Original Article

Relationship between parathyroid gland size and responsiveness to maxacalcitol therapy in patients with secondary hyperparathyroidism

Senji Okuno¹, Eiji Ishimura², Kayoko Kitatani¹, Hidenori Chou¹, Kyoko Nagasue¹, Kiyoshi Maekawa¹, Tsuyoshi Izumotani¹, Tomoyuki Yamakawa¹, Yasuo Imanishi³, Tetsuo Shoji³, Masaaki Inaba³ and Yoshiki Nishizawa³

¹Shirasagi Hospital Kidney Center, ²Department of Nephrology and ³Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan

Abstract

Background. Although vitamin D has been reported to be useful in the treatment of patients with secondary hyperparathyroidism, it is not effective in some of them. The goal of this study was to see whether a relationship could be found between maxacalcitol responsiveness and parathyroid gland size.

Methods. Parathyroid gland size was measured by ultrasonography in 25 patients with secondary hyperparathyroidism [serum intact parathyroid hormone (PTH) >300 pg/ml, 58.1 ± 2.8 years old, 15 males and 10 females], who were treated with maxacalcitol. Patients were divided into two groups according to the mean value of the maximum diameter of the glands: group S with a diameter <11.0 mm and group L with a diameter ≥11.0 mm. Between the two groups there were no significant differences in serum intact PTH, calcium or phosphate level or duration of haemodialysis.

Results. Mean (± SE) maximal diameter of detectable parathyroid glands was 11.0 ± 0.7 mm before treatment. At 4–24 weeks after administration of maxacalcitol, intact PTH concentrations decreased significantly in group S (from 546 ± 39 to 266 ± 34 pg/ml at 24 weeks; P < 0.01), but did not significantly change in group L (from 481 ± 39 to 403 ± 49 pg/ml at 24 weeks). At 24 weeks after maxacalcitol administration, the number of detectable parathyroid glands was significantly decreased in group S (from 2.2 ± 0.3 to 1.8 ± 0.4; P < 0.05), but not in group L. Serum calcium increased significantly in group L (from 9.6 ± 0.2 to 10.2 ± 0.3 mg/dl; P < 0.05), but not in group S. There was a significant correlation between reduction in PTH and parathyroid gland size (r = −0.42, P < 0.05).

Conclusions. These results indicate that the responsiveness to maxacalcitol therapy of secondary hyperparathyroidism is dependent on parathyroid gland size and that the simple measurement of maximum parathyroid gland diameter by ultrasonography may be useful for predicting responsiveness to maxacalcitol treatment.

Keywords: maxacalcitol; parathyroid hormone; secondary hyperparathyroidism; ultrasonography

Introduction

Secondary hyperparathyroidism is one of the most serious complications of patients with chronic renal failure on long-term haemodialysis. To prevent the progression of secondary hyperparathyroidism, oral administration of phosphate binder and vitamin D is currently performed [1,2]. In particular, administration of vitamin D is an important tool for directly suppressing the synthesis and secretion of parathyroid hormone (PTH) [3]. However, vitamin D treatment in these patients not infrequently causes hypercalcaemia, limiting the indications for treatment. Recently, in Japan, maxacalcitol (previously called 22-oxacalcitriol) was developed and has been clinically used in the treatment of secondary hyperparathyroidism, since it has been reported to have a reduced calcemic effect [4,5]. Although maxacalcitol is effective in suppressing elevated PTH levels, it is not effective in all patients [6,7]. Similar limitations in the treatment of secondary hyperparathyroidism have been reported for alfacalcidol and calcitriol pulse therapy [2,8–10].
Subjects and methods

Patients

Between January and July 2001, among 545 chronic renal failure patients on maintenance haemodialysis at Shirasagi Hospital, 38 had intact PTH levels > 300 pg/ml at two measurements within 3 months. To suppress increased PTH levels, intravenous administration of maxacalcitol was started in these patients. Maxacalcitol was withdrawn when serum calcium was > 11.5 mg/dl at two measurements within 1 month. Although this level of calcium appears to be high, it was set in accordance with protocols previously reported by others who examined the therapeutic effects of maxacalcitol [4,6]. There were no patients with liver disease. In all patients, 4 h haemodialysis was performed three times a week with bicarbonate dialysate containing a 3.0 mEq/l calcium concentration. Calcium carbonate 1.5–3.0 g/day was prescribed for patients with serum phosphate 5–6 mg/dl. When serum phosphate rose to > 6.0 mg/dl, calcium carbonate was increased to 3–8 g/day.

