

Original Article

Calcium-mediated parathyroid hormone release changes in patients treated with the calcimimetic agent cinacalcet

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Abstract

Background. The parathyroid-calcium (Ca²⁺-PTH) curve expresses modulation of parathyroid hormone (PTH) secretion by the parathyroid gland as a function of changing extracellular Ca²⁺ concentration. Patients with hyperparathyroidism (HPT) show a rightward shift of the curve compared with controls, suggesting a reduced sensitivity of parathyroid cells to Ca²⁺. Increasing the sensitivity of the parathyroid gland to extracellular Ca²⁺ by manipulation of the Ca²⁺-sensing receptor (CaR) may have therapeutic potential. Calcimimetics allosterically modify CaR and render it more sensitive to extracellular Ca²⁺, accounting for the simultaneous reduction of Ca²⁺ and PTH seen in most patients.

Methods. The Ca²⁺-PTH curve was evaluated in 10 haemodialysis patients, with baseline intact PTH levels >300 pg/ml in two haemodialysis sessions, one before and the other after (range, 9–22 weeks) cinacalcet treatment. In each session a 2-h low-dialysate Ca²⁺ concentration was used to induce hypocalcaemia and maximally stimulate PTH secretion, followed immediately by a 2-h high-dialysate Ca²⁺ concentration to induce hypercalcaemia and maximally inhibit PTH secretion.

Results. Significant decreases in ionized Ca²⁺ and intact PTH were observed following cinacalcet treatment. Cinacalcet treatment also led to a decrease in the set point for Ca²⁺ and to a leftward shift of the Ca²⁺-PTH curve. Significant differences were present in all segments of the Ca²⁺-PTH curves.

Conclusion. The pathological rightward shift of the Ca²⁺-PTH curve seen in many HPT patients may be reversed by cinacalcet treatment.

Keywords: calcimimetic; calcium sensing receptor; calcium; cinacalcet; hyperparathyroidism; parathyroid hormone; Ca²⁺-PTH curve

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Introduction

The regulation of parathyroid hormone (PTH) release in advanced chronic kidney disease is a complex process with three main components: extracellular fluid (ECF) calcium (Ca²⁺), 1,25-dihydroxyvitamin D₃ and serum phosphorus levels. Regulation of PTH secretion by Ca²⁺ is accomplished through interactions with the Ca²⁺-sensing receptor (CaR), a G protein-coupled receptor sensitive to extracellular Ca²⁺ levels [1] via acidic residues in its extracellular domain and second extracellular loop [2]. Under physiological conditions, high ECF Ca²⁺ results in decreased PTH secretion. However, in secondary hyperparathyroidism (HPT), some patients exhibit elevated PTH despite elevated ECF Ca²⁺ levels. This functional dysregulation is thought to result from down-regulation of CaR expression associated with parathyroid hyperplasia, particularly if nodular [3]. Brown *et al.* [4], studying parathyroid cells *in vitro*, used a four-parameter formula to construct the Ca²⁺-PTH curve, which expresses the modulation of PTH secretion by the parathyroid gland as a function of the variation in Ca²⁺ concentration. In the same study, Brown demonstrated a rightward shift in the curve in tissue from patients with primary or secondary HPT compared with controls, suggesting a lower sensitivity of parathyroid cells to Ca²⁺ in these patients. Malberti *et al.* [5] also documented a rightward shift of the curve and an increase in the set point with worsening of secondary HPT, while Felsenfeld *et al.* [6] showed differences in the curve and set point in dialysis patients with different forms of osteodystrophy, and found that patients with end-stage renal disease and osteitis fibrosa also showed a rightward shift of the curve. Set point abnormalities have been documented *in vivo*, both in primary HPT and in familial hypocalciuric hypercalcaemia (FHH) [7–9]. Such findings are consistent with *in vitro* results obtained in studies of dispersed parathyroid cells from patients with primary HPT, and with the described alteration in CaR expression in patients with FHH [4]. In acknowledging these findings, it should be noted that the available data are inconsistent and the view that the set point for calcium-regulated

PTH release is abnormal in secondary HPT [10] is controversial. However, set point abnormalities have been clearly documented in patients with primary HPT and those with advanced secondary HPT.

