Comparison of the effects of calcitriol and maxacalcitol on secondary hyperparathyroidism in patients on chronic haemodialysis: a randomized prospective multicentre trial

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Abstract

Background. To identify differences between the effects of calcitriol and the calcitriol analogue, maxacalcitol, on parathyroid hormone (PTH) and bone metabolisms, we conducted a randomized prospective multicentre study on patients on chronic haemodialysis.

Methods. We randomly assigned 91 patients with secondary hyperparathyroidism (intact PTH (iPTH) ≥150 pg/ml) to have either calcitriol (47 patients) or maxacalcitol (44 patients) therapy, for 12 months after a 1 month control period. Serum electrolytes, bone alkaline phosphatase (bAP), iPTH, total PTH and PTH(1–84) (whole PTH) levels were measured periodically. The first end point was a serum iPTH of <150 pg/ml, the second was the iPTH levels obtained.

Results. Treatment was discontinued for various reasons in nine patients in each group, but no serious side effects were observed in either group. The numbers of cases reaching the first end point were not significantly different between the two groups. Serum calcium concentration was significantly higher in the maxacalcitol than the calcitriol group during early treatment, but not at the end of treatment. Throughout the treatment period there were no significant differences between the two groups in serum iPTH, inorganic phosphate, the product of the serum calcium and inorganic phosphorus concentrations, bAP, or the ratio of whole PTH to total PTH minus whole PTH. Nor were the changes in these parameters significantly different between the two groups comparing the patients with moderate to severe hyperparathyroidism (basal iPTH ≥500 pg/ml).

Conclusion. Calcitriol and maxacalcitol are equally effective on PTH and bone metabolism.

Keywords: bone alkaline-phosphatase; calcitriol; end-stage renal failure; maxacalcitol; secondary hyperparathyroidism; vitamin D analogue

Introduction

Impairments of bone and mineral metabolism are major complications in patients on chronic haemodialysis (HD). Because of the increasing number of patients with end-stage renal failure (ESRF) and their improved prognosis, nephrologists are devoting increasing attention to metabolic bone diseases [1]. There are several varieties of metabolic bone disease in ESRF patients, including adynamic bone disease, osteomalacia and hyperparathyroidism (high-turnover) bone disease—the hyperparathyroid bone disease being thought to be attributable to impaired vitamin D metabolism induced by renal failure. Hyperparathyroidism currently is being treated medically and surgically [2,3]. Calcitriol has been widely used to treat secondary hyperparathyroidism in patients on chronic HD; remarkable progress has been made in the treatment of this disorder, though this is limited by the adverse effects of the therapy, which include hypercalcaemia, hyperphosphataemia, and the development of adynamic bone disease [1,4]. To overcome these adverse effects, several vitamin D analogues have recently been developed and are now being used clinically [5]. Maxacalcitol, 1,25dihydroxy-22-oxavitamin D3, was developed in Japan, and is now in clinical use. During the basic studies in rats, it was found to have a marked suppressive effect on secondary hyperparathyroidism...
and to be associated with only minor changes in calcium and phosphate levels [6–9], but clinical studies showed that maxacalcitol caused hypercalcaemia in patients on chronic HD [6,10–12]. However, it is not known if this side effect of maxacalcitol is less severe than of calcitriol, or if the effects of maxacalcitol on bone and parathyroid hormone (PTH) metabolism differ from those of calcitriol. To answer these questions, in this study we performed a 12 month randomized prospective trial of the effects of maxacalcitol and calcitriol on outpatients on chronic HD in multiple centres. We randomly assigned 91 patients to receive either maxacalcitol or calcitriol, and periodically measured their intact PTH (iPTH), serum calcium and phosphorus, and bone alkaline phosphatase (bAP). We concluded that the suppressive effects of both compounds on the secretion and metabolism of PTH are similar and that the changes each produces in biochemical parameters are essentially comparable.

Patients and methods

Study protocol

We enrolled 91 patients who were 18 years or older, had stable chronic renal failure, were on HD twice or thrice a week and met the following criteria, and who consented to take part in this study: (1) iPTH ≥150 pg/ml; (2) pre-dialysis adjusted serum calcium ≥10.5 mg/dl; (3) no history of treatment with vitamin D preparations, or at least a 4 week wash-out period; (4) on dialysis for at least 12 months, and stable clinical findings; (5) absence of severe liver disease.