Administration of maxacalcitol and measurement of serum parameters

Five μg maxacalcitol was administered intravenously at the end of each dialysis session. Before the start of maxacalcitol, some patients received small oral doses of intermittent or daily calcitriol or alfalcacidol (see 'Results') and the patients were converted from intermittent or daily calcitriol or alfalcacidol to intravenous maxacalcitol, according to the advice from the Ethics Committee of the hospital. Doses of maxacalcitol were increased from 5 to 10 μg when intact PTH was > 500 pg/ml after 1 month. When serum calcium concentration was > 11.5 mg/dl and/or calcium–phosphate product was > 70, maxacalcitol was temporarily discontinued. Maxacalcitol administration (5 μg) was resumed when the condition disappeared. When PTH levels were decreased below 150 pg/ml, maxacalcitol was temporarily discontinued. Maxacalcitol administration (5 μg) was resumed when PTH increased again to > 150 pg/ml.

In all patients, serum calcium and phosphate concentrations were measured twice a month and intact PTH once a month. Serum calcium was corrected with serum albumin as follows (in this case serum albumin was < 4.0 g/dl):

\[
\text{corrected calcium} = \frac{\text{measured calcium concentration}}{\left(4 - \text{measured albumin concentration}\right)}
\]

where the units for measured calcium concentration and measured albumin concentration are mg/dl and g/dl, respectively.

Ultrasonography of parathyroid glands

Ultrasonography was performed within 1 month before administration of maxacalcitol and at 24 weeks after initiation of maxacalcitol administration, by a single examiner (H.C.) who was blind to clinical data. Using an 8 MHz ultrasonography probe (SSA-350A; Toshiba, Japan), a gland as small as 2.0 mm in maximum diameter can be detected in our hospital. The coefficient of variance of parathyroid gland measurement by the examiner (H.C.) was 2.7%.

Statistical analysis

Data are presented as means ± SE. Unpaired Student’s t-test was used for comparison between the two groups and paired Student’s t-test for comparison between the baseline and follow-up data after maxacalcitol administration. Correlation and linear regression analyses were performed to examine the relationship between the responsiveness to maxacalcitol and clinical parameters. Findings of \( P < 0.05 \) were considered significant. All analyses were performed using statistical software (StatView 5; SAS Institute Inc., Cary, NC, USA) designed for the Macintosh computer.

Results

Maxacalcitol therapy

Of the total 38 patients, maxacalcitol was withdrawn between 4 and 16 weeks in 9 patients, because serum calcium was > 11.5 mg/dl in two measurements within 1 month. In four patients, maxacalcitol was discontinued at 4–16 weeks after start of administration, due to pruritus (\( n = 1 \)), the patient’s desire for discontinuation (\( n = 2 \)) and unknown physician’s judgment (\( n = 1 \)). In the remaining 25 patients (58.1 ± 2.8 years old, 15 males and 10 females), maxacalcitol was continued through 24 weeks and the effect of maxacalcitol on PTH reduction was analysed. Causes of renal failure were chronic glomerulonephritis in 14, diabetes in four, hypertension in two, polycystic kidney disease in two and unknown causes in three.

Parathyroid glands detected by ultrasonography

Before the start of maxacalcitol, one to four parathyroid glands were detected in all the patients, the smallest gland being 3.0 mm in maximum diameter. The mean maximum parathyroid gland diameter detected by ultrasonography in 25 patients was 11.0 ± 0.7 mm. In the analysis, these 25 patients were divided into two groups according to the mean value of maximum diameter of the parathyroid gland: group S (\( n = 14 \)) with maximum diameter less than the mean value (11.0 mm) and group L (\( n = 11 \)) with maximum diameter equal to or greater than the mean value. The age, duration of haemodialysis and clinical parameters related to parathyroid function of the patients of groups S and L are summarized in Table 1. Vitamin D dosages (μg/week) during the 3 month period preceding maxacalcitol therapy were calculated, with estimation of calcitriol...
observed between groups S and L in levels of intact PTH at any point of measurement of intact PTH through-Student's t-test). After 4 weeks through 24 weeks, intact PTH levels were significantly decreased in group S [from 546 ± 39 pg/ml; range: 340–850 pg/ml] to 481 ± 39 pg/ml (range: 300–730 pg/ml). In contrast, in group L that before treatment was not significantly different from that at 24 weeks (5.3 ± 5.0 mm; P < 0.05, paired Student’s t-test). There was no significant correlation between parathyroid gland size and serum calcium or phosphate level before treatment.

