Preliminary Communication

Effects of cinacalcet on bone mineral density in patients with secondary hyperparathyroidism

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Abstract

Background. Cinacalcet, a calcimimetic agent, is effective in treating both primary and secondary hyperparathyroidism. Because hyperparathyroidism induces mineralized bone loss, we investigated the effects of cinacalcet treatment on bone mineral density (BMD) in patients with secondary hyperparathyroidism due to chronic kidney disease.

Methods. Ten patients who were receiving haemodialysis and four patients, who had stage 4 chronic kidney disease participated and completed the multicentre, randomized, double-blind, placebo-controlled trials evaluating the safety and efficacy of cinacalcet for treating secondary hyperparathyroidism. The efficacy of cinacalcet was assessed by plasma intact parathyroid hormone (iPTH) levels. A dual energy X-ray absorptiometry was performed to measure the BMD of total proximal femurs and lumbar spine (L2–L4) before and after 26 weeks of treatment.

Results. Cinacalcet reduced iPTH from 912±296 to 515±359 pg/ml in haemodialysis patients and from 210±46 to 56±51 pg/ml in pre-dialysis patients (means±SD; both P<0.05). When data from haemodialysis and pre-dialysis patients were pooled for analysis, cinacalcet treatment increased proximal femur BMD from 0.945±0.169 to 0.961±0.174 g/cm² (P<0.05), but did not affect lumbar spine BMD. There was a correlation between the change in femur BMD and the change in iPTH during the study period (R²=0.39, P<0.05).

Conclusions. Secondary hyperparathyroidism is associated with progressive bone loss. Suppression of plasma iPTH with cinacalcet appears to reverse bone loss in the proximal femur, but does not affect BMD of the lumbar spine. A larger study is warranted to confirm that cinacalcet has a beneficial effect on the skeletal system in patients with secondary hyperparathyroidism.

Keywords: bone mineral density; calcium-sensing receptor; cinacalcet; cortical bone; secondary hyperparathyroidism; trabecular bone

Introduction

Cinacalcet belongs to a new class of drugs known as calcimimetics that target the calcium-sensing receptor in the parathyroid gland [1]. The release of parathyroid hormone (PTH) is tightly regulated by extracellular calcium levels via the calcium-sensing receptor [2]. Cinacalcet is a small organic compound that functions as an allosteric activator of the calcium-sensing receptor by binding directly to the receptor membrane-spanning domains. As a result, it increases the sensitivity of the calcium-sensing receptor to extracellular calcium, thereby reducing PTH secretion [3]. Cinacalcet has been shown to be effective in treating primary hyperparathyroidism [4]. In patients with secondary hyperparathyroidism due to chronic kidney disease, cinacalcet lowers PTH levels without increasing calcium and phosphorus levels [5]. It has been established that elevated serum phosphorus and Ca×PO₄ product are strongly associated with cardiac mortality in chronic haemodialysis patients [6]. Because cinacalcet lowers PTH while also reducing serum calcium and phosphorus levels, it is useful in managing secondary hyperparathyroidism particularly in patients with a high Ca×PO₄ product.

Secondary hyperparathyroidism is the most common cause of renal osteodystrophy in patients receiving dialysis [7]. There is a significant inverse correlation between cortical bone mineral density (BMD) and PTH levels in haemodialysis patients [8]. PTH stimulates receptor activator of nuclear factor-κB ligand production by pre-osteoblasts and stromal cells, thereby increasing osteoclast formation and bone...
resorption [9]. In secondary hyperparathyroidism, there is increased bone loss manifested mainly as thinning of cortical bone due to increased resorption of the endocortical surface [10]. To evaluate whether lowering the PTH level by cinacalcet would affect the BMD, we measured the BMD of the proximal femur and lumbar spine in all patients who participated in cinacalcet clinical trials at a single centre.

Subjects and methods

Patients

Fourteen patients, who participated and completed the multicentre, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of cinacalcet for treating secondary hyperparathyroidism, were included in the present study. Ten patients who received haemodialysis participated in the study designed for ESRD patients, and four patients who had chronic kidney disease stage 4 (glomerular filtration rate between 15 and 29 ml/min) participated in the study designed for pre-dialysis patients. The study protocols for the use of cinacalcet in study patients were reviewed and approved by the institutional review board at the University of Arizona and a written informed consent was obtained from each patient before enrolment.

BMD measurements were collected as part of routine clinical care in patients with secondary hyperparathyroidism at our clinic.