In secondary HPT, the CaR-mediated relationship between PTH and Ca^{2+} is often distorted with excessive release of PTH. This finding suggests that measures to increase the sensitivity of the parathyroid gland to extracellular Ca^{2+} may have therapeutic potential. Calcimimetics allosterically modify the CaR such that it is more sensitive to extracellular Ca^{2+} [11]. These agents have been shown to shift the Ca^{2+} -PTH curve to the left in experimental animals [11] and in some circumstances to retard parathyroid hyperplasia. The utility of cinacalcet in the treatment of secondary HPT has been demonstrated in several clinical trials [12–14]. The rapid development of simultaneous reductions of Ca^{2+} and PTH in most cinacalcet-treated patients implies that a leftward shift of the Ca^{2+} -PTH curve may have occurred, although this has not been examined systematically. The goal of the present study was to evaluate, in a group of haemodialysis patients with secondary HPT and baseline intact PTH levels >300 pg/ml, the effect of acute serum Ca^{2+} changes on the Ca^{2+} -PTH curve, Ca^{2+} and PTH secretion before and after several weeks of treatment with the calcimimetic, cinacalcet.

Subjects and methods

The study, undertaken to further evaluate the Ca^{2+} -PTH relationship, was performed in 10 stable haemodialysis patients (five females and five males) with marked secondary HPT. The mean age was 64 ± 4.7 years (range, 38–90 years), and their average length of time on dialysis was 101 ± 31.6 months (range, 6–315 months). All patients had serum intact PTH levels >300 pg/ml at the start of the study. None of the patients had received calcitriol, or other forms of vitamin D, within 3 months prior to the study. All patients used calcium carbonate as their principle phosphate binder, and haemodialysis was performed with high-flux HD (Helixone[®] FX60, Fresenius Medical Care AG & Co. KGaA, Bad Homburg, Germany). Diabetic patients were excluded. Patients were on a 4-h-3-times-per-week haemodialysis schedule. Studies were performed at the Hospital Universitario Valdecilla, Santander, Spain, and were approved by the appropriate committee for human studies. The Ca^{2+} -PTH curve was obtained twice: before receiving cinacalcet and 13 ± 1.2 weeks after treatment initiation (range, 9–22 weeks). Thus, each patient was studied in two haemodialysis sessions. In each dialysis session, a 2-h low-dialysate Ca^{2+} concentration of 1.5 mEq/l (0.75 mmol/l) was used to induce hypocalcaemia and maximally stimulate PTH secretion. In all patients, with the exception of one (patient 7), a further decrease in Ca^{2+} did not influence PTH, confirming that maximal PTH had been achieved. These data are not available for patient 7. A 2-h high-dialysate Ca^{2+} concentration of 3.5 mEq/l (1.75 mmol/l) was then used to induce hypercalcaemia and maximally inhibit PTH secretion. In all patients, a further increase in Ca^{2+} did not influence PTH, confirming that

maximal PTH inhibition had been achieved. The mean cinacalcet dose at the beginning of the second curve was 54 ± 6 mg/day (range, 30–90 mg/day). The dialysis session began at 8:00 AM and the last calcimimetic dose was given at noon on the preceding day (16–18 h before the second phase of the study). None of the patients received calcitriol or other vitamin D compounds during cinacalcet treatment. Blood was drawn at regular intervals (baseline, 30, 60, 90, 120, 150, 180, 210 and 240 min) from the beginning of the haemodialysis session to measure ionized Ca^{2+} and intact PTH.

