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ORIGINAL ARTICLE

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Comparison of the efficacy of an oral calcitriol pulse or intravenous 22-oxacalcitriol therapies in chronic hemodialysis patients

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Abstract
Background. 1,25-dihydroxy-22-ovavitamin D_3 (22-oxacalcitriol, OCT) was recently introduced commercially as an analogue of 1,25 $(OH)_2$ vitamin D_3, but one which has less pronounced calcemic activity.
Methods. To examine the efficacy and tolerability of OCT, 46 hemodialysis patients with secondary hyperparathyroidism were randomly assigned to receive either intravenous OCT or oral calcitriol pulse therapies. The patients were monitored for serum calcium, phosphate, intact parathyroid hormone (PTH), and bone alkaline phosphatase (BAP) for 24 weeks. The efficacy of intravenous OCT was also examined in 24 additional patients who were refractory to oral calcitriol pulse therapy.
Results. In the randomized trial, intact PTH levels were significantly suppressed within 4 weeks after the initiation of each therapy, and this effect was well maintained thereafter in both treatment groups. While intact PTH was significantly lower at 4 weeks in the calcitriol pulse group than in the OCT group ($P = 0.02$), no statistical differences were observed during later treatment periods. BAP was reduced equally by each treatment. At 4 weeks ($P = 0.02$) and thereafter ($P = 0.06$), serum calcium was higher among calcitriol-treated patients than among those who received OCT treatment. Eight of 24 patients who were refractory to oral calcitriol pulse therapy responded to intravenous OCT. The patients who responded tended to have lower serum intact PTH and phosphorus levels and smaller parathyroid glands at the start of OCT treatment than nonresponders.
Conclusions. OCT is as effective as oral calcitriol pulse therapy in suppressing intact PTH and BAP in chronic hemodialysis patients. It was confirmed that OCT exhibits less calcemic activity than calcitriol. Moreover, under certain conditions, switching to OCT may help in the treatment of hyperparathyroidism, which is refractory to conventional oral calcitriol pulse therapy.

Key words Hemodialysis · Secondary hyperparathyroidism · 22-oxacalcitriol (OCT) · Oral calcitriol pulse therapy

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Introduction

One of the most important and inevitable complications of long-term hemodialysis is renal osteodystrophy, which is caused by abnormal secretions of parathyroid hormone (PTH). This is known as secondary hyperparathyroidism.[1] While remarkable progress has been made in therapy for this complication since the clinical use of active vitamin D_3 derivatives was introduced, there are limitations in the medical treatment of advanced secondary hyperparathyroidism, in which the suppression of PTH to adequate levels is rather difficult owing to the common adverse effects of vitamin D treatment.

Slatopolsky et al.[2] reported that intravenous administration of $1,25(OH)_2D_3$ at the end of each dialysis was more effective in suppressing intact PTH secretions than oral daily administration of $1,25(OH)_2D_3$. High-dose intermittent oral (oral pulse) calcitriol was also effective in lowering levels of intact PTH in hemodialysis patients.[3] Intermittent oral or intravenous vitamin D_3 administrations were reported to have almost the same effect in controlling secondary hyperparathyroidism in hemodialysis patients.[4–6] However, vitamin D administration can often lead to hypercalcemia. Recently, analogues of $1,25(OH)_2D_3$ have been synthesized to achieve better control of hyperparathyroidism. 1,25-dihydroxy-22-ovavitamin D_3 (OCT) is one such synthetic analogue of calcitriol. In animal studies,[7,8] OCT has been reported by some investigators[7] to be less hyper-

calcemic than calcitriol in uremic rats, but not by others.[8] Clinical studies show that OCT may represent an important tool in the treatment of secondary hyperparathyroidism.[9,10] This study compares the efficacy and tolerability of OCT injections versus oral calcitriol pulse administration in the treatment of secondary hyperparathyroidism.

Patients and methods

Patient selection and treatment protocol

From a total of 670 patients in three dialysis units, patients treated by maintenance hemodialysis were surveyed for the presence of secondary hyperparathyroidism.

