Effect of 22-oxacalcitriol on hyperparathyroidism of dialysis patients: results of a preliminary study

K. Kurokawa1, T. Akizawa2, M. Suzuki3, T. Akiba4, E. Ogata5 and E. Slatopolsky6

1Departments of Medicine, University of Tokyo, Tokyo, 2Fujigaoka Hospital, Showa University, Yokohama, 3Shinrakuen Hospital, Niigata, 4Tokyo Medical and Dental University, Tokyo, 5Cancer Institute Hospital, Tokyo, Japan, and 6Washington University School of Medicine, St Louis, USA

Abstract. Intermittent high dose administration of calcitriol or alfacalcidol is effective in suppressing secondary hyperparathyroidism in chronic dialysis patients, however calcaemic action of these vitamin D derivatives is a major obstacle. 22-Oxacalcitriol (OCT) has been reported to have less calcaemic action than calcitriol, while preserving a comparable suppressive effect on parathyroid hormone (PTH) secretion. This preliminary study was conducted to examine the effects of OCT on secondary hyperparathyroidism in chronic dialysis patients.

OCT was administrated intravenously immediately after every haemodialysis session three times a week for 12 weeks to three haemodialysis patients with secondary hyperparathyroidism. An initial dose of OCT of 5.5 ug/haemodialysis session was increased stepwise by 5.5 ug/haemodialysis up to 22 ug/haemodialysis according to the suppression of PTH and calcaemic action. OCT was discontinued for at least a week when serum calcium adjusted to albumin concentration measured just before haemodialysis exceeded 11.5 mg/dl. Marked reduction in plasma PTH, alkaline phosphatase and tartrate-resistant acid phosphatase was observed in all three patients. Although the dose of OCT was increased to 22 ug/haemodialysis in one patient, the final dose of OCT remained 5.5 ug/haemodialysis in the other two patients because of hypercalcaemia. It is concluded that OCT is highly effective in suppressing PTH in dialysis patients with secondary hyperparathyroidism. Hypercalcaemia may be a major factor which limits the use of OCT, though it may occur with higher doses of OCT than those of calcitriol usually given to suppress PTH hypersecretion.

Key words: secondary hyperparathyroidism; calcitriol; 22-oxacalcitriol; vitamin D pulse therapy; haemodialysis; hypercalcaemia

Introduction

Secondary hyperparathyroidism is a major complication in chronic dialysis patients. In addition to the standard regimen to manage this complication, intermittent administration of high doses of calcitriol (called 'pulse therapy') is an effective tool to suppress plasma parathyroid hormone (PTH) level [1–3], to decrease enlarged hyperplastic parathyroid glands [4,5], to up-regulate reduced vitamin D receptors in parathyroid cells and to normalize right-shifted PTH–calcium sigmoidal curve [6,7]. However, hypercalcaemia resulting from the high dose of calcitriol is a major limiting factor in increasing the dose of calcitriol or continuing the pulse therapy.

22-Oxacalcitriol (OCT), a synthetic analogue of calcitriol (Chugai Pharmaceutical, Tokyo, Japan) [8], has been reported in both in vitro and in vivo systems of normal animals and animal models of chronic renal failure to have a less calcaemic effect than calcitriol, while it maintains a strong suppressive effect on PTH comparable to calcitriol [9–13]. Thus, OCT may be useful clinically in the management of secondary hyperparathyroidism in chronic dialysis patients. This preliminary study was designed to investigate the safety and efficacy of OCT in chronic haemodialysis patients with secondary hyperparathyroidism.

Subjects and methods

Subjects had more than 20 ng/ml high sensitive mid-terminal PTH (HS-PTH) and/or more than 6 ng/ml carboxy-terminal PTH (C-PTH), normal range of serum calcium, and serum phosphorus of less than 7 mg/dl. The study protocol was approved by the Institutional Review Board for clinical studies.

After securing the subjects' informed consent, vitamin D analogues including calcitriol or alfacalcidol were withdrawn. Two weeks later, OCT was administrated intravenously at the end of every haemodialysis for 12 weeks. Initial dose of OCT was 5.5 µg/haemodialysis for 3 weeks. The dose after 3 weeks was increased by 5.5 µg/haemodialysis to 11 µg/haemodialysis if serum intact PTH did not decrease by more
Fig. 1. Administering schedule of 22-oxacalcitriol (OCT). Each patient was given OCT at the end of each haemodialysis (HD) at a dose specified in the protocol. All patients underwent dialysis three times a week.

than 30% and serum calcium adjusted for albumin (adjusted calcium) remained less than 10.5 mg/dl; otherwise the dose was not altered during the following 3 weeks. The dose after 6 and 9 weeks was again adjusted following the serum PTH and calcium criteria described above (Figure 1).

When serum-adjusted calcium just before haemodialysis exceeded 11.5 mg/dl, OCT was discontinued for at least 1 week, and restarted with a one rank lower dose after confirming that the adjusted calcium was less than 11 mg/dl. The dose was decreased to 3.3 μg/haemodialysis, and then 1.1 μg/haemodialysis if hypercalcaemia developed.