**Changes in PTH levels after maxacalcitol**

At baseline there was no significant difference in intact PTH levels between groups S and L (546 ± 39 vs 481 ± 39 pg/ml; range: 340–850 vs 300–730 pg/ml). The cumulative dosages of maxacalcitol in groups S and L were 369 ± 35 and 418 ± 33 μg, respectively, and not significantly different (P = 0.311). In group S, compared with baseline levels, intact PTH levels were significantly decreased at 4 weeks after maxacalcitol administration (353 ± 45 pg/ml; P < 0.01, paired Student’s t-test). After 4 weeks through 24 weeks, intact PTH levels continued to be significantly lower than baseline levels (P < 0.01). In contrast, in group L no significant changes in intact PTH levels were seen at any point of measurement of intact PTH throughout the 24 week period. Significant differences were observed between groups S and L in levels of intact PTH at 20 and 24 weeks after maxacalcitol administration (P < 0.05, unpaired Student’s t-test; Figure 1).

Per cent changes in intact PTH levels are shown in Figure 2. Per cent decrease in intact PTH was significantly greater in group S than in group L at 16, 20 and 24 weeks after maxacalcitol administration (P < 0.05, P < 0.01 and P < 0.05, respectively).

**Ultrasonography of the parathyroid gland at 24 weeks after initiation of maxacalcitol administration**

At 24 weeks after initiation of maxacalcitol administration, ultrasonography was performed again in all 25 patients. The number of detectable parathyroid glands was significantly decreased in group S [from 2.2 ± 0.3 at baseline to 1.8 ± 0.4 at 24 weeks (P < 0.05)], but not significantly so in group L (3.2 ± 0.2 at baseline vs 2.9 ± 0.2 at 24 weeks). The maximum diameter of the parathyroid gland before treatment was significantly larger than the diameter of the same gland at 24 weeks (8.5 ± 2.1 vs 5.3 ± 5.0 mm; P < 0.05, paired t-test) in group S, although in group L that before treatment was not significantly different from that at 24 weeks (14.1 ± 2.3 vs 13.4 ± 2.5 mm).

**Changes in calcium and phosphate**

Serum calcium level (corrected calcium value) was not significantly changed after maxacalcitol administration in group S, whereas serum calcium in group L significantly increased after maxacalcitol administration (P < 0.05, paired Student’s t-test). Serum calcium concentrations in group L were significantly higher than those in group S at 4, 8, 12 and 24 weeks after initiation of maxacalcitol administration (Figure 3). Serum calcium at 4 weeks, when the highest calcium values were observed, was significantly positively correlated with both parathyroid gland size (r = 0.54, P < 0.01) and baseline calcium level (r = 0.61, P < 0.01), but not with baseline serum phosphate or intact PTH level. Serum phosphate concentrations were not significantly changed during the 24 weeks.
following initiation of maxacalcitol administration in group S, while they tended to increase in group L. Although baseline calcium–phosphate product did not differ significantly between the two groups (51.7 ± 13.5 vs 56.1 ± 12.1 in groups S and L, respectively; \( P = 0.354 \)), at 24 weeks it was significantly higher in group L than in group S (50.2 ± 16.5 vs 65.2 ± 14.9 in groups S and L, respectively; \( P < 0.05 \)).

Relationships between responsiveness to maxacalcitol and clinical parameters

Correlation and linear regression analyses were performed to examine the relationships between responsiveness to maxacalcitol and clinical parameters, such as parathyroid gland size, serum calcium and phosphate and cumulative dose of maxacalcitol. In the analysis, responsiveness to maxacalcitol was
represented by average per cent reduction in intact PTH during 4–24 weeks. There were significant negative correlations between average per cent reduction in intact PTH and parathyroid gland size and between average per cent reduction in intact PTH and baseline serum calcium, indicating that maxacalcitol responsiveness was greater as the parathyroid gland was smaller and baseline serum calcium level was lower. The relationship between average per cent reduction in intact PTH and baseline serum phosphate was of borderline significance ($P = 0.08$) and that between average per cent reduction in intact PTH and cumulative maxacalcitol was not significant (Figure 4).

**Discussion**

In the present study we examined the relationship between responsiveness to maxacalcitol and parathyroid gland size measured by ultrasonography in patients with secondary hyperparathyroidism in long-term treatment. Patients were divided into two groups according to the mean of the maximum parathyroid gland diameter (11.0 mm). Although intact PTH levels at baseline were not significantly different between the two groups, intact PTH levels significantly decreased in patients with smaller parathyroid glands (group S), whereas they remained unchanged in patients with

![Graph showing changes in serum calcium and phosphate levels after maxacalcitol therapy](link_to_graph)
larger parathyroid glands (group L). We found that responsiveness to maxacalcitol was dependent on parathyroid gland size, as measured by ultrasonography before treatment.

