Restoration of reversed whole PTH/intact PTH ratio and reduction in parathyroid gland vascularity during cinacalcet therapy for severe hyperparathyroidism in a uraemic patient

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Restoration of reversed whole PTH/intact PTH ratio and reduction in parathyroid gland vascularity during cinacalcet therapy for severe hyperparathyroidism in a uraemic patient

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Abstract

Parathyroid hormone (PTH) levels measured with the intact PTH assays are generally higher than those measured with the whole PTH assay; however, rare exceptions to this rule have been reported in patients with severe hyperparathyroidism associated with N-PTH overproduction. We report a haemodialysis patient with severe secondary hyperparathyroidism, in whom abnormally higher whole PTH levels than intact PTH levels were normalized during cinacalcet therapy. Moreover, we observed a marked reduction in parathyroid gland vascularity during this treatment. Our findings suggested that increased sensitivity of the parathyroid calcium sensing receptor by calcimimetics may modulate the secretion or truncation of N-PTH or other PTH molecules that can be detected by the whole PTH assay but not by the intact PTH assays.

Keywords; cinacalcet hydrochloride, intact PTH assay, N-PTH, whole PTH assay

Introduction

Parathyroid hormone (PTH) levels measured with the second-generation PTH assays, also called intact PTH assays, are generally higher than those obtained with the third-generation PTH assays such as the whole PTH assay or bio-intact PTH assay. This is because intact PTH assays cross-react with large C-terminal fragments, whereas the whole PTH assay is more specific for measuring PTH (1–84), due to its very proximal 1–4 epitope (1). Usually, the ratio of whole PTH/intact PTH is between 0.6 and 0.7 in dialysis patients (2). It has been reported that this ratio can be reduced by therapy with intravenous active vitamin D analogues (3) but not be modified by calcimimetic therapy (4).

Rarely, abnormally higher whole PTH levels than intact PTH levels have been observed in patients with severe hyperparathyroidism associated with overproduction of N-PTH (5–9). This new molecular form of PTH is detectable by the whole PTH assay, but is less reactive in intact PTH assays, particularly in the Total intact PTH assay using a detection antibody against the 12–18 epitope rather than the Elecsys intact PTH assay using a detection antibody against the 26–32 epitope (10). These findings suggest that N-PTH may be modified in the 15–20 amino acid region (11). Theoretically, it can be assumed that the whole PTH assay can react with PTH (1–84) and N-PTH; the Total intact PTH assay can react with PTH (1–84) and PTH (7–84); and the Elecsys intact PTH assay can react with PTH (1–84), PTH (7–84), and N-PTH in partial. Although still unclear, previous case studies have suggested that N-PTH may exhibit a significant biological effect on bone turnover (7–9).

In a previous study, we have reported five haemodialysis patients with reversed whole PTH/intact PTH ratio associated with severe hyperparathyroidism (9). Here we report the effect of cinacalcet hydrochloride in one of these patients, in whom the reversed whole PTH/intact PTH ratio normalized during amelioration of secondary hyperparathyroidism by this therapy.

Case

A 61-year-old man had been receiving haemodialysis since November 2001 for end-stage renal disease due to diabetic nephropathy. The clinical course of the patient before initiating cinacalcet therapy was reported elsewhere (9). In brief, the patient developed severe secondary hyperparathyroidism refractory to intravenous maxacalcitol treatment in December 2007, and we found that whole PTH levels (801 pg/ml, Whole PTH; Scantibodies Laboratories, Santee, CA, USA; normal range, 5–39 pg/ml) were abnormally higher than Total intact PTH levels (244 pg/ml, Total PTH; Scantibodies Laboratories; normal range, 14–66 pg/ml) and Elecsys intact PTH levels (612 pg/ml, Elecsys PTH; Roche Diagnostics, Mannheim, Germany; normal range, 15–65 pg/ml). Serum bone-specific alkaline phosphatase levels increased to 54 U/l, indicating high bone turnover. Power Doppler ultrasonography revealed an enlarged parathyroid gland (23.2 × 21.1 × 21.2 mm) with hypervascularity in the right thyroid parenchyma (Figure 1).

We initiated cinacalcet hydrochloride (Regpara®, Kyowa Hakko Kirin Co., Ltd.,

Tokyo, Japan) at a daily dose of 25 mg in January 2008 when Total intact PTH, Elecsys intact PTH and whole PTH levels were 219, 628 and 907 pg/ml, respectively. The dose of maxacalcitol remained unchanged after the initiation of cinacalcet therapy. After 4 weeks of cinacalcet therapy, serum Elecsys intact PTH and whole PTH levels effectively decreased with normalization of the reversed whole PTH/intact PTH ratio (Elecsys intact PTH, 165 pg/ml; whole PTH, 143 pg/ml). A corresponding result was also obtained in the Total intact PTH assay after 10 weeks of cinacalcet therapy (Total intact PTH levels, 43 pg/ml; Elecsys intact PTH, 55 pg/ml; whole PTH, 38 pg/ml). More interestingly, a neck ultrasonography revealed significantly reduced vascularity of the enlarged gland (Figure 1). Serum bone-specific alkaline phosphatase levels gradually decreased to 24 U/l in June 2008.

