Marked increase in bone formation markers after cinacalcet treatment by mechanisms distinct from hungry bone syndrome in a haemodialysis patient

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Case Report

A 59-year-old female who was on dialysis due to diabetic nephropathy was referred to our hospital for severe hyperparathyroidism refractory to intravenous vitamin D receptor activator treatment. With subsequent cinacalcet hydrochloride treatment, parathyroid hormone (PTH) levels were only slightly suppressed. However, progressive increases were observed in serum alkaline phosphatase (ALP) and bone-specific alkaline phosphatase (BAP) levels with mild hypocalcaemia. A bone biopsy, obtained immediately before surgical parathyroidectomy after 3 months of cinacalcet treatment, revealed no disappearance of osteoclasts. These data suggest that cinacalcet hydrochloride treatment may induce a marked promotion of bone formation by mechanisms distinct from hungry bone syndrome that usually develops after parathyroidectomy.

Keywords: bone formation; cinacalcet hydrochloride; secondary hyperparathyroidism

Introduction

Cinacalcet hydrochloride is a new class of drugs for the treatment of severe secondary hyperparathyroidism in haemodialysis patients. It has also been reported that successful suppression of parathyroid hormone (PTH) levels results in a decrease in serum markers for bone formation [1,2].

Here, we report a case of a dialysis patient presenting with severe hyperparathyroidism, who was treated with cinacalcet hydrochloride. Without significant suppression or further increases in PTH levels, marked and progressive increases in serum markers for bone formation were observed. Bone histology did not support the development of hungry bone syndrome, as was presumed in previous cases.

Case report

A 59-year-old female with diabetic nephropathy was referred to our hospital for bone pain. She was on dialysis therapy three times a week for 9 years. She had severe hyperparathyroidism (whole PTH level, 904 pg/mL; normal, 9–39 pg/mL) with a single enlarged parathyroid gland (16 mm × 15 mm × 19 mm). Although intensive intravenous vitamin D receptor activator (VDRA) treatments were performed several years ago, secondary hyperparathyroidism progressed. The dose of vitamin D was decreased because of concomitant hypercalcaemia. Although 22-oxacalcitriol (OCT) was administered at a dose of 2.5 μg twice a month since January 2007, OCT was stopped in August 2007. Because of the progression of secondary hyperparathyroidism, OCT was started again at a dose of 10 μg once a week since October 2007. However, OCT was stopped in February 2008. Although calcium carbonate was administered at a dose of 1.5 g/day, no phosphate binder was administered since January 2007.

While planning a surgical parathyroidectomy that was scheduled to be conducted in the near future, cinacalcet hydrochloride was started at a dose of 25 mg/day and was finally increased to 75 mg/day. Cinacalcet hydrochloride therapy induced a mild decrease in the patient’s serum calcium and phosphate levels. PTH levels also decreased slightly, whereas serum alkaline phosphatase (ALP) levels (normal: 109–321 IU/L) increased significantly and progressively after the start of cinacalcet treatment, as shown in Figure 1. Serum bone-specific alkaline phosphatase (BAP) levels also significantly increased from 295 U/L to 995 U/L (normal: 9.6–35.4 U/L) during the therapy. The patient had no evidence of bone fracture by x-ray imaging. There was no difference in bone scintigraphies obtained before and after 3 months of initiating cinacalcet therapy. On the other hand, serum bone resorption marker type I collagen cross-linked N-telopeptide (NTx) levels were significantly high (1058.4 nmol BCE/L; normal, 10.7–20.4 nmol BCE/L) after 3 months of initiating cinacalcet therapy.
We performed surgical parathyroidectomy 3 months after the start of cinacalcet treatment. Four glands were removed and the smallest gland that weighed 100 mg was autotransplanted into the forearm. During the operation, an iliac bone biopsy was performed before removing the parathyroid tissue to identify the cause of elevation of serum ALP and BAP levels. The bone biopsy specimen demonstrated osteitis fibrosa (fibrosis volume/tissue volume 21.4%) and defective mineralization (osteoid volume/bone volume 29.1%) (Figure 2A). With regard to bone formation parameters, osteoblast surface/bone surface (BS) increased (25.3%). The bone formation rate (BFR)/BS also increased to 0.094 m³/m²/year (normal: 0.015 ± 0.008 m³/m²/year). However, we could not measure BFR precisely due to blurred tetracycline labels. Multinucleated osteoclasts resorbing mineralized bone were observed, in contrast to the mechanisms observed in hungry bone syndrome after parathyroidectomy (Figure 2B). Staining for aluminium was negative and she had never been treated with aluminium gels.