From the data obtained during dialysis-induced hypocalcaemia [15–17] and hypercalcaemia, the following terms were defined:

- (1) Baseline PTH was the predialysis PTH level.
- (2) Maximal PTH was the highest PTH level observed in response to hypocalcaemia; the designation of maximal PTH required that an additional reduction of the serum Ca^{2+} concentration did not further increase the PTH value.
- (3) Minimal PTH was the lowest PTH level during suppression by hypercalcaemia; the designation of minimal PTH required that an additional increase of the serum Ca^{2+} concentration did not further decrease the PTH value.
- (4) The ratio of baseline to maximal PTH (baseline/maximal PTH) was multiplied by 100 to provide a percentage, which in normal volunteers is 20–25% [18]; by correcting the actual PTH for the overall capacity to produce PTH (maximal PTH), a measure of the relative degree of PTH stimulation was obtained.
- (5) The set point of Ca^{2+} was defined as the serum Ca^{2+} concentration at which maximal PTH secretion was reduced by 50% [6,19–21]. Moreover, as performed in other studies, the set point of Ca^{2+} was calculated by the method of Brown [4], according to which the set point of Ca^{2+} is the serum Ca^{2+} level at the mid-range between the minimal and maximal PTH [22,23].
- (6) The baseline serum ionized Ca^{2+} was the serum Ca^{2+} concentration at the baseline (predialysis) PTH.
- (7) The serum Ca^{2+} level at maximal PTH secretion (Ca^{2+} max) was the serum Ca^{2+} level at which maximal PTH secretion was achieved.
- (8) The serum Ca^{2+} level at minimal PTH secretion (Ca^{2+} min) was the serum Ca^{2+} level at which minimal PTH secretion was achieved.

To assess the Ca^{2+} -dependent changes, the plasma PTH concentration and the percentage of maximal PTH stimulation were plotted against the Ca^{2+} values extrapolated from the parathyroid function curve of each patient. Composite Ca^{2+} -PTH curves for each group were compiled from the individual curves [15,16,21]. Immunoreactive PTH (total intact PTH) was measured in all patients by a second-generation PTH assay (immunoradiometric assay, Scantibodies Ria kit, Scantibodies Laboratory Inc., Santee, CA, USA). Using a pooled normal serum, intra- and inter-assay variations were determined as 2.6% and 5.8%, respectively. The sensitivity of the method is 1 ng/l and normal values are <45 ng/l. During the low- and high- Ca^{2+} studies, ionized Ca^{2+} was measured at the bedside by Ca^{2+} -selective

Table 1. Ca²⁺-PTH curve parameters before and after the treatment

	Before		Difference after cinacalcet		<i>P</i> -value
	Mean	SD	Mean	SD	
Baseline ionized Ca ²⁺ (mmol/l)	1.24	0.10	-0.28	0.26	<0.001
Set point of Ca ²⁺ (mmol/l)	1.25	0.08	-0.22	0.13	<0.001
Baseline PTH (pg/ml)	1116	612	-414	303	0.002
Maximal PTH (pg/ml)	2108	896	-730	507	0.001
Minimal PTH (pg/ml)	496	240	-190	177	0.02
Ca ²⁺ max (mmol/l)	1.05	0.07	-0.185	0.12	<0.001
Ca ²⁺ min (mmol/l)	1.41	0.07	-0.22	0.11	<0.001
Baseline/maximal PTH (%)	54	16.0	7.4	17.8	0.63 (NS)

NS, not significant.

electrodes automated in a Ciba Corning 634 Ca²⁺/pH Analyzer (Ciba Corning Diagnostics Corp. Medfield, MA, USA). The normal range for ionized Ca²⁺ obtained with this method is 1.16–1.35 mmol/l).

Statistics

Data were analysed by the *t*-test for paired comparisons. Differences between more than two means were evaluated by the analysis of variance for repeated measures. A *P*-value of <0.05 was considered significant. The data are expressed as the mean ± SD.

Results

The study included 10 patients with varying underlying nephropathies, including nephroangiosclerosis (*n* = 3), tubulointerstitial nephritis (*n* = 3), polycystic kidney disease (*n* = 1) and renal hypoplasia (*n* = 1). The nephropathy remained undetermined in one patient. Males and females were equally represented and the median age was 64 years (range, 38–90 years). Dialysis was uneventful in all patients, and no patient experienced adverse events associated with calcimimetic treatment.