However, cinacalcet therapy had to be discontinued due to its adverse gastrointestinal effect. Subsequently, serum levels of intact PTH and whole PTH increased again with revival of the reversed whole PTH/intact PTH ratio (Total intact PTH levels, 195 pg/ml; Elecsys intact PTH, 358 pg/ml; whole PTH, 391 pg/ml). Serum bone-specific alkaline phosphatase levels also increased to 47 U/l, and the enlarged parathyroid gland became hypervascular again (Figure 1).

Discussion

Cinacalcet hydrochloride, an allosteric modulator of the calcium sensing receptor (CaSR), is widely accepted for the treatment of secondary hyperparathyroidism (12). This agent enhances sensitivity of the parathyroid CaSR to extracellular calcium ions and thereby inhibits secretion of PTH, even in patients with advanced parathyroid hyperplasia. However, the effect of cinacalcet therapy on the regulation of PTH molecular forms remains unclear.

Several studies have shown that extracellular calcium ions regulate the generation of N-terminally truncated forms of PTH degraded from PTH (1–84) (13). It is thus reasonable to surmise that calcimimetics may also regulate this process. In fact, a clinical study by Martin et al. reported that although response to cinacalcet is nearly identical for intact PTH and bio-intact PTH levels, the ratio of PTH (1–84)/non-PTH (1–84) was lower in patients receiving cinacalcet compared with control subjects (4). More recently, Valle et al. reported that cinacalcet shifts the inverse sigmoidal curve of PTH (1–84)/non-PTH (1-84) ratio versus calcium to the left (i.e. less calcium is required to reduce the ratio) (14). These findings may underscore the possibility that cinacalcet facilitates the N-terminal truncation of PTH (1–84) induced by extracellular calcium ions.

In this context, the next point of issue is whether N-PTH secretion could be regulated by CaSR stimulation with extracellular calcium ions or calcimimetic agents. In the present case, cinacalcet therapy effectively decreased intact PTH and whole PTH levels together with normalization of the reversed whole PTH/intact PTH ratio. Withdrawal of the drug, however, revived the reversed whole PTH/intact PTH ratio concomitantly with a rebound in PTH levels. The clinical course of our patient suggests that calcimimetics pharmacologically suppress or truncate PTH molecules that can be detected by the whole PTH assay but not by the intact

PTH assays, including N-PTH as a possibility. In healthy subjects, in whom N-PTH represents 8% of whole PTH, acute induction of hypercalcaemia results in a decrease in N-PTH (15). It is possible that induction of hypercalcaemia or administration of calcimimetics may also decrease circulating N-PTH levels even in patients with its overproduction. This is not in line with the previous study on patients with parathyroid carcinoma, where cinacalcet effectively reduced serum calcium levels but not N-PTH and PTH (1-84) levels (6). However, in these patients, calcimimetics may have directly acted on the CaSR in the functional kidney and reduced calcium concentrations, which may, in turn, have decreased the allosteric effect of calcimimetics on the CaSR of parathyroid carcinoma. Further studies are required to elucidate the effect of calcimimetics on the regulation of PTH molecular forms in patients with hyperparathyroidism.

Interestingly, we also observed a marked reduction in parathyroid gland vascularity during cinacalcet therapy. Although similar findings have been reported in a recent study (16), this is the first case showing that such a reduction in vascularity was partly reversible when cinacalcet therapy was discontinued. These findings suggest that reduced vascularity may be associated with reduced parathyroid activity caused by cinacalcet therapy. However, the precise mechanism of this phenomenon is unclear and future experimental studies should investigate the direct effect of calcimimetics on parathyroid gland vascularity.

Finally, it should be noted that we did not analyse the patient's sera by HPLC fractionation. Thus, we could not directly confirm the presence of N-PTH in the circulation of the patient. However, previous studies have consistently shown that the reversed whole PTH/intact PTH ratio is associated with high HPLC peak of N-PTH (5–7). Furthermore, the findings that in our patient Elecsys intact PTH levels were higher than Total intact PTH levels support the possibility of N-PTH overproduction, because N-PTH has been shown to react well with the Elecsys PTH assay compared with the Total PTH assays (10,11). Additional HPLC studies are needed to confirm these possibilities that were raised in the present case.

In conclusion, we report the first case of severe parathyroid hyperplasia in whom normalization of the reversed whole PTH/intact PTH ratio was induced by cinacalcet therapy. The response to cinacalcet therapy in our patient raises the possibility that calcimimetics may pharmacologically modulate the secretion or truncation of N-PTH or other PTH molecules that can be exclusively detected by the whole PTH assay. Given the possibility of its biological activity, future N-PTH studies will produce useful insight into treatments for parathyroid disease.

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Conflict of interest statement. M.F. has received lecture fees and a grant from Kyowa Hakko Kirin, Co. Ltd, Japan and was a member of advisory committee on clinical trials of cinacalcet in Japan. The other authors declared they have no competing interests.