We applied the following acceptance criteria for patients in the randomized study. Despite daily vitamin D oral administration (0.25–0.5 μg/day calcitriol or 0.25–1.0 μg/day alphacalcidol), (1) serum intact PTH levels greater than 400 pg/ml (normal, 15–65 pg/ml), (2) alkaline phosphatase levels greater than 250 IU/l (normal 70–220 IU/l) or serum bone gla protein levels greater than 75 ng/ml (normal 3.1–12.7 ng/ml), and (3) serum albumin-adjusted calcium levels less than 10.5 mg/dl (normal 8.0–10.8 mg/dl). Patients treated by oral calcitriol pulse therapy within the previous 3 months were excluded. Patients with major liver disease, heart failure, obvious aluminum accumulation, primary hyperparathyroidism, malignancies, or serious infectious disease were excluded. Patients who were pregnant or had a history of drug allergies were also excluded. Patients were stratified by sex, age, and presence of diabetes mellitus, since these factors can affect bone metabolism among dialysis patients.

The 46 patients (28 men and 18 women) who agreed to participate in the study were randomized into an OCT group (23 subjects, 13 men and 10 women) and an oral calcitriol pulse group (23 subjects, 15 men and 8 women). All patients were fully informed of the risks and benefits of each treatment, and provided their written informed consent. The study was approved by the Ethics Committee of each hospital.

The patients were treated for 24 weeks under the protocol described below. Using samples collected at the start of the first hemodialysis session each week, serum Ca and phosphate were monitored twice a month, and intact PTH and bone alkaline phosphatase (BAP) were examined monthly. Intact PTH was measured by the Allegro Intact PTH assay kit (Nichols Institute Diagnostics, San Clemente, CA, USA).

OCT was administered as follows: for patients with intact PTH levels lower than 500 pg/ml, 5 μg OCT was administered after each hemodialysis session; for patients with intact PTH levels exceeding 500 pg/ml, 10 μg OCT was administered as a starting dose. In the oral calcitriol group, 4 μg oral calcitriol was administered twice per week after the hemodialysis session. OCT and oral calcitriol doses were adjusted based on serum calcium, phosphate, and intact PTH levels to avoid hypercalcemia (calcium >11.5 mg/dl) and hyperphosphatemia (phosphate >7.0 mg/dl) and to achieve reductions to the clinically appropriate range (150 pg/ml < intact PTH < 300 pg/ml), or a minimum of 50% reduction in PTH concentrations. In cases in which serum calcium levels exceeded 11.5 mg/dl, in which serum phosphate levels exceeded 7.0 mg/dl on two consecutive examinations, or in which intact PTH levels fell below 150 pg/ml treatment was discontinued until these parameters returned to acceptable levels (calcium <10.5 mg/dl, phosphate <7.0 mg/dl, and intact PTH >300 pg/ml). On resumption, treatment began at lower doses, based on the judgment of the physicians responsible. Calcium carbonate was provided with meals as a phosphate-binding agent, and the administration of other medications was kept as constant as possible during the study.

The effects of OCT injections for 24 patients (15 men and 9 women) refractory to oral calcitriol pulse therapy were also analyzed (switching study). The criteria for patient selection were as follows. Despite oral calcitriol pulse therapy (the intermittent administration of calcitriol at 1.0–8.0 μg/week) for at least 3 months, (1) serum intact PTH levels could not be suppressed below 300 pg/ml, and/or (2) doses of oral calcitriol could not be increased owing to the development of hypercalcemia or hyperphosphatemia.

Statistical analysis

All results for continuous variables are expressed as mean ± SD. In the randomized trial, the differences between the two treatment groups were analyzed using analysis of variance (ANOVA) for serum-intact PTH, BAP, calcium, and phosphorus levels during the 24-week treatment periods. A Mann–Whitney U test was performed to compare the differences in these parameters at each time point. A χ^2 test was used to assess the differences in the prevalence of dichotomous variables. A value of $P < 0.05$ was considered to be significant. All these analyses were performed using statistical software (SAS Institute Inc., Cary, NC, USA) for Windows personal computers.