As shown in Table 1, significant decreases in baseline and maximal and minimal PTH levels were observed with calcimimetic therapy (*P* = 0.002, 0.001 and 0.02, respectively). Additionally, significant decreases in baseline and maximal and minimal ionized Ca²⁺ concentrations were observed with calcimimetic therapy (*P* < 0.001). The set point of Ca²⁺, defined as the Ca²⁺ concentration associated with 50% maximal PTH stimulation, decreased significantly after calcimimetic treatment (*P* < 0.001). When the Ca²⁺ set point was calculated by Brown's method [4], (maximal PTH – minimal PTH) × 0.5, similar results were observed (data not shown). The ratio of baseline to maximal PTH declined slightly, but not significantly, during treatment.

Figure 1 shows the individual Ca²⁺-PTH curves before and after calcimimetic therapy for each of the 10 patients. In Figure 2, the Ca²⁺-PTH curves before and after calcimimetic therapy are presented as PTH expressed as the percentage of maximal PTH, while in Figure 3 they are presented unadjusted.

Calcimimetic treatment led to a decrease in the baseline serum Ca²⁺ and the set point of Ca²⁺, with the curve after treatment shifting to the left. Significant differences (*P* < 0.05) were present in all segments of the Ca²⁺-PTH curves pre- and post-treatment. The magnitude of the shift of the steep linear part of the curve was equivalent to ~0.15 mmol/l on the ionized Ca²⁺ axis.

As shown in Figure 4, the set point of Ca²⁺ and the predialysis serum Ca²⁺ decreased during cinacalcet therapy, with correlations between the set point and predialysis ionized Ca²⁺ seen before and during cinacalcet treatment.

Discussion

Calcimimetics are allosteric modulators of the CaR, inducing a conformational change that increases its sensitivity to extracellular ionized Ca²⁺ via enhanced signal transduction [24]. This results in rapid, dose-dependent decreases in serum PTH and ionized Ca²⁺, and, to a lesser degree, increases in serum calcitonin levels, as demonstrated in preclinical models [25–27]. In addition, the present study shows that calcimimetic therapy with cinacalcet given to patients with HPT modified the Ca²⁺-PTH curve, by shifting it to the left and reducing both PTH levels and the set point of Ca²⁺. Prior to treatment, the Ca²⁺ set point was 1.25 ± 0.08 mmol/l, which is slightly higher than, but comparable to, values reported in normal subjects (1.15 ± 0.02 mmol/l) [28]. This reduction in the Ca²⁺ set point is particularly important, since studies of the parathyroid glands from uraemic patients have suggested that an increase in the Ca²⁺ set point may represent an intrinsic abnormality of the regulation of PTH secretion by the hyperplastic parathyroid gland [4]. Baseline PTH levels were very close to the calcium set point, regardless of treatment, which would normally predict for large fluctuations in PTH levels. However, although such fluctuations are generally observed, they are largely attributable to the dominant effect of calcium on PTH secretion; these effects are modified in patients treated with calcimimetics.

As shown previously, calcimimetics also induce a decrease in the serum ionized Ca²⁺ concentration, raising the important question as to whether this decrease could explain the changes in the Ca²⁺-PTH curve. Several investigators have reported that the set point of Ca²⁺ changes with