The patients were randomly assigned to two treatment groups, a calcitriol group and a maxacalcitol group. The calcium concentration of the dialysate was 3.0 mEq/l in all patients. The patients in the calcitriol group received 1 μg of calcitriol/HD session, and the patients in the maxacalcitol received either 10 μg (for basal iPTH ≥500 pg/ml) or 5 μg (for basal iPTH <500 pg/ml) of maxacalcitol/HD session. The inclusion criteria and the doses of calcitriol and maxacalcitol were determined based on the results of previous long-term trials of maxacalcitol [10,11] and calcitriol [13].

In a different double-blind comparison study with four doses of maxacalcitol [10], the drug was discontinued as a result of hypercalcaemia in patients receiving 5, 10 or 15 μg/HD maxacalcitol; and all patients who dropped-out for hypercalcaemia while on 10 μg/HD maxacalcitol had an initial PTH <500 pg/ml. Based on this result, two initial doses of maxacalcitol for secondary hyperparathyroidism were recommended. In another clinical trial with maxacalcitol [11], patients with high-sensitivity PTH (HS-PTH) ≥20,000 pg/ml were enrolled in the maxacalcitol trial and assigned to receive one of two doses of maxacalcitol, the same as in the present study. The iPTH of the patients in that trial ranged between 147 and 3930 pg/ml at the start; and again two different doses of maxacalcitol, based on the basal iPTH levels, were recommended by this trial [11]. Patients with HS-PTH ≥20,000 pg/ml or iPTH ≥150 pg/ml were enrolled in the calcitriol trial [13]. Three doses of calcitriol were evaluated, and the investigators concluded that 1 μg calcitriol/HD is appropriate and safe for initial treatment, regardless of the iPTH level. We followed these study protocols and recommendations in designing the protocol of the present study.

Maxacalcitol and calcitriol were given intravenously at the end of every HD session for 12 months. Pre-dialysis adjusted serum calcium (measured calcium concentration + 4.0 – serum albumin concentration) and phosphate levels were measured, every 2 weeks after the longest of interdialysis periods. When the adjusted serum calcium level exceeded 11.5 mg/dl, calcitriol or maxacalcitol was discontinued or their doses were decreased at the treating physician’s discretion. When iPTH decreased to <150 pg/ml, treatment was stopped, but if the iPTH level subsequently exceeded 150 pg/ml, the assigned therapy was re-started at a lower dose than before its interruption. When the adjusted serum calcium was <11.5 mg/dl and iPTH was >150 pg/ml, the doses of calcitriol and maxacalcitol were increased to 1.5 and 20 μg/HD, respectively. This dose adjustment was made monthly at the treating physician’s discretion. Calcium carbonate was used as the phosphate binder, and its dose was adjusted to maintain phosphate levels below 6.0 mg/dl whenever possible. The doses of calcium carbonate in this study were not significantly different between the two groups.

Blood specimens were collected from each patient, at the start of the dialysis session after the longest interdialysis period, before the start of the treatment and after 1, 2, 4, 6, 8, 10 and 12 months of treatment. The blood samples were analysed for iPTH (IRMA), bone-alkaline phosphatase (bAP, EIA), serum calcium and phosphorus by the Mitsubishi Medical Co. (Tokyo, Japan); total and whole PTH were measured by Scantibodies Laboratory (Santee, USA) using an IRMA. The total PTH assay [14] detects not only PTH (1–84), which is true iPTH, but also PTH fragments, such as PTH(7–84), which lack the N-terminus of PTH. The whole PTH assay, on the other hand, detects only PTH(1–84) but not PTH fragments. The whole PTH to non-PTH(1–84) ratio was calculated by using the following formula:

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\text{whole PTH to non-PTH}(1–84) = \frac{\text{whole PTH}}{(\text{total PTH} – \text{whole PTH})}
\]

Serum biochemical parameters, such as total protein, albumin, electrolytes and creatinine, were measured independently at each clinic. This study was conducted from October 2001 to December 2002 after obtaining the approval of the institutional review board at each centre.

Patients

A total of 91 patients were enrolled in this study, but nine patients (three in the maxacalcitol group and six in the calcitriol group) were later found to not satisfy the inclusion criteria, and their data were excluded from analysis. In the maxacalcitol group, six patients did not complete the study—one died of complications unrelated to treatment, three moved, and one underwent kidney transplantation. In the calcitriol group, three patients did not complete the study—one died of complications unrelated to treatment and two moved. In the maxacalcitol group, 35 patients, and in the calcitriol group, 38 patients, completed the 12 month treatment. In the maxacalcitol group, 15 patients, and in the calcitriol group, 14 patients, had been on an active form of
vitamin D (four in the maxacalcitol group and eight in the calcitriol group) or maxacalcitol (11 in the maxacalcitol group and six in the calcitriol group), but all medications had been stopped at least 1 month before the start of this study. The difference between the numbers of previously treated patients in the two groups was not statistically significant. The final doses of maxacalcitol and calcitriol were 11.5±1.5 and 2.2±0.2 mg/week, respectively. There were no significant differences in patients’ characteristics between the two groups (Table 1).