Results

Table 1 gives the characteristics of the participants in the randomized trial. No significant differences were noted between intravenous OCT and oral calcitriol groups with respect to patient age, sex, duration of hemodialysis, or the presence of diabetes mellitus. Neither biochemical parameters nor the maximum diameter of the enlarged parathyroid glands differed significantly.

Following vitamin D administration, intact PTH levels were significantly reduced in both treatment groups. At 4 weeks after the initiation of each treatment, patients receiving oral calcitriol had significantly lower intact PTH levels than those receiving OCT injection (228.2 ± 99.1 pg/ml vs. 371.5 ± 209.8 pg/ml, respectively; $P = 0.02$; Fig. 1A). This is

Table 1. Patient characteristics in the randomized trial

	Group		*P* value
	OCT	Oral pulse	
Male/female	13/10	15/8	NS
Age (years)	63.3 ± 6.8	60.6 ± 12.3	NS
Dialysis duration (months)	114.4 ± 65.8	117.8 ± 66.7	NS
Non-DM/DM	21/2	20/3	NS
Biochemical parameters			
Intact-PTH (pg/ml)	598.9 ± 207.7	619.9 ± 178.9	NS
Ca (mg/dl)	9.07 ± 0.95	9.40 ± 0.67	NS
P (mg/dl)	5.62 ± 0.88	5.81 ± 1.05	NS
Bone-ALP(U/l)	39.2 ± 17.5	39.9 ± 21.3	NS
Maximum diameter (mm) of swollen parathyroid glands			
Before treatment	6.75 ± 6.01	8.65 ± 7.23	NS
After treatment	7.22 ± 6.12	9.89 ± 6.90	NS

Statistical analyses were assessed by χ^2 test and Mann–Whitney *U* test
NS, not significant