Study design

The study design of the multicentre cinacalcet trial for chronic haemodialysis patients has been reported previously [5]. In brief, the treatment phase lasted 26 weeks for patients receiving haemodialysis. It included a 12 week dose titration phase followed by a 14 week efficacy assessment phase. The initial dose of cinacalcet was 30 mg given orally once daily. The doses could be increased sequentially every 3 weeks to 60, 90, 120 and 180 mg once daily. For pre-dialysis patients, the study design was identical to that for chronic haemodialysis patients except that the efficacy assessment phase was shortened to 6 weeks.

Biochemical measurements

Plasma intact PTH (iPTH) and serum calcium and phosphorus levels were measured at each study visit before the dose of study medication. Serum levels of alkaline phosphatase were measured at baseline and at the end of the study. All biochemical measurements were made at the reference laboratory (Covance Laboratory Services, Indianapolis).

BMD measurements

Since hyperparathyroidism is associated with bone loss [8,11], we routinely measure lumbar spine (L2–L4) and total proximal femur BMD using dual energy X-ray absorptiometry (DEXA) in patients with secondary hyperparathyroidism. The total proximal femur BMD includes the femoral neck, the greater trochanter and proximal femur shaft. In this study, DEXA was performed at the screening and at the end of the study. The measurements were made with a GE Medical Systems Lunar in-office DEXA scanner and software (GE, Madison, WI). The reference data for BMD consists of the data for age- and sex-matched controls obtained from the DEXA manufacturer’s reference population. The DEXA results were analysed in a blinded fashion.

Statistical analysis

All values are expressed as means ± SD. Statistical comparisons between pre- and post-treatment values were performed by paired, one-tailed Student’s t-tests. For comparisons of data between the cinacalcet and placebo groups, non-paired, two-tailed Student’s t-tests were used. P-values < 0.05 are considered statistically significant.

Results

Demographic characteristics

There were 10 chronic haemodialysis patients, six in the cinacalcet group and four in the placebo group, and four pre-dialysis patients, two in each group. Table 1 shows the demographic data of the study patients. Because these studies were part of two multicentre clinical trials of cinacalcet, they were not designed to match subjects for a single centre. The placebo group had a lower mean of age (not significant, P > 0.05) and had more male patients (P < 0.05). The ethnic distribution was comparable between the two groups. All but one haemodialysis patient received vitamin D analogues, while none of the pre-dialysis patients were on vitamin D treatment.

Biochemical measurements

Table 2 shows the results of biochemical measurements before and after treatment. Cinacalcet markedly decreased plasma iPTH levels in both haemodialysis and pre-dialysis patients, but did not affect other parameters including serum calcium, phosphorus and alkaline phosphatase levels. One haemodialysis patient in the cinacalcet group, who admitted non-compliance...
with treatment, showed no significant change in plasma iPTH level at the end of the study (before, 1283 pg/ml; after, 1255 pg/ml).

The serum calcium levels were not different from the baseline level at the end of cinacalcet treatment because calcium supplementation was added or the dosage of vitamin D analogues was increased when hypocalcaemia was observed. When the lowest serum calcium levels after cinacalcet treatment for each patient were calculated, there was a significant decrease in cinacalcet-treated patients (7.7±0.8 mg/dl, range 6.4–8.7, \( P < 0.01 \) vs baseline levels). Placebo, as expected, did not significantly affect any parameters.

Bone mineral densitometry studies

The results of bone mineral densitometry studies are listed in Table 3. Cinacalcet treatment significantly increased both BMD and T-score of the proximal femur, while placebo treatment was associated with a significant decrease in the proximal femur BMD. There were no differences in lumbar spine BMD or T-score in either group. Figures 1 and 2 depict the results of individual patient proximal femur and lumbar spine BMD measurements before and after treatment. All patients in the cinacalcet group except the non-compliant patient had an increase in proximal femur BMD, while most patients in the placebo group had a decrease in BMD. The changes in lumbar spine BMD were mixed.

To evaluate the correlation between the changes in BMD and the changes in iPTH, we plotted the former against the latter of all 14 patients. Figure 3A shows that the change in the femur BMD correlates well with the change in the iPTH (\( R^2 = 0.39, \ P < 0.05 \)), while no correlation was found between the lumbar spine BMD and the iPTH (Figure 3B).

Figure 4 shows the percentage change in BMD in haemodialysis patients. The non-compliant patient was removed from this analysis. Cinacalcet treatment was associated with a 2.2±1.1% increase in proximal femur BMD, while placebo was associated with a 1.9±2.5% decrease (\( P < 0.05 \)). Again, the lumbar spine BMD did not show any significant changes in either group.