**Statistical analysis**

One-way analysis of variance with repeated measurements followed by Fisher’s test was used for comparisons between pre- and post-treatment data within each group. The differences in the effects of the two drugs were statistically analysed by two-way analysis of variance with repeated measurements. The chi-square test was used for inter-group comparisons of background factors that had a categorical distribution. Values are expressed as means±standard error of the mean (SEM). *P*<0.05 was considered statistically significant.

**Results**

As shown in Figure 1A, serum calcium concentrations increased significantly in both groups, and a two-way analysis of variance showed that the time-courses of changes in calcium concentrations were significantly different between the two, probably because of differences during the early phase of treatment. The differences in the changes in serum phosphorus and the products of the serum calcium concentration and serum inorganic phosphorus concentration (Ca × IP) did not reach statistical significance during the 12 month period in either group (Figures 1B and C). In the maxacalcitol group, two patients (two episodes), and in the calcitriol group, one patient (two episodes), developed hypercalcaemia (adjusted calcium concentration >11.5 mg/dl) during the study. In each group, 30 patients developed hyperphosphataemia, with phosphorus...
concentrations > 6.0 mg/dl (121 episodes in the maxacalcitol group, 112 episodes in the calcitriol group). The numbers of patients and episodes with hypercalcaemia or hyperphosphataemia were not significantly different between the two groups.

Changes in iPTH levels are shown in Figure 2A. At 1 month after the start of the treatment, iPTH had decreased significantly (P < 0.001) in both the maxacalcitol group and the calcitriol group, and the decrease persisted until the end of the study. The response of iPTH to treatment, however, was not significantly different between the two groups. The maximum inhibition rates, calculated as [basal iPTH – the lowest iPTH]/basal iPTH, were not different between the two groups (maxacalcitol 67.4 ± 4.2%, calcitriol 60.8 ± 3.4%). In the maxacalcitol group, 18 patients, and in the calcitriol group, 13 patients, reached the primary end point (iPTH < 150 pg/ml) during the study; the difference was not statistically significant. As shown in Figure 2B, the levels of whole PTH obtained by treatment were not significantly different between the two groups, but they decreased significantly compared with pre-treatment levels in each group. The patterns of changes in the whole PTH/non-PTH(1–84) ratio were similar in the two groups (Figure 2C). During the first 6 months, the whole PTH/non-PTH(1–84) ratio showed small and insignificant decreases, but at the end of the 12 month period the ratio showed a significant increase in the maxacalcitol group. The whole PTH/non-PTH (1–84) ratio showed a tendency to increase in the calcitriol group, but the increase reached statistical significance only at 10 months. The difference at 12 months was not significant, probably due to large variations among the 12 month values.

The bAP showed a significant and consistent decrease in the maxacalcitol group after 8 months of treatment (Figure 3). In the calcitriol group, on the other hand, bAP showed a significant decrease after 8 and 10 months of treatment, but the change in bAP after 12 months did not reach statistical significance, probably due to large variations within the data. There were no statistically significant differences between the effects of the two drugs on bAP, based on the results of the two-way analysis of variance.

Since we had included patients with mild hyperparathyroidism in this study, and since the initial dose of maxacalcitol was adjusted according to the basal level of iPTH, we also analysed the data for the patients with basal iPTH ≥500 pg/ml (21 patients in the maxacalcitol group and 17 patients in calcitriol group). In the maxacalcitol group, nine patients, and in the calcitriol group, seven patients, reached the primary end point, and the difference was not significant. The maximum iPTH inhibition rates did not significantly differ between the two groups (70.5 ± 4.7% in the maxacalcitol group and 69.6 ± 4.8% in the calcitriol group). The tendencies of the changes in calcium concentration, iPTH and bAP in the patients with basal iPTH ≥500 pg/ml did not differ from the results of the analysis of the entire cohort. The levels of iPTH decreased significantly in both groups (maxacalcitol: from 784 ± 52 to 394 ± 72 pg/ml, P < 0.001; calcitriol: from 910 ± 116 to 396 ± 82 pg/ml, P < 0.001) after 12 months of treatment; the levels of bAP also decreased significantly in both groups (maxacalcitol: from 29.5 ± 2.7 to 24.6 ± 2.1 U/l, P < 0.001; calcitriol: from 34.5 ± 2.9 to 28.4 ± 2.9 U/l,
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Recent studies have reported that the