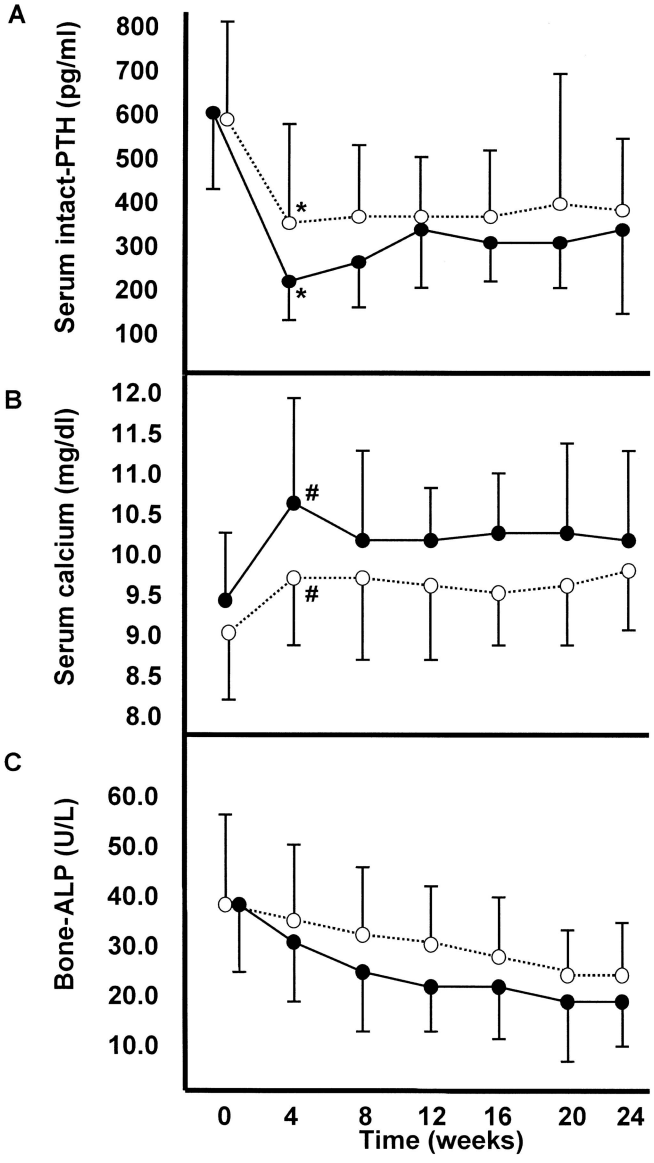

Table 2. Doses of OCT and calcitriol administered during the treatment periods

Treatment period (W)	Dose administered (μg/W)	
	OCT	Calcitriol
0–4	23.8 ± 6.99	6.53 ± 1.39
4–8	21.1 ± 9.86	4.09 ± 2.13*
8–12	18.6 ± 12.9	3.00 ± 2.02*
12–16	20.4 ± 13.1	2.73 ± 1.37*
16–20	20.9 ± 13.5	2.73 ± 1.51*
20–24	21.3 ± 14.2	2.47 ± 1.76*

* $P < 0.01$ vs. 0–4(W)
Statistical analyses were assessed by Scheffe's test

in accordance with serum calcium data obtained at 4 weeks, which were significantly higher for the calcitriol group than for the OCT group ($P = 0.02$; Fig. 1B). These findings suggest that oral calcitriol at a predefined initial dose (4 μg) in our current study was more potent in suppressing PTH and inducing hypercalcemia than intravenous OCT. The doses were adjusted according to a dose modification protocol to maintain intact PTH levels within 150–300 pg/ml, and to keep calcium levels under 11.5 mg/dl. As shown in Table 2, while the mean doses of OCT remained relatively constant

Fig. 1A–C. Changes in serum biochemical parameters following treatment by 22-oxacalcitriol (OCT) injection and oral calcitriol pulse. Effects of therapy on **A** serum intact parathyroid hormone (*PTH*), **B** serum calcium, and **C** serum bone alkaline phosphatase (*BAP*) levels are shown. The OCT injection group is represented by *open circles*, and the oral calcitriol pulse group is represented by *closed circles*. Intact PTH and BAP levels were significantly reduced in both treatment groups. No statistical differences were seen in these parameters between the groups over the 24-week treatment period ($P = 0.14$ and 0.29, respectively), while significant differences in intact PTH levels were seen at 4 weeks (*; $P = 0.02$). Serum calcium levels were elevated in both treatment groups after the initiation of each treatment. In particular, we observed a significant increase in the calcitriol group relative to the levels at the start of this study ($P = 0.006$ vs. $P = 0.26$ in the OCT group). Significant differences were observed between the two groups at 4 weeks (#; $P = 0.02$). Values are given as mean values ± SD. Statistical analyses were assessed by ANOVA and the Mann–Whitney *U* test

Table 3. Adverse effects of OCT and oral pulse treatment

	Group		*P* value
	OCT ($N = 20$)	Oral pulse ($N = 17$)	
Ca × P >70 at least once during treatment	8/20	10/17	NS
Ca × P >70 at least twice during treatment	4/20	4/17	NS
Ca × P >70 at least three times during treatment	2/20	2/17	NS
Ca × P >70 at least four times during treatment	1/20	1/17	NS
Ca × P >70 at least five times during treatment	0/20	1/17	NS
Ca × P <55 at least once during treatment	15/20	11/17	NS
Ca × P <55 at least twice during treatment	13/20	10/17	NS
Ca × P <55 at least three times during treatment	11/20	3/17	0.02
Ca × P <55 at least four times during treatment	10/20	3/17	0.04
Ca × P <55 at least five times during treatment	7/20	2/17	NS

Statistical analyses were assessed by χ^2 test
NS, not significant

throughout the study (ranging from 23.8 ± 7.0 μg/week in the first 4 weeks to 21.3 ± 14.2 μg/week in the last 4 weeks), those of calcitriol were significantly reduced from 6.53 ± 1.39 μg/week in the first 4 weeks to 2.47 ± 1.76 μg/week in the final 4 weeks. Consequently, past from the 4-week time point ($P = 0.02$), no significant differences were observed in intact PTH levels between the OCT and oral calcitriol pulse groups during later treatment periods ($P = 0.14$; Fig. 1A), while serum calcium levels were higher in calcitriol-treated patients than in those receiving OCT treatment during the entire treatment periods ($P = 0.06$; Fig. 1B). The number of patients whose intact PTH was reduced by 50% or more was 17 in the OCT group and 15 in the calcitriol group ($P = 0.77$, χ^2) among patients who completed the entire 24-week study (20 subjects in the OCT group and 17 subjects in the calcitriol group).