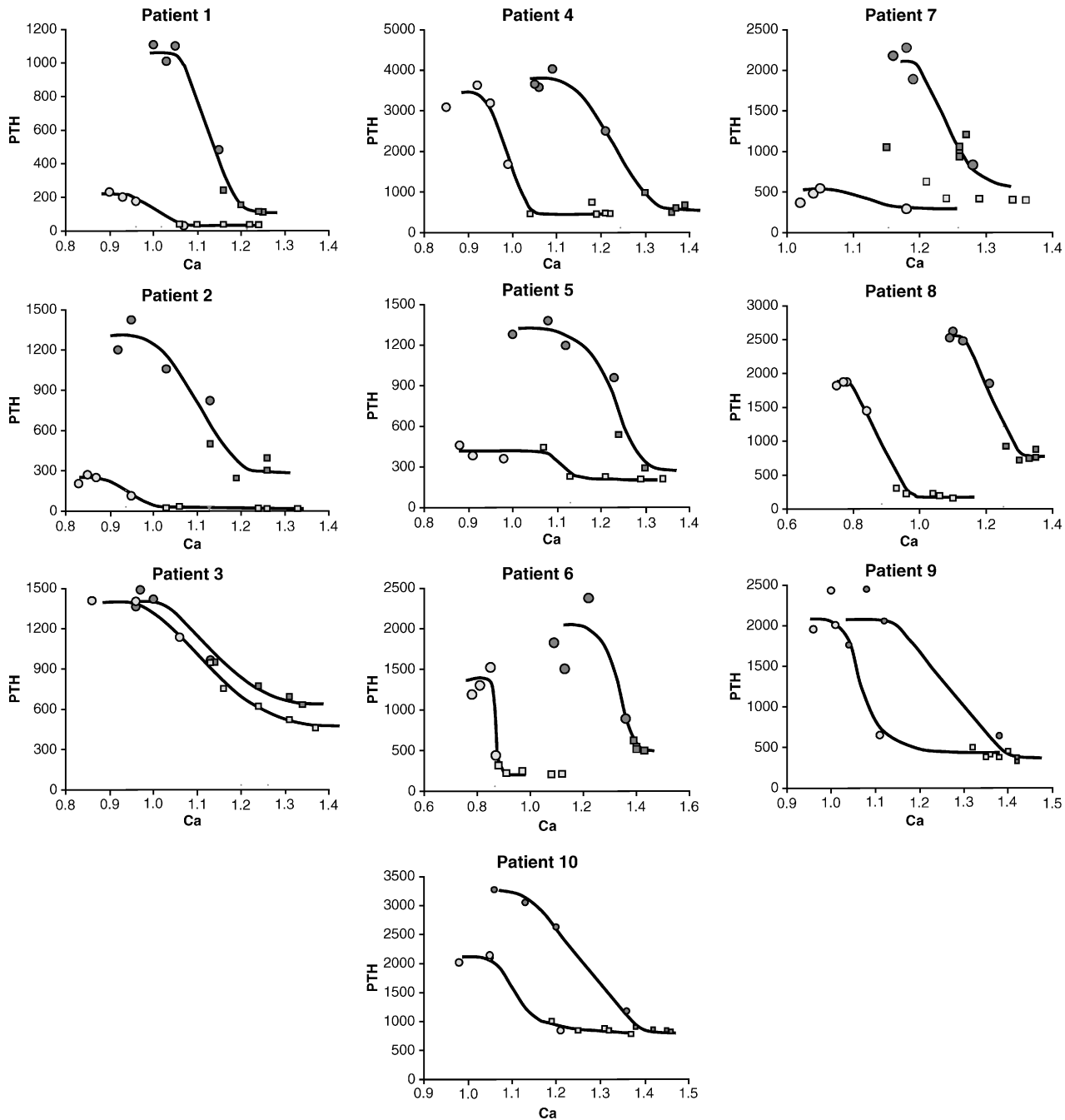


Fig. 1. Ca^{2+} -PTH curves for the individual 10 patients obtained during haemodialysis with low calcium levels (circle) versus high calcium levels (square) before (dark shade) and after (light shade) therapy with cinacalcet.

variations in extracellular ionized Ca^{2+} concentration, decreasing with hypocalcaemia and increasing with hypercalcaemia [19,20,28,29]. These findings are supported by our own data (Figure 4). Borrego *et al.* [30] studied haemodialysis patients to determine whether the set point of Ca^{2+} and the dynamics of PTH secretion were modified by sustained changes in serum Ca^{2+} levels, and found that the Ca^{2+} set point followed changes in serum Ca^{2+} levels independently of PTH secretion. The parathyroid gland appeared to be able to adjust the position of PTH secretion on the