Maxacalcitol is a recently developed vitamin D analogue, which has been found to exhibit less calcemic activity in animal studies [5]. It has been proven to be effective in the treatment of secondary hyperparathyroidism [4,6,7]. However, it has been reported to be ineffective in some patients [7], as has also been observed with calcitriol pulse therapy [6,7]. Tsukamoto et al. [7] recently reported that serum calcium levels at the start of treatment in patients who responded well to maxacalcitol (n = 5) were significantly lower than those in patients who did not respond well to it (9.1 ± 0.3 vs 10.3 ± 0.3 mg/dl). Malberti et al. [9] also reported that the serum ionized calcium level of the patients who were responsive to calcitriol therapy was significantly lower than that of those who were not responsive (ionized calcium: 5.0 ± 0.2 vs 5.3 ± 0.2 mg/dl). In the present study, however, baseline serum calcium in group S was also slightly lower than that in group L, although not to a statistically significant extent (9.3 ± 0.2 vs 9.6 ± 0.2 mg/dl; P = 0.09). On linear regression analysis, however, we found a significant relationship between average per cent reduction of PTH and baseline serum calcium level. This finding suggests that baseline serum calcium level also predicts responsiveness to maxacalcitol.

In the present study, after maxacalcitol treatment, serum calcium level was significantly increased in group L, in which maxacalcitol did not significantly suppress PTH levels. This suggests that the parathyroid glands of group L patients may have been very close to being maximally suppressed by higher levels of serum calcium. Serum calcium at 4 weeks, when the highest mean calcium level was observed, was
positively correlated with parathyroid gland size. Malberti et al. [9] also reported that serum ionized calcium levels after calcitriol therapy in patients who were non-responsive to calcitriol therapy were significantly higher than in those who were responsive to it. Our results are consistent with their findings. Furthermore, in nine excluded patients for whom maxacalcitol therapy was discontinued due to increase in serum calcium >11.5 mg/dl at two measurements in 1 month between 4 and 16 weeks, baseline maximal parathyroid gland diameter was 14.9 ± 2.8 mm, showing that the level of serum calcium in patients with larger parathyroid glands was readily increased by maxacalcitol. The study performed by Kurz et al. [12] demonstrated that the PTH level of histologically proven low turnover bone disease was 116 ± 30 pg/ml (maximum: 390 pg/ml) and the study by Qi et al. [13] demonstrated that the specificity of serum intact PTH >450 pg/ml for prediction of high bone turnover is 100% for haemodialysis patients. These two studies suggest that most of our patients with higher PTH levels (481 ± 39 pg/ml) in group L may have had high bone turnover. The significant increases in serum calcium and phosphate levels also seen in group L may reflect a more advanced stage of secondary hyperparathyroidism and may have been caused not only by increased bone absorption induced by high PTH levels (high bone turnover), but also by increased intestinal absorption of calcium and phosphate induced by maxacalcitol. The increase in serum calcium levels after maxacalcitol therapy, however, may have been induced by adynamic bone disease or low bone turnover due to prior vitamin D therapy and maxacalcitol initiation in our patients. Goodman et al. [14] reported that bone formation decreased in some patients despite persistently high serum PTH levels after intermittent calcitriol therapy in peritoneal dialysis patients. In their study, PTH levels of adynamic bone after calcitriol pulse therapy were reported to be usually <150 pg/ml. In the present study, prior vitamin D treatment and initiation of maxacalcitol may have caused bone formation to fall and led to a tendency towards low bone turnover from high bone turnover. This tendency may have caused a decreased pool size for calcium added to extracellular fluid, thus, possibly leading to hypercalcaemia in group L following intestinal calcium absorption enhanced by maxacalcitol. Low bone turnover favouring hypercalcaemia, in spite of high PTH levels in the present study, may therefore have been present in at least some patients, particularly when considering the prompt increase in serum calcium after maxacalcitol therapy. Further studies with bone biopsies must be performed to examine the issue of the possible induction of low bone turnover despite persisting high PTH levels and hypercalcaemia after active vitamin D treatment.

A higher serum phosphate has been reported to be a predictor of poor responsiveness to calcitriol therapy in patients with secondary hyperparathyroidism as well [10,15], although this was not observed by others [9]. In the present study, although baseline serum phosphate levels did not differ significantly between groups S and L, a borderline significant (P=0.08) relationship between baseline serum phosphate level and average per cent PTH reduction after maxacalcitol treatment was observed and phosphate levels tended to increase in group L. Since hyperphosphataemia is an important contributor to hyperparathyroidism [16], our results also suggest the importance of phosphate control in vitamin D treatment in patients with secondary hyperparathyroidism.

