Effect of 22-oxacalcitriol on Secondary Hyperparathyroidism in Hemodialysis Patients

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Abstract

Objective A synthetic analogue of calcitriol, 22-oxacalcitriol (OCT), strongly suppresses parathyroid hormone (PTH) secretion. This study investigated the influence of OCT on PTH secretion and bone metabolism in 12 hemodialysis patients with secondary hyperparathyroidism.

Methods OCT was intravenously injected after every hemodialysis session (three times weekly) for 22 weeks. The levels of the following parameters were measured: intact PTH, whole PTH, whole PTH/7–84 PTH ratio, adjusted calcium, phosphorus, alkaline phosphatase (ALP), bone-specific alkaline phosphatase (BAP), intact osteocalcin (OC), type I collagen carboxyterminal propeptide, tartrate-resistant acid phosphatase (TRAP), cross-linked C-terminal telopeptides of type I collagen, and interleukin-6.

Patients The subjects were 12 hemodialysis patients (8 men and 4 women) with an intact PTH level of more than 460 pg/ml, a normal serum calcium level, and a serum phosphorus of less than 7 mg/dl.

Results The levels of intact PTH, whole PTH, whole PTH/7–84 PTH ratio, ALP, BAP, OC, and TRAP were significantly decreased after OCT administration, while adjusted calcium was significantly increased. Serum phosphorus and the other parameters showed no significant changes.

Conclusion OCT effectively suppressed the PTH level and bone metabolism parameters in hemodialysis patients with secondary hyperparathyroidism.

Key words: hemodialysis, secondary hyperparathyroidism, 22-oxacalcitriol

Introduction

Secondary hyperparathyroidism is a major complication in patients on chronic hemodialysis. In addition to the standard regimen for this complication, intermittent administration of high-dose calcitriol (so-called ‘pulse therapy’) is effective for reducing the plasma parathyroid hormone (PTH) level (1–3), decreasing the size of hyperplastic parathyroid glands (4, 5), up-regulating vitamin D receptor expression by parathyroid cells, and normalizing the rightward shift of the PTH-calcium curve (6, 7). However, hypercalcemia caused by calcitriol is a major factor limiting the dose that can be given or the use of pulse therapy.

It has been reported that 22-oxacalcitriol (OCT), a synthetic analogue of calcitriol (8), has a weaker calcemic effect than calcitriol itself, while strongly suppressing PTH in a comparable manner (9–13). Thus, OCT may be clinically useful for the management of secondary hyperparathyroidism in chronic hemodialysis patients. This study was designed to investigate the influence of OCT on PTH secretion and bone metabolism parameters.

Subjects and Methods

Subjects

This study was performed on 12 patients (8 men and 4 women) from among the 272 patients on chronic hemodialysis at Ichiyokai Clinic in Japan. The subjects had an intact PTH level of more than 460 pg/ml, a normal serum calcium level, and a serum phosphorus level of less than 7 mg/dl. We excluded patients who did not fit these criteria. The primary disease was chronic glomerulonephritis in 9 patients, nephrosclerosis in 1 patient, and other diseases in 2 patients. The patient ages ranged from 39 to 71 years and the duration of dialysis ranged from 120 to 276 months. All patients were dialyzed 3 times per week and had enlarged parathyroid glands with a volume of more than 1.0 cm³.
Methods

After obtaining informed consent, OCT was administered intravenously immediately after every dialysis session (three times per week) for 22 weeks. The initial dose of OCT was 10 µg per session and this was decreased to 5 µg per session when the intact PTH level was less than 500 pg/ml. Subsequently, the dose of OCT was increased or decreased in increments of 2.5 µg based on its suppression of PTH and its calcemic action. OCT was discontinued for at least one week when the serum calcium level adjusted for albumin (adjusted calcium) exceeded 11.0 mg/dl just before dialysis. The calcium concentration of the dialysate was 3.0 mEq/l, and other dialysis conditions remained constant throughout the study period. Calcium carbonate was used as the oral phosphate binder, and its dose was not changed in relation to the serum phosphorus level. However, when the adjusted calcium level was greater than 10.5 mg/dl, treatment with calcium carbonate was suspended or the dose was reduced.