Serum levels of bone alkaline phosphatase (BAP) provide an additional efficacy variable reflecting bone remodeling activity. Like intact PTH, BAP was suppressed significantly in both treatment groups. We found no statistical differences in BAP levels between the OCT and the oral calcitriol pulse groups ($P = 0.29$; Fig. 1C).

During the 24 weeks, we observed no significant difference between the OCT and the oral calcitriol groups in serum phosphorus levels ($P = 0.60$). The initial calcium carbonate doses of both groups were also similar ($P = 0.42$).

Three of 23 patients in the OCT group and 6 of 23 in the oral calcitriol pulse group were withdrawn from the study owing to hypercalcemia, hyperphosphatemia, or marked suppression of intact PTH. Hypercalcemia, which led to the cessation of medication (adjusted serum calcium levels >11.5 mg/dl), was more common in the calcitriol group (6 patients) than in the OCT group (1 patient) ($P = 0.04$, χ^2). The incidence of hyperphosphatemia (>7.0 mg/dl in two consecutive measurements) and marked suppression of intact PTH (<150 pg/ml) did not differ significantly between the two treatment groups ($P = 1.00$ and 0.73, respectively, χ^2).

We also analyzed the incidence of elevated calcium–phosphorus (Ca × P) products (>70 mg^2/dl^2) and decreased Ca × P products (<55 mg^2/dl^2) during the treatment periods once a month. No significant differences were observed between treatment groups in the prevalence of Ca × P >70 mg^2/dl^2 during the treatment periods (Table 3). However, the prevalence of achieving Ca × P <55 mg^2/dl^2 was significantly higher in the OCT group than in the oral calcitriol pulse group. The chances of achieving Ca × P <55 mg^2/dl^2 three to four times out of six examinations were significantly higher in the OCT group ($P = 0.02$ and 0.04, respectively Table 3).

The parathyroid glands of a total of 30 patients, 15 from the OCT group and 15 from the calcitriol pulse group, were examined by ultrasound. No significant differences were found between the two groups in the number or size of swollen parathyroid glands. Neither treatment significantly reduced the number or size of swollen parathyroid glands (data not shown).

In the switching trial, 24 patients (15 men and 9 women) were treated with OCT injection therapy instead of oral calcitriol pulse therapy. The intact PTH levels of these patients were 761.4 ± 393.8 pg/ml at the initiation of OCT. Two of the 24 patients were withdrawn after the start of OCT therapy, one because of itching and the other because of a colon carcinoma that was identified incidentally. The remaining 22 patients continued with OCT injection therapy for more than 16 weeks. Patients whose intact PTH was reduced to levels below 300 pg/ml were regarded as responders to OCT therapy. Based on this criterion, 8 patients were classified as responders and 14 patients as nonresponders. In responders, serum intact PTH levels were reduced from 624.9 ± 287.2 pg/ml on entry to 353.7 ± 269.5 pg/ml at 24 weeks after the initiation of OCT treatment, while this level was unchanged from 864.9 ± 430.4 pg/ml to 872.9 ± 362.1 pg/ml in nonresponders. Responding patients tended to have lower serum intact PTH and phosphorus levels at the start of OCT treatment than nonresponders ($P = 0.067$ and 0.081, respectively). No statistically significant differences were found between responders and nonresponders in serum calcium levels or alkaline phosphatase levels at the start of OCT therapy ($P = 0.137$ and 0.477, respectively). Parathyroid glands were examined by ultrasound before and at 24 week after the start

of OCT therapy in 6 of 8 responders and in 10 of 14 nonresponders. The parathyroid glands were found to be smaller in diameter in responders than in nonresponders, although this difference was not statistically significant ($P = 0.060$ at entry).

