1.71, which was the highest level among all participants, and it remained at a high level (1.41) at week 8. In contrast, her serum TRACP5b levels were 1470, 1180, and 931 mU/dl at week 0, 2, and 8, respectively. The basal level was the highest among these patients. These findings might support our speculation that cinacalcet-induced hypocalcemia might be mediated in part by uncoupling between bone formation and resorption. Based on this theory, cinacalcet-induced hypocalcemia should be regarded with care, especially for those patients with very high bone turnover.

There are some limitations in this study. First, the sample size was small and the study duration was too short for conclusive results, even if statistical significance was observed. However, supportive findings have been reported previously [16, 29]. Second, we speculated bone turnover from bone markers, but not from bone histomorphometry data. Thus, we could not rule out the potential occurrence of temporal osteomalacia or mineralization impairment rather than hungry bone syndrome, as BAP can be increased when there is a defect in primary mineralization of bone. Recent bone histology data, however, strongly support a cinacalcet-induced hungry bone phenomenon [28, 31]. Third, we did not detect early changes in serum BAP and TRACP5b before a decrease in serum Ca level.

In conclusion, our results suggest that cinacalcet might transiently accelerate bone formation with rapid suppression of bone resorption. This uncoupling could be partly involved in a mechanism by which cinacalcet rapidly decreases serum Ca level.

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