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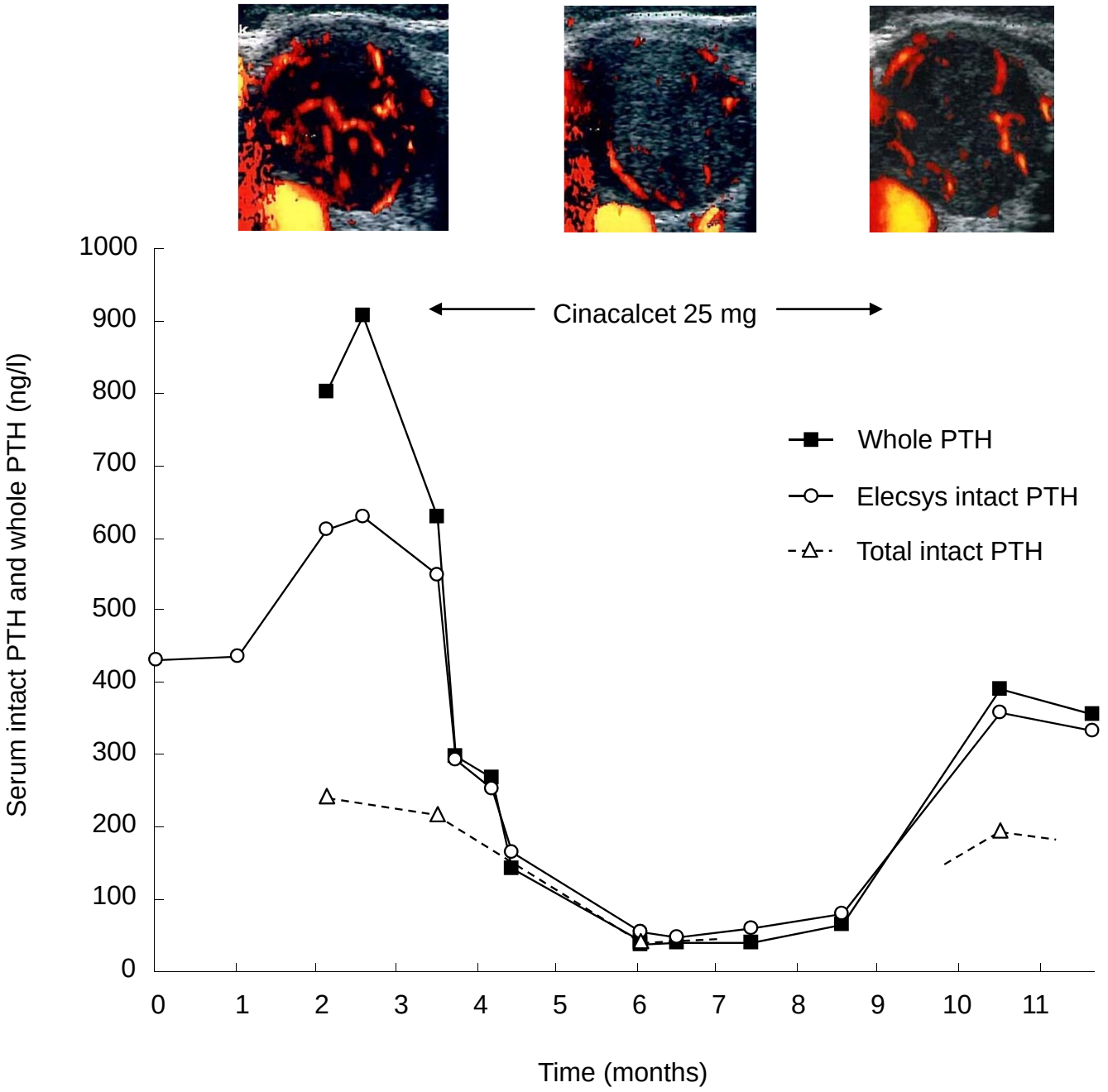
Figure Legend

Figure 1. The patient's power Doppler ultrasonography and changes in serum intact and whole PTH levels before and after cinacalcet therapy. Initially, whole PTH levels were abnormally higher than intact PTH levels that were detected by the Total PTH assay and the Elecsys PTH assay. A neck ultrasonography revealed a severely enlarged parathyroid gland with hypervascularity. After 4 weeks of cinacalcet therapy, serum intact PTH and whole PTH levels effectively decreased with normalization of the reversed whole PTH/intact PTH ratio. However, withdrawal of cinacalcet resulted in a re-increase of intact PTH and whole PTH levels and a revival of the reversed whole PTH/intact PTH ratio. Although a reduction in the vascularity of the enlarged gland was observed during cinacalcet therapy, it became hypervascular again after cessation of this therapy.


Cinacalcet 25 mg
Whole PTH
Elecsys intact PTH
Total intact PTH
Serum intact PTH and whole PTH (ng/l)
Time (months)
0
100
200
300
400
500
600
700
800
900
1000
0
1
2
3
4
5
6
7
8
9
10
11