IRMA (whole PTH) is a more useful assay for the effect of PTH on bone than the Allegro intact PTH assay in CAPD patients with low bone turnover marker

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Abstract

The common intact parathyroid hormone (i-PTH) assay detects not only PTH (1–84) but also the PTH (7–84) fragment. Recently, it was reported that the PTH (7–84) fragment is an antagonist to the biological action of PTH (1–84). It was also reported that the accumulation of the PTH (7–84) fragment plays a role in skeletal resistance in haemodialysis (HD) patients. However, the role of accumulation of the PTH (7–84) fragment in continuous ambulatory peritoneal dialysis (CAPD) patients, with a different clearance rate from that of HD patients, is still unclear. Therefore, we have measured only the active form of PTH (1–84) using a new method of whole PTH (w-PTH) assay in 20 CAPD patients (15 male and five female; mean age 51.0 ± 13.0 years). The mean w-PTH value was 88.5 ± 14.2 pg/ml in CAPD patients, which was 42.1% of i-PTH (152.6 ± 23.6 pg/ml). The approximate value of w-PTH was calculated using the following formula (w-PTH = 0.58 × i-PTH – 0.4, R² = 0.94). PTH (7–84) fragment was calculated by the formula i-PTH – w-PTH. The PTH (7–84) fragment/w-PTH ratio as an index of skeletal resistance, and serum alkaline phosphatase activity as an osteoblastic marker were negatively correlated (P = 0.02). From these results, we concluded that the i-PTH level as calculated using the common assay method might lead to an overestimation of parathyroid function and bone turnover in CAPD patients similarly to HD patients. The w-PTH assay may be useful for more precise evaluation of PTH activity in end-stage renal disease patients.

Keywords: CAPD; end-stage renal disease; low turnover bone disease; PTH (7–84)/PTH (1–84) ratio; skeletal resistance; whole PTH assay

Introduction

Renal osteodystrophy is a major problem in patients with end-stage renal disease (ESRD), and the most harmful form is osteitis fibrosa caused by the secondary hyperparathyroidism (2HPT).

In treating 2HPT, it has been observed that the target concentration of serum intact parathyroid hormone (i-PTH) can be 3- to 5-fold the normal concentration for prevention of low turnover bone disease [1]. The effect of a deficiency of i-PTH on bone is called ‘skeletal resistance to PTH in uraemic patients’. It was reported recently that the i-PTH levels determined by the Allegro i-PTH commercial radioimmunoassay (RIA) kit were misleading because of significant overestimation of the parathyroid function in haemodialysis (HD) patients [2].

Slatopolsky et al. demonstrated that intracellular production of a fragment(s) of the PTH 1–84 molecule occurred in the parathyroid gland, thus producing a non-(1–84) PTH fragment (most probably, the 7–84 PTH) [3]. In addition to the biologically active 1–84 PTH molecule, this truncated non-1–84 PTH fragment is also present in the blood as well as in parathyroid cells of uraemic patients. RIA is used to measure i-PTH as well as 1–84 PTH and 7–84 PTH. It has also been shown that the 7–84 PTH fragment has an antagonistic effect on the biological activity of 1–84 PTH in rats by causing a decrease in both the calcemic and phosphaturic responses to 1–84 PTH [3]. Thus, the accumulation of 7–84 PTH resulting from renal dysfunction is proposed as an explanation for ‘skeletal resistance to PTH’.
Recently, a new, third-generation immunoradiometric assay [IRMA or whole PTH (w-PTH) assay] has been developed, which can detect the 1–84 PTH (biologically active form) without cross-reacting with a large C-terminal PTH fragment such as 7–84 PTH [4].

In HD patients, the non-1–84 PTH as the 7–84 PTH was reported to account for up to 55% of i-PTH assay immunoreactivity, which might influence the pathophysiology of ‘uraemic skeletal resistance’ [5]. However, there is no report regarding the 7–84 PTH fragment in continuous ambulatory peritoneal dialysis (CAPD) patients. The ESRD patients who undergo CAPD are known to have a high frequency of low turnover dynamic bone disease. The accumulation of 7–84 PTH might be responsible for this because of the increase in ‘uraemic skeletal resistance’ in CAPD patients.

Methods and Results

In the present study, we attempted to prove this hypothesis by investigating the relative concentration of 7–84 PTH compared with 1–84 PTH and a bone marker in CAPD patients. Twenty CAPD patients with i-PTH concentration < 300 pg/ml were selected as subjects, and all provided informed written consent. All subjects were treated with low calcium dialysate PD4 (Baxter Co). The i-PTH assay was determined by the Allegro ‘intact’ PTH RIA kit, and the w-PTH was determined using the new IRMA (CAP assay: Scanti Body Co. Ltd). The PTH-7–84 fragment was recognized by the difference between i-PTH and w-PTH. Alkaline phosphatase (ALP) concentration was measured by standard methodology to estimate bone turnover of osteoblasts.

The results of the w-PTH assay were always lower than that of the i-PTH assay in all patients. The mean w-PTH was 88.5 ± 14.2 pg/ml, which was 42.1% lower than the i-PTH (152.6 ± 23.6 pg/ml). However, a good positive correlation between i-PTH and w-PTH is shown in the following results: w-PTH = 0.58 × i-PTH–0.35 ($R^2 = 0.94$), which shows that the presence of biologically active 1–84 PTH can be assumed from the i-PTH result without severe 2HPT. Conversely, we were not able to observe a significant positive correlation between 1–84 PTH and 7–84 PTH in uremic patients with severe 2HPT (data not shown). The 7–84 PTH/1–84 PTH ratio was ~0.74, which is similar to the results in HD patients reported previously [3]. So far, several reports have shown that ALP is a good bone metabolic osteoblastic marker in ESRD patients [6]. In the present study, we found a negative relationship between the 7–84 PTH/1–84 PTH ratio and the serum ALP results: ALP = 335.0–151.3 × (7–84 PTH w-PTH) ($P = 0.02$) (Figure 1). PTH acts on bone via PTH receptors on osteoblasts. Our results suggest that 7–84 PTH may affect the skeletal response to 1–84 PTH by competitive inhibition of the PTH receptor on the osteoblast.

In conclusion, the i-PTH concentration derived from the second-generation PTH RIAs might be misleading through overestimation of both the parathyroid function and bone turnover in CAPD patients, as in HD patients. The new IRMA (w-PTH assay) has more useful diagnostic potential than the present i-PTH assay for PTH biological activity on osteoblastic bone metabolism in ESRD patients without severe hyperparathyroidism undergoing CAPD.

Fig. 1. Relationship between the 7–84 PTH/1–84 PTH ratio and serum ALP concentration. The 7–84 PTH fragment was calculated by the formula i-PTH–w-PTH. Negative correlation was observed between the 7–84 PTH fragment (1–84 PTH (w-PTH)) ratio and serum ALP concentrations [s-ALP = 335.0–151.3 × (7–84 PTH w-PTH); $P = 0.02$].

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<th>7–84-PTH (CIP)</th>
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<td>Y=335.0–151.3X</td>
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<td>$R^2=0.27$ P=0.044</td>
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**References**