Discussion

In this study, we report for the first time that cinacalcet treatment increases the proximal femur BMD in patients with secondary hyperparathyroidism.
In contrast, when secondary hyperparathyroidism is not effectively treated, there is a progressive loss of the proximal femur BMD. On average, our haemodialysis patients with persistent secondary hyperparathyroidism lose \( \frac{1}{2} \% \) mineralized bone in the proximal femur and lumbar spine in 6 months. As a comparison, elderly women aged 60–75 years lose 0.2% in the lumbar spine and 1.1% in the total proximal femur per year [12]. Cinacalcet treatment for 6 months not only halted bone loss, but resulted in a 2% increase in mineralized bone in the proximal femur, but did not stop the bone loss in the lumbar spine. These data suggest that cinacalcet may protect cortical bone in patients with secondary hyperparathyroidism.

Cinacalcet appears to have a preferential effect on the femur over the lumbar spine. The proximal femur contains both cortical and trabecular bone, while the vertebrae are primarily composed of trabecular bone. Hyperparathyroidism is characterized by a preferential loss of cortical bone [13]. Cortical thinning is frequently found in asymptomatic primary hyperparathyroidism patients [14] and in patients with early secondary hyperparathyroidism due to kidney disease [15]. Ilium bone biopsy in patients with osteitis fibrosa showed

**Fig. 1.** Changes in femur bone mineral density of an individual patient after cinacalcet (A) and placebo (B) treatment. Means (X) and SDs (bars) are indicated. Solid lines, haemodialysis patients; dashed lines, pre-dialysis patients. Femur bone mineral density was significantly increased after cinacalcet treatment (n = 8), but decreased after placebo treatment (n = 6, both \( P < 0.05 \)).

**Fig. 2.** Changes in lumbar spine bone mineral density of an individual patient after cinacalcet (A) and placebo (B) treatment. See legend of Figure 1.

**Fig. 3.** Plots of changes in femur (A) and lumbar spine (B) bone mineral density against changes in intact PTH levels. Data include both cinacalcet and placebo patients (n = 14). There is a correlation between changes in femur bone mineral density and changes in iPTH (\( P < 0.05 \)), but not between changes in lumbar spine bone mineral density and iPTH.

**Fig. 4.** Changes in femur and lumbar spine bone mineral density in haemodialysis patients after 6 months treatment with cinacalcet (n = 5) and placebo (n = 4).
a 45% reduction in mineralized cortical bone, but a 36% increase in mineralized trabecular bone volume [13]. The fact that PTH has a preferential effect on cortical bone may explain why suppression of PTH by cinacalcet resulted in an increase in femur BMD, but not in lumbar spine BMD. Improvement of BMD in cortical bone by calcimimetics in secondary hyperparathyroidism has been reported previously in animal studies. Wada et al. [16] have demonstrated that NPS-R-568, a prototype of cinacalcet, when given daily increased not only BMD in cortical bone, but also stiffness at the femoral midshaft in uraemic rats. Continuous infusion of NPS-R-568, however, does not improve bone mass. It is likely that daily oral administration of a calcimimetic results in a cyclic decline in PTH that increases bone density [17].

Although cinacalcet treatment is considered as ‘medical parathyroidectomy’, the effects of cinacalcet on BMD are different from those of surgical parathyroidectomy. After parathyroidectomy in patients with end-stage renal disease, lumbar and femoral BMD increases by 22 and 14%, respectively, in 6 months [18]. There are several possibilities to explain the differences in magnitude and sites of BMD changes between parathyroidectomy and cinacalcet treatment. Parathyroidectomy markedly reduces PTH levels, usually to normal or near normal levels [18], while the trough levels of PTH after cinacalcet treatment in our study remained elevated (Table 2). Parathyroidectomy causes a constant level of PTH, while cinacalcet treatment generates cyclic changes of the PTH level. In addition, it is possible that cinacalcet may have direct effects on the skeletal system. Although initial results were controversial, recently, the calcium-sensing receptor has been identified in freshly isolated fetal rat calvarial cells, and in bone tissues [19,20]. Furthermore, activation of the calcium-sensing receptor in osteoblasts is associated with increased cell survival, proliferation and osteoblast differentiation markers [19,20]. Further studies, particularly with bone histomorphometry before and after cinacalcet treatment, may shed light on the mechanisms of different effects of cinacalcet on cortical and trabecular bone.

Although our study is limited by the small number of patients and by unmatched patients between the cinacalcet and placebo groups, the findings of this pilot study are significant. Our study is a prospective, double-blind, longitudinal study. Each patient serves as his/her own control. The DEXA scans were performed and analysed before data were unblinded, therefore potential bias was avoided. Our study provides important preliminary information of cinacalcet effects on the proximal femur BMD in patients with secondary hyperparathyroidism. With the increase in BMD, it is possible that cinacalcet-induced hypocalcaemia is related to a decrease in calcium efflux from the cortical bone tissue. Further, larger scaled and longer term studies are needed to confirm our findings and to verify whether cinacalcet has different effects on trabecular and cortical bone.

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