Discussion

Several analogues of $1,25(OH)_2D_3$ have been synthesized in attempts to achieve better control of secondary hyperparathyroidism. Four of these analogues have recently been marketed for clinical use in patients with chronic kidney disease: 19-nor-1,25-dihydroxyvitamin D_2 (paricalcitol), 1-α hydroxyvitamin D_2 (doxercalciferol), 22-oxacalcitriol (OCT), and 1,25-dihydroxy 26,27F6D_3 (falecalcitriol). Among these synthetic calcitriol analogues, OCT shows little calcemic activity.[7] In this study, we compared the effects and acceptance levels of intravenous OCT injection with oral calcitriol pulse therapy.

In a randomized controlled study, both OCT and oral calcitriol therapy effectively suppressed intact PTH and BAP. Serum calcium levels in the calcitriol pulse group were greater than those in the OCT group over the 24 weeks of the treatment course. A significant decline in serum intact PTH levels occurred in the first 4 weeks of treatment, concomitant with an increase in serum calcium levels. The initial dose of oral pulse calcitriol was selected on the basis of previous reports. Shigematsu et al.[11] hypothesized that a single oral dose of 8.0 μg calcitriol is necessary to suppress PTH. However, to reduce the risk of hypercalcemia, Tsukamoto et al.[3] recommended administering 4.0 μg oral calcitriol twice a week. In this study, although we began oral calcitriol pulse therapy with an initial dose of 4.0 μg, the doses were significantly decreased in adherence to a predefined dosing schedule. On the other hand, the doses of OCT were kept almost constant during the treatment periods. Six patients discontinued oral calcitriol therapy due to hypercalcemia, with 4 of the 6 cases developing hypercalcemia between weeks 4 and 8 of the study. In contrast, only 1 patient in the OCT group developed hypercalcemia that required the cessation of the medication. Thus, our study confirms the hypothesis that OCT exhibits less calcemic activity than oral calcitriol, although the conclusions that can be drawn from the trial are somewhat qualified by the potentially excessive loading dose of calcitriol.

The effects of secondary hyperparathyroidism and its management on vascular disease have attracted considerable attention. A recent report indicates that patients receiving paricalcitol appear to have a significant edge in survival rates over those receiving calcitriol.[12] Other reports indicate that chronic hemodialysis patients with elevated calcium–phosphorus (Ca × P) products (>72 mg^2/dl^2) face a significantly greater risk of mortality than patients with products of 42–52 mg^2/dl^2.[13] These results suggest that improved control of hyperparathyroidism and calcium phosphorus metabolism may improve the survival rate of dialysis patients. According to NKF K/DOQI guidelines,[14] calcium–phosphorus products must be maintained at levels below 55 mg^2/dl^2. In this study, we observed that the prevalence of Ca × P <55 mg^2/dl^2 was significantly higher in the OCT group than in the oral calcitriol pulse group (see Table 3). In this regard, OCT may be a better choice than calcitriol in controlling hyperparathyroidism in hemodialysis patients. Further study is needed to determine whether OCT is superior to calcitriol for preventing the acceleration of vascular disease.

In the switching study, patients in whom oral vitamin D pulse therapy failed to control hyperparathyroidism were treated with OCT injection therapy. Eight of 22 patients appeared to respond to OCT therapy. These 8 patients tended to show lower serum intact PTH and phosphorus levels and smaller parathyroid glands at the start of the study. These parameters may serve as predictive markers to help determine which patients may benefit from switching vitamin D therapy.

In conclusion, OCT was shown to be as effective as oral calcitriol pulse therapy in suppressing intact PTH and BAP levels in chronic hemodialysis patients, while calcium levels were maintained at lower levels than with calcitriol pulse therapy. Discontinuation because of hypercalcemia was more frequent in the oral calcitriol group. Moreover, in certain patients, OCT may offer significant advantages in treating hyperparathyroidism which is refractory to conventional oral calcitriol pulse therapy.

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