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Letters

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The administration of cinacalcet hydrochloride just before a haemodialysis session suppresses the transient rise in intact parathyroid hormone induced by a low-calcium dialysate: when should cinacalcet hydrochloride be administered?

Sir,

Parathyroid cells can sense small changes in plasma calcium ion (Ca^{2+}) levels by virtue of a cell surface calcium receptor (CaR). Calcimimetics such as R-568 and cinacalcet hydrochloride (cinacalcet) are positive allosteric modulators that activate CaRs and thereby suppress parathyroid hormone (PTH) secretion [1]. Clinical trials have demonstrated that cinacalcet treatment lowers not only the serum PTH but also the serum Ca levels in haemodialysis (HD) patients with secondary hyperparathyroidism (2HPT) [1]. In clinical use, the dosage of cinacalcet is not restricted by the time of the HD session because HD does not affect the pharmacokinetics of this compound [2]; this is attributed to cinacalcet's high binding capacity to plasma proteins.

The use of a so-called low-Ca dialysate (2.5 mEq/L) can increase the usage opportunities and doses of vitamin D drugs and Ca-containing phosphate binders. During each HD session, diffusion is the main route of Ca^{2+} transport, and the rate of passage of a given dialysate Ca^{2+} across the membrane depends on the direction and magnitude of its concentration gradient between the blood and dialysate [3]. Therefore, many HD patients show a transient elevation in serum PTH levels in response to the decreased plasma Ca^{2+} levels at the end of every HD session with a low-Ca dialysate [4]. In our experience, injection of calcitriol or its analogue (maxacalcitol) just before the HD session has failed to suppress this elevation in PTH levels. Here, we report that if cinacalcet is administered just before an HD session, it successfully suppresses the increase in the intact PTH (i-PTH) induced by a low-Ca dialysate.

The subjects of this study were 14 HD patients (9 female subjects) with a mean age of 58.5 ± 9.0 (SD) years and an HD vintage of 19.8 ± 9.4 (SD) years. All the patients had been diagnosed as 2HPT with parathyroid gland (PG) nodular hyperplasia on the basis of the findings of ultrasonography (maximum PG volume ≥ 500 mm^3 or maximum PG diameter ≥ 10 mm) and had been treated with intravenous calcitriol or maxacalcitol. Before the cinacalcet treatment started, an HD session (2.5 mEq/L Ca dialysate, 4 h in 10 patients and 4.5 h in 4 patients) significantly decreased the plasma Ca^{2+} levels and increased the serum i-PTH levels (Figure 1A). One week after the cinacalcet treatment (25 mg, daily), the basal levels of the serum i-PTH and plasma Ca^{2+} decreased (Figure 1B, Pre-HD). Cinacalcet (25 mg) administered just before the HD session caused a significant further decrease in the serum i-PTH levels without affecting the plasma Ca^{2+} levels (Figure 1B, Post-HD). During the subsequent cinacalcet treatment (25 mg, daily, for another 3 weeks), we increased the dose of calcitriol or maxacalcitol to prevent hypocalcaemia. Consequently, the plasma Ca^{2+} levels recovered to the baseline levels and the serum i-PTH levels decreased further (Figure 1C, Pre-HD).