Some studies have examined the relationship between responsiveness to vitamin D and parathyroid gland size in patients with secondary hyperparathyroidism [2,8–11]. Fukagawa et al. [2,8] reported that, in their experience, patients with at least one gland larger than 0.5 cm³ or 1 cm in diameter were usually refractory to calcitriol pulse therapy. Katoh et al. [11] recently reported that the suppressive effect of a single oral dose of 8 µg calcitriol on PTH was reduced in patients with enlargement of parathyroid glands detectable by ultrasonography. Malberti et al. [9] examined 35 patients with secondary hyperparathyroidism and found response heterogeneity to calcitriol. They also found that parathyroid gland volume was a significant predictor of responsiveness [9]. Quarles et al. [10] also found response heterogeneity to calcitriol, but parathyroid gland volume was not predictive of calcitriol response. In the present study, we examined effect of maxacalcitol on reduction of PTH level. We demonstrated that patients with larger parathyroid glands with maximum diameter ≥11.0 mm did not significantly respond to maxacalcitol treatment, whereas those with maximum diameter <11.0 mm significantly responded to treatment. This finding is similar to the experience of Fukagawa et al. [8], although a statistical analysis was not performed to elucidate parathyroid gland size as a limitation of calcitriol therapy. On linear regression analysis, we found a significant relationship between parathyroid gland size and per cent reduction of intact PTH after maxacalcitol. Our findings are consistent with those of Malberti et al. [9], but not with those of Quarles et al. [10]. These discrepant findings may be due to the fact that Quarles et al. treated patients with more advanced hyperparathyroidism, higher PTH levels (mean: 920 pg/ml) and larger parathyroid volume (mean: 2.0 cm³). Indeed, the parathyroid gland volume in calcitriol responders in the study by Malberti et al. was 0.4 ± 0.3 cm³ and significantly smaller than that of non-responders (2.4 ± 2.1 cm³). If the parathyroid glands are assumed to be spherical in the patients of our study, the parathyroid volume of group S can be calculated (πr³ / 6) to be 0.32 ± 0.1 cm³ and that of group L 1.50 ± 0.7 cm³.

Taken together, the results of the present study and of previous studies by others suggest that limitation of suppression of PTH levels by vitamin D therapy depends on parathyroid gland size and that the limitation is parathyroid glands ~11 mm in maximum diameter, even when vitamin D analogues are used. It appears that larger parathyroid glands are refractory
to calcitriol therapy and also exhibit poor suppression of PTH secretion in the presence of calcium increase [17]. We further found that, after maxacalcitol treatment, the number of detectable parathyroid glands significantly decreased in group S, although the decrease in number was not significant in group L. Maximum parathyroid gland diameter before treatment was not significantly different from that at 24 weeks. Serial ultrasonography performed by Fukagawa et al. [8] also demonstrated decrease in parathyroid gland size in some cases after calcitriol treatment. In our previous study, a rapidly growing, large parathyroid gland had significantly less vitamin D receptor content (32.6 ± 9.6 fmol/mg protein) than a non-growing, small parathyroid gland in the same patient (111.8 ± 0.8 fmol/mg protein) [18]. The former had nodular hyperplasia and the latter diffuse hyperplasia. Since calcitriol is reported to induce apoptosis in parathyroid cells of secondary hyperparathyroidism in vitro [19], the ultrasonographically visible reduction in the number and size of parathyroid glands in the present study may have been induced by apoptosis in group S, in which parathyroid glands may have had diffuse hyperplasia and higher content of vitamin D receptor, while apoptosis was not markedly induced in group L whose parathyroid gland may have had nodular hyperplasia and lower content of vitamin D receptors. Parathyroid glands of size > 0.5 cm³ usually appear to present nodular hyperplasia [20]. The nuclei of hyperplastic parathyroid cells have a lower vitamin D receptor expression [18,21], leading to refractoriness to vitamin D therapy.

In summary, responsiveness to maxacalcitol therapy of secondary hyperparathyroidism is dependent on parathyroid gland size. A simple measurement of the maximum diameter of parathyroid glands by ultrasonography can be useful for predicting responsiveness to treatment. When a poor reduction in serum intact PTH and an increase in serum calcium are observed after vitamin D treatment in patients with large parathyroid glands, parathyroidectomy and/or percutaneous ethanol injection treatment [22] should be considered without delay. We propose, based on the findings of the present study, that parathyroid glands with a maximal diameter > 11.0 mm do not respond well to maxacalcitol therapy.

Conflicts of interest statement. None declared.

References


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