Ca^{2+} -PTH curve, and to adapt that PTH secretion to the prevailing serum Ca^{2+} concentration. Moreover, a recent study showed that the calcimimetic R-568 also decreased PTH gene expression [31], suggesting an independent, not Ca^{2+} -related effect on PTH. Preliminary data presented at the European Renal Association European Dialysis Transplant Association meeting 2005 [32] showed similar PTH reductions regardless of baseline Ca^{2+} concentration. Borrego *et al.* [30] found a direct correlation between the set point of Ca^{2+} and the predialysis serum Ca^{2+} level, and

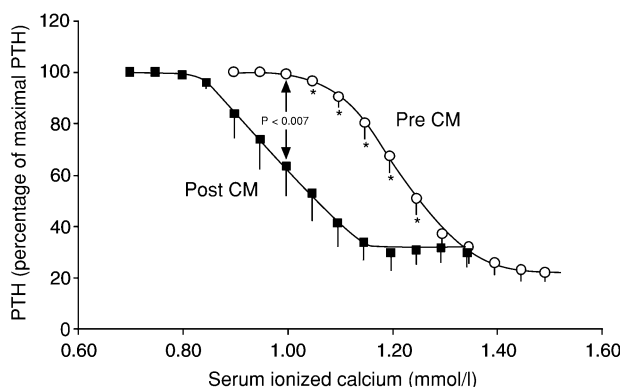


Fig. 2. Ca^{2+} -PTH curve obtained before (circle) and after (square) calcimimetic (CM) therapy with cinacalcet as a percentage of maximal PTH (* $P < 0.01$).

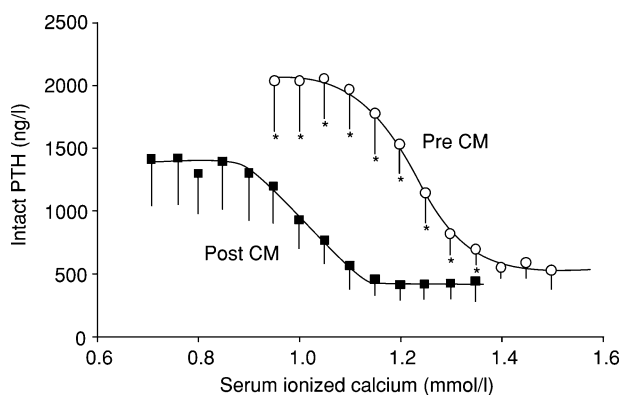


Fig. 3. Ca^{2+} -PTH curve obtained before (circle) and after (square) calcimimetic therapy with cinacalcet, as intact PTH levels (* $P < 0.01$).

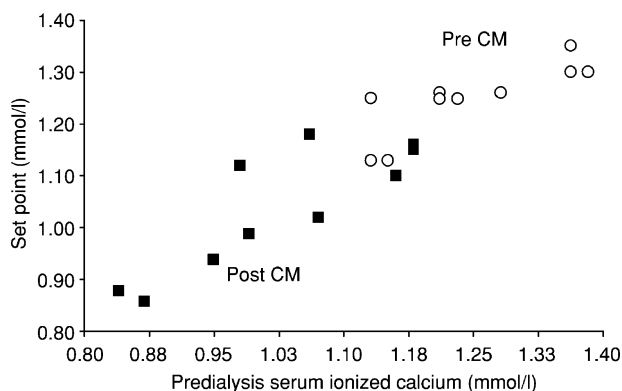


Fig. 4. Correlation of set point with predialysis serum Ca^{2+} [data from before (circle) and after (square) calcimimetic treatment with cinacalcet are included].

an inverse correlation between the change in set point and the change in PTH. In our study, the direction of travel was consistent: decreases in ionized Ca^{2+} , Ca^{2+} set point and PTH. Borrego *et al.* studied patients with moderate HPT in whom diffuse, rather than nodular, hyperplasia was more likely to be present. These patients were probably less severely affected than ours, who manifested markedly in-

creased PTH levels and a high probability of nodular hyperplasia, typically characterized by evidence of increased set point, decreased expression of the vitamin D receptor [33] and decreased expression of CaR messenger ribonucleic acid [3]. Conversely, in a group of patients with chronic kidney disease, Messa *et al.* [34] found that, while PTH increased as renal function decreased, the Ca^{2+} set points for the three groups were similar, despite a more than sixfold difference in PTH levels.