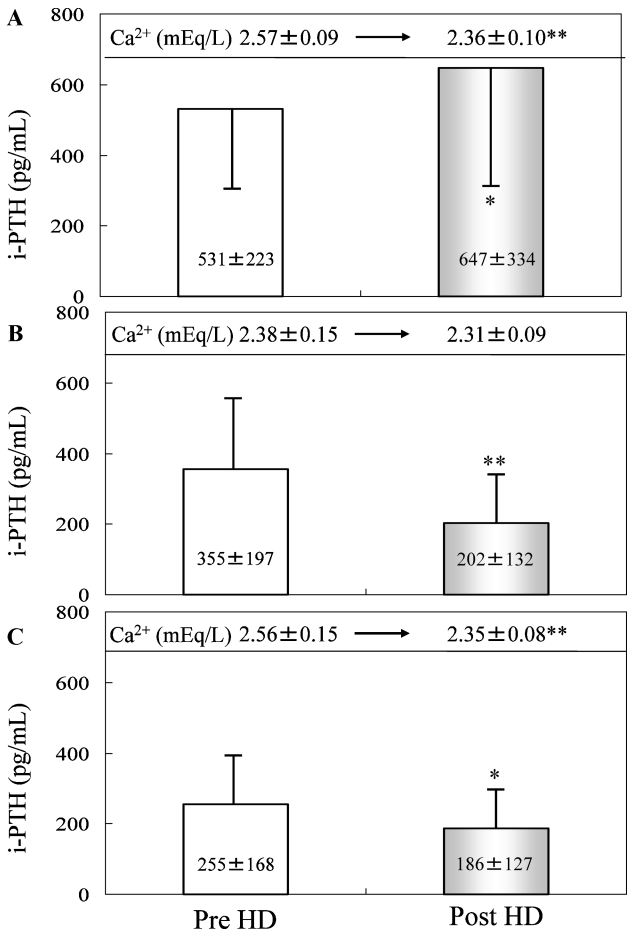

Fig. 1. Plasma Ca^{2+} and serum i-PTH levels just before (Pre-HD) and after (Post-HD) an HD session (2.5 mEq/L Ca dialysate, for 4 or 4.5 h). (**A**) The changes in Ca^{2+} and i-PTH after the HD without cinacalcet. (**B**) One week after cinacalcet treatment (25 mg, daily). Cinacalcet (25 mg) was administered just before an HD session, and the Ca^{2+} and i-PTH were examined at Pre- and Post-HD. (**C**) Four weeks after the cinacalcet treatment (25 mg, daily). Cinacalcet (25 mg) was administered just before an HD session, and the Ca^{2+} and i-PTH levels were examined at Pre- and Post-HD. All data are expressed as the mean ± SD ($n = 14$). $^{*}P < 0.05$, $^{**}P < 0.01$ versus the values at Pre-HD (paired *t*-test).

Once more, the administration of cinacalcet (25 mg) just before the HD session caused a significant further decrease in the serum i-PTH levels despite a significant reduction in the plasma Ca^{2+} levels (Figure 1C, Post-HD).

Even if an elevation in PTH levels is transient, it should be avoided that basal high PTH levels increase further at the end of every HD session with a low-Ca dialysate. In addition, a transient decrease in plasma Ca^{2+} levels can stimulate not only PTH secretion but also PG cell proliferation. Over the long term, PG hyperplasias often progress from diffuse to nodular forms. We have demonstrated that calcimimetics are powerful inhibitors of PG cell proliferation in rats with 2HPT, regardless of calcimimetic-induced hypocalcaemia [1,5]. Therefore, we propose that cinacalcet should be administered just before HD sessions to prevent the hyperfunctioning of PG cells that is induced by the transient hypocalcaemia caused by a low-Ca dialysate. This seems to be reasonable because the maximal plasma concentration (C_{max}) of cinacalcet is achieved 4–6 h after its oral administration [2]. Further investigations are clearly required to determine when cinacalcet should be administered, especially in the context of bone metabolism and the gastrointestinal adverse effects.

Conflict of interest statement. Other than N.N. who is a scientist at Kirin Pharma that manufactures and sells cinacalcet in Asia, none of the authors have reported any conflict of interest.

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Vertebral fractures in patients on dialysis: a clinically relevant problem with insufficient investigation

Sir,

Chronic kidney disease mineral and bone disorder (CKD-MBD), previously denominated renal osteodystrophy [1], is a major clinical problem, with increasing prevalence and adverse outcomes, including high bone turnover associated with secondary hyperparathyroidism, low bone turnover or adynamic bone disease, cardiovascular calcifications and bone fractures. The impact of such outcomes on patient morbidity and mortality has not been fully elucidated. We would like to point out a poorly investigated subject, which we feel is of great clinical importance: vertebral fractures in CKD patients.

Studies on the prevalence of fractures in dialyzed patients have focused mainly on hip fractures, while available data on vertebral fractures remain limited and inconsistent, suggesting a prevalence very similar to that of the general population [2,3]. However, improvements in diagnostic methods could be of great importance in better estimating the incidence and prevalence of vertebral fractures [4]. We therefore advocate the adoption of the following approach: the term vertebral fracture (VF) should be used to mean any deformation of the vertebral body following a reduction of one of its dimensions beyond a given threshold (4 mm or 15%). We speak of wedge, biconcave or crush fractures (or deformities) depending on whether the reduction affects the anterior, central or posterior dimension of the vertebra, respectively (Figure 1).

At least two different approaches are suitable for identifying these fractures: one is a semiquantitative visual method, according to Genant [4], which involves an expert radiologist visually identifying the fractures and classifying them, according to the extent of the reduction in the dimension of the vertebral body, as mild (20–25%), moderate (25–40%) or severe (>40%), as illustrated in Figure 1; the other approach is a quantitative morphometric method. In particular, vertebral morphometry (VM) involves the manual or computerized measurement of the anterior, central and posterior dimensions of the dorsal and lumbar vertebral bodies (T4-L5) of the spine using conventional radiological apparatus (MRX: morphometric X-ray radiography) or densitometric apparatus (MXA: morphometric X-ray absorptiometry).

Bone mass, reflected by bone mineral density, bone strength and bone quality should be considered when evaluating bone fractures. The contribution of bone mass to bone strength is of uncertain value in patients with CKD who actually exhibit a wide spectrum of bone quality. Often, bone mineral density has been measured with dual energy X-ray absorptiometry (DEXA), but this approach has been criticized because of the lack of good correlations between DEXA and bone histology in CKD patients. In addition, findings on the correlation of DEXA BMD values to fracture risk in the CKD population are inconsistent. Moreover, in the K-DIGO position statement, there is concern that hip