Laboratory tests

Blood samples were taken from the arterial end of the extracorporeal set at the commencement of hemodialysis. Blood was collected after an overnight fast for measurement of the serum concentrations of intact PTH, whole PTH, adjusted calcium, phosphorus, alkaline phosphatase (ALP), bone-specific alkaline phosphatase (BAP), intact osteocalcin (OC), type I collagen carboxyterminal propeptide (PICP), tartrate-resistant acid phosphatase (TRAP), cross-linked C-terminal telopeptides of type I collagen (ICTP), and interleukin-6 (IL-6). Intact PTH was measured using a Nichols IRMA kit (Nichols Institute, San Juan Capistrano, CA, USA), and whole PTH was measured using a Scantibodies IRMA kit (Scantibodies Laboratories, Santee, CA, USA). BAP was measured using an Alkphor System EIA kit (Jokoh, Tokyo, Japan), for which the intra-assay and inter-assay coefficients of variation were 2.3% and 5.4%, respectively. OC was measured using an Osteocalcin Test Kokusai-F IRMA kit (International Reagents Corporation, Tokyo, Japan), for which the intra-assay and inter-assay coefficients of variation were 5.2% and 7.2%, respectively. PICP was measured with a Type I procollagen PICP RIA kit (Chugai Diagnostics Science, Tokyo, Japan), its intra-assay and inter-assay coefficients of variation were 3.1% and 7.6%, respectively. TRAP was measured using an N-Assay ACP Nittobo EIA kit (Nitto Boseki, Tokyo, Japan), which had intra-assay and inter-assay coefficients of variation of 1.5% and 3.2%, respectively. ICTP was determined with a Type I Telopeptide ICTP RIA kit (Chugai Diagnostics Science), for which the intra-assay and inter-assay coefficients of variation were 5.0% and 8.7%, respectively. IL-6 was measured with a Fuji Rebio IL-6 CLEIA kit (Fuji Rebio, Tokyo, Japan), its intra-assay and inter-assay coefficients of variation were 2.1% and 7.1%, respectively. 7-84 PTH was calculated by subtracting intact PTH from whole PTH. The adjusted calcium level was calculated using Payne’s formula.

Statistical analysis

Results are expressed as the mean±SE. Data were analyzed by the Wilcoxon signed rank test, with p<0.05 indicating a significant difference. All analyses were performed with Stat View 5 software (Abacus Concepts, Inc., Berkeley, CA).

Results

The intact PTH level showed a significant decrease, falling from 950±97.7 pg/ml to 539±54.3 pg/ml after eight weeks of OCT therapy and then to 434±56.1 pg/ml after 12 weeks. It rose again to 620±74.9 pg/ml after 16 weeks, but
OCT in Dialysis Patients
decreased to $419\pm53.6$ pg/ml at 22 weeks. The whole PTH level was decreased significantly after 12 weeks of OCT therapy and remained almost the same at 22 weeks (Fig. 1). In contrast, the whole PTH/7–84 PTH ratio showed no significant changes (Fig. 2). After the start of OCT therapy, the adjusted calcium level showed a significant increase from the 6th week onward (except in weeks 15, 16, and 21). Serum phosphorus levels did not change significantly at any time (Fig. 3). Serum ALP was decreased in weeks 8, 12, and 22 (Fig. 4). The levels of BAP, OC, and TRAP were significantly decreased in weeks 12 and 22. ICTP levels were significantly decreased after 12 weeks, but not after 22 weeks. The PICP level showed no significant changes at any time (Table 1), and serum IL-6 also showed no significant changes during OCT treatment (Fig. 5). The changes of the OCT dose over time are shown in Fig. 6. The initial dose of

| Table 1. Changes of Serum Bone Metabolism Parameters |
|-----------------|---------|---------|---------|
|                 | Week 0  | Week 12 | Week 22 |
| BAP (IU/l)      | 43.4±4.6| 33.9±4.9*| 30.1±4.6*|
| OC (ng/ml)      | 96.6±13.4| 70.9±14.7*| 75.0±14.9*|
| PICP (ng/ml)    | 246.4±22.0| 270.6±22.5| 268.2±15.8|
| TRAP (IU/l)     | 10.2±0.6| 9.3±0.7*| 9.1±0.7*|
| ICTP (ng/ml)    | 65.5±6.6| 56.4±5.4*| 57.7±5.6|

*p<0.05

![Figure 3. Adjusted calcium level and phosphorus level. The adjusted calcium level showed a significant increase from the 5th week onward (except in weeks 6, 15, 16, and 21). Serum phosphorus levels did not change significantly at any time.](image)

![Figure 4. Changes of ALP. Serum ALP was decreased in weeks 8, 12, and 22.](image)

![Figure 5. Changes of IL-6. The serum IL-6 level showed no significant changes.](image)

![Figure 6. Modification of the 22-oxacalcitriol dose. The initial dose of 22-oxacalcitriol was 10 µg per session and this was decreased to 5 µg per session when the intact PTH level was less than 500 pg/ml. Subsequently, the 22-oxacalcitriol dose was increased or decreased in increments of 2.5 µg per session based on its suppression of PTH and its calcemic action.](image)
22-oxacalcitriol was 10 μg per session and this was decreased to 5 μg per session when the intact PTH level was less than 500 pg/ml. Subsequently, the dose of 22-oxacalcitriol was increased or decreased in increments of 2.5 μg per session based on its suppression of PTH and its calcemic action. There were no patients who needed parathyroidectomy or percutaneous ethanol injection therapy throughout this study.