After parathyroidectomy, serum PTH levels decreased immediately to levels below the detection limit. In addition, the patient reported the disappearance of bone pain. Serum ALP levels decreased slowly and returned to a normal range at 6 months after parathyroidectomy. At that time, serum calcium levels were 8.5 mg/dL, serum phosphate levels were 3.8 mg/dL and serum whole PTH levels were 25.1 pg/mL.

Discussion

Cinacalcet hydrochloride reduces serum PTH levels by direct action in the parathyroid calcium-sensing receptor, therefore decreasing bone formation markers in haemodialysis patients [1,2]. Nevertheless, in a recent report of a clinical trial, it has been shown that serum BAP levels increase early after the start of cinacalcet treatment [2,3]. This temporary increase of BAP was assumed to be a result of hungry bone syndrome without a bone biopsy. Although the development of hungry bone syndrome by cinacalcet was previously reported in two reports [4,5], the authors failed to describe the changes in bone formation markers after the administration of cinacalcet. Typical hungry bone syndrome develops after surgical parathyroidectomy and is characterized by hypocalcaemia and a temporary increase in bone formation. According to another recent report, osteoclasts disappear immediately after parathyroidectomy [6]. Bone histology of this particular case did not support the development of hungry bone syndrome seen after parathyroidectomy.

In the present case, neither the progression of hyperparathyroidism nor the sudden decrease of PTH level, as in spontaneous infarction, was observed during cinacalcet treatment. We could not find any evidence of bone fracture by x-ray or in changes of bone scintographies. Although we could not completely rule out the possibility of microfractures, we hypothesized that bone formation is possibly enhanced as a result of cinacalcet treatment by unknown mechanisms. We failed to demonstrate the...
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pathomechanism of a bone biopsy clearly because the bone biopsy specimen was taken only at the end of the cinacalcet treatment and not prior to treatment.

Cinacalcet reduces serum PTH levels maximally 2–4 h after administration. Therefore, cinacalcet induces daily fluctuation of serum PTH levels, which differs from VDRA treatments. As previously reported, PTH (1–34) has different effects on bone mass when administered by intermittent injections or by continuous infusion [7]. Furthermore, it has been suggested that intermittent decreases in serum PTH levels by oral administration of calcimimetics have an anabolic-like effect on the bones, whereas continuous suppression of PTH by calcimimetics infusion does not have a similar effect [8]. Therefore, we conclude that daily fluctuations of PTH, as induced by cinacalcet treatment, may have promoted bone formation.

Osteoblasts express calcium-sensing receptors. It has been shown that high extracellular ionized calcium concentration stimulation induces mitogenic action of osteoblasts via calcium-sensing receptors [9]. However, the calcium-sensing receptor in osteoblasts may be different from parathyroid [10]. Therefore, further studies will be necessary to clarify whether cinacalcet has direct effects on osteoblasts.

The bone histology in our case also showed defective mineralization. Hypovitaminosis D probably induced defective mineralization because serum vitamin D levels at bone biopsy were low [1,25(OH)2D3 level, 5.6 pg/mL; normal, 20–60 pg/mL; 25(OH)D3 level, 21 ng/mL; normal, 7–41 ng/mL]. However, since hypovitaminosis D may be recognized before the start of cinacalcet treatment, the significance of hypovitaminosis D for bone formation markers in this case is unclear.

In summary, we have reported a case with a marked increase of serum markers for bone formation due to cinacalcet treatment. The mechanism responsible for bone formation was distinct for hungry bone syndrome. We concluded that the fluctuation of PTH levels may have promoted bone formation.

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References

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