Dialysate calcium concentration was either 3.0 mEq/l or 2.5 mEq/l, but kept at each value throughout the study, and other dialysis conditions were also kept constant throughout the study period. Calcium carbonate or acetate was used as oral phosphate binders.

Results

Case 1

Case 1 was a 55 year old female (Figure 2). She had been on regular haemodialysis since 1983 because of end-stage renal disease (ESRD) due to chronic glomerulonephritis. She had severe secondary hyperparathyroidism with 2730 pg/ml intact PTH and 179 ng/ml HS-PTH at the start of OCT (week 0). Although serum-adjusted calcium, 9.4 mg/dl at week 0, gradually increased and reached 9.9 mg/dl at week 12, the dose of OCT was stepwise increased from 5.5 to 22 μg/dialysis without any hypercalcaemic episodes. Intact PTH and HS-PTH decreased to 1390 pg/ml and 134 ng/ml, respectively, in spite of the increase in serum phosphorus. Alkaline phosphatase (ALP) and tartrate-resistant acid phosphatase (TRACP) were also reduced from 957 and 14.2 IU/l to 614 and 9.4 IU/l, respectively. A rebound increase in intact PTH was observed 2 weeks after discontinuation of OCT.

Case 2

Case 2 was a 50 year old female (Figure 3). She had been on haemodialysis since 1981 because of ESRD from chronic glomerulonephritis. Her plasma intact PTH level, 620 pg/ml at week 0, was decreased remarkably to 259 pg/ml at week 5 in response to 5.5 and then 11 ug/dialysis OCT. However, the dose of OCT had to be reduced to 5.5 μg/dialysis because serum-adjusted calcium reached 11.3 mg/dl at week 5 from 10.0 mg/dl at week 0. Following 12 weeks administration of OCT, considerable decreases in intact PTH (620 to 375 pg/ml), HS-PTH (41.2 to 39.3 ng/ml), ALP (379 to 264 IU/l) and TRACP (10.3 to 8.4 IU/l) were observed. Serum phosphorus was well controlled in this patient. A rapid rebound in intact PTH was noted.
Clinical use of 22-oxa-calcitriol in secondary hyperparathyroidism

Discussion

Since the first report of the use of intravenous calcitriol 'pulse therapy' in secondary hyperparathyroidism by Slatopolsky [1], much attention has been directed to the route of calcitriol administration (i.e. intravenous or oral), the dose and interval of calcitriol administration and other vitamin D derivatives for similar use [14]. However, hypercalcaemia has been a major obstacle to continuing the 'pulse therapy' in many patients. The clinical use of OCT was anticipated for the treatment of secondary hyperparathyroidism, because it has been shown that OCT could suppress enhanced PTH secretion and PTH mRNA in normal as well as uraemic rats and dogs without causing hypercalcaemia [15,16].

The present clinical study, although the number of patients was very small, clearly demonstrated that OCT could suppress PTH secretion at doses of 5.5–22 μg/haemodialysis. Reduction of intact PTH before increase in serum-adjusted calcium was noted in Cases 1 and 3. These findings are consistent with the results obtained in uraemic animal models.

However, serum-adjusted calcium was increased in all cases at the end of the study, i.e. by week 12, and reduction of OCT dosage was necessary in one patient because of hypercalcaemia. The reasons for the difference in calcaemic effect in these patients are immediately clear. It has been reported that calcaemic action may be observed with high doses of OCT in animals and the sensitivity for calcaemic action of OCT may differ among the different species [16]. For example, dogs were about 100 times more sensitive than rats to calcaemic action of OCT. But even in dogs, serum calcium did not show any increase after 1 μg/kg bolus injection of OCT [16]. In healthy humans, neither 0.11 μg/kg bolus injection nor 0.055 μg/kg 4 times consecutive administration of OCT every other day had a calcaemic effect [17].

However, in the most sensitive case among the present patients, adjusted calcium increased by 0.6 mg/dl after 3 times administration of 0.12 μg/kg OCT (Case 2), whereas it increased by 1.4 mg/dl after 24 times administration of 0.14 μg/kg OCT in Case 3. In Case 1, serum calcium increased by only 0.5 mg/dl even after the stepwise increase in OCT up to 22 μg/haemodialysis. From these results, it may be concluded that OCT at clinically effective doses to suppress PTH can increase serum calcium, and the calcaemic response to OCT may differ widely among the patients. No adverse effect of OCT other than hypercalcaemia was observed during this preliminary study. Thus, it may be important to elucidate the determinants of calcaemic response to OCT in patients to establish the clinical significance and indications of OCT in the treatment of secondary hyperparathyroidism in dialysis patients.

In conclusion, OCT is highly effective in suppressing secondary hyperparathyroidism of dialysis patients. However, hypercalcaemia may be a major adverse effect, though it may occur at higher doses of OCT than those of calcitriol usually given to treat secondary hyperparathyroidism. Further studies are necessary to verify the difference in suppressive effects on PTH and calcaemic actions between OCT and calcitriol, and among different patients.

References

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