**Discussion**

Since the first report on the use of intravenous calcitriol pulse therapy for secondary hyperparathyroidism by Slatopolsky et al (1), much attention has been directed to the route of calcitriol administration, the dose and interval of administration, and the use of other vitamin D derivatives for a similar purpose (14). However, hypercalcemia has been a major obstacle to the continuation of pulse therapy in many patients. Clinical use of OCT for the treatment of secondary hyperparathyroidism has been anticipated, because it has been shown that OCT suppresses PTH secretion and PTH mRNA expression in normal as well as uremic rats and dogs without causing hypercalcemia (10, 15).

In the present patients, the mean pretreatment intact PTH level and whole PTH level were consistent with severe secondary hyperparathyroidism (951±97.7 pg/ml and 551±69.1 pg/ml, respectively), and measurement of bone metabolism parameters indicated that the patients had high bone turnover. Their average age was fairly young (55.3±2.8 years), the average dialysis period was quite long (189.3±15.2 months), and 75% of them had glomerulonephritis. It was thought that these features might have been associated with severe secondary hyperparathyroidism.

In this study, the levels of intact PTH and whole PTH were significantly decreased by OCT administration. Although the number of patients was very small, we clearly demonstrated that OCT could suppress PTH secretion at a dose of 2.5–10 μg per session. These findings are consistent with the results obtained in uremic animal models. Because the whole PTH/7–84 PTH ratio showed no significant changes, the reduction of whole PTH was similar to the reduction of intact PTH. Such serious secondary hyperparathyroidism is conventionally considered to be an indication for parathyroidectomy or percutaneous ethanol injection therapy. In this study, OCT was able to delay the need for such measures by at least 6 months, which may suggest the superior efficacy of this drug.

Although the adjusted calcium level was significantly increased after 5 weeks of OCT administration, the actual rise of adjusted calcium was slight. In addition, because the adjusted calcium level decreased soon after stopping OCT or reducing the dose, hypercalcemia seems to be easy to control during OCT administration. OCT has a very weak affinity with vitamin D-binding protein, so its calcemic effect was expected to be mild. However, an increase of serum calcium still occurred, thus in the future the calcemic effect will need to be compared with that of other drugs.

In this study, the adjusted calcium level increased, and therefore we were not able to administer high enough doses of calcium carbonate. Thus, the serum phosphorus level was increased, but phosphorus showed no significant changes. These findings suggest that OCT does not promote an increase of phosphorus.

Among the bone metabolism parameters, BAP, OC, and TRAP were significantly decreased throughout treatment. It was reported that BAP (16), OC (17), and TRAP (18) are useful markers of bone metabolism in hemodialysis patients, so our results suggested that high bone turnover might have been improved. Although it is unknown whether OCT acts directly on the bone, it seems that bone turnover was improved along with the suppression of PTH secretion. The level of ALP, a bone formation marker, was decreased in weeks 8, 12, and 22, but there were no other changes. These findings suggested the occurrence of bone formation similar to that caused by vitamin D and improvement of high bone turnover. There were no significant changes in PICP or ICTP levels. Although a long-term study is necessary to better evaluate these parameters, they may not be suitable markers to judge the effect of OCT. In addition, there were no patients who developed low bone turnover, judging from the bone metabolism parameters that we monitored.

It has been reported that OCT induces IL-6 production (19) and it has been suggested that OCT may preferentially stimulate the systemic or local production of cytokines and growth factors involved in the recruitment of bone cells (20). Although serum IL-6 levels showed no significant changes in this study, the influence of OCT on the bone needs to be clarified in the future.

In conclusion, OCT is highly effective for suppressing secondary hyperparathyroidism in chronic hemodialysis patients without inducing low bone turnover. The dose of OCT should be modified on the basis of the PTH level, adjusted calcium level, and bone metabolism parameters.

**References**

OCT in Dialysis Patients