The set point of Ca^{2+} has been considered to be an important indicator of the magnitude of HPT and was thought initially to also be an indicator of parathyroid gland mass. Using rabbits, Bas *et al.* [35] showed a reduction in the set point, which correlated with the decrease in extracellular ionized Ca^{2+} , 2–3 weeks after the induction of HPT. However, the progression of parathyroid gland hyperplasia tended to increase the set point, even though extracellular ionized Ca^{2+} was markedly reduced. This increase in the set point in the course of secondary HPT reflects a decreased sensitivity of the parathyroid cells to ionized Ca^{2+} and could be related to the reduction in CaR expression or function [28,30]. The dynamic assessment of parathyroid gland function in patients with end-stage renal disease, while more informative than static measurements, presents distinct methodological problems [10,36]. It is accepted that PTH secretion cannot be totally suppressed, even at very high Ca^{2+} concentrations. In the present study, the minimal PTH, defined as the lowest PTH concentration achieved during suppression by hypercalcaemia, did not change with calcimimetic treatment. Some investigators consider the minimal PTH to be an expression of the parathyroid mass [37,38] and, if true, the lack of change in minimal PTH with calcimimetic treatment would be consistent with little or no change in parathyroid mass after a relatively short period of therapy. Nevertheless, calcimimetic agents have diminished parathyroid gland hyperplasia in partially nephrectomized rats, emphasizing the crucial role of signalling through the CaR as a key determinant of parathyroid cell proliferation in an experimental model of chronic renal failure. Because measurement of the parathyroid gland mass in humans is difficult, studies to date have not explored changes in this mass in patients treated with cinacalcet.

Treatment with this oral calcimimetic reduced baseline and maximally stimulated PTH levels. However, the maximal response of PTH secretion to hypocalcaemia depends on the direction of changes of Ca^{2+} , as well as its magnitude. In normal humans, a hysteretic relationship between ionized Ca^{2+} and levels of intact PTH can be induced by reversing the direction of change in Ca^{2+} level: that is, at a given Ca^{2+} level, the PTH levels are higher during hypocalcaemia induction than during hypocalcaemia recovery [39]. In some studies, regression slopes defining the Ca^{2+} -PTH relationships during decreasing and increasing Ca^{2+} levels were significantly different [39], with significant directional hysteresis (higher PTH level during falling than during rising Ca^{2+}) found in haemodialysis patients [40]. This potential artefact is unlikely to have confounded our results because the regression slopes were obtained in each patient in the same way, by inducing hypercalcaemia and then increasing dialysate Ca^{2+} . Patients

were compared with themselves to minimize the lack of comparability.

This study has certain real and potential limitations: the number of patients was small and the duration of treatment with cinacalcet was variable (9–22 weeks); phosphorus levels were not followed during the acute perturbations, although previous studies have shown that the set point of the Ca^{2+} -PTH curve is not affected by extracellular phosphorus concentration [16,41].

Finally, note should be made of the cyclical nature of the PTH response to cinacalcet. The decrease in PTH levels associated with cinacalcet treatment is rapid and transient, with a nadir occurring within 4 h after dosing followed by a slow return towards pre-dose levels [12,13]. In our patients, the interval between cinacalcet administration and the experimental perturbations was 12–18 h, a timing approximately midway between the expected maximal cinacalcet effect and the subsequent dose.

Concluding remarks

Ten haemodialysis patients with marked secondary HPT were treated for several weeks with the calcimimetic agent, cinacalcet. Mean baseline Ca^{2+} , baseline PTH, maximal PTH levels and the set point of Ca^{2+} decreased significantly. PTH concentration throughout the entire Ca^{2+} -PTH curve also decreased significantly. Treatment with cinacalcet produced a shift to the left in the Ca^{2+} -PTH curve, reflecting the increasing parathyroid sensitivity to Ca^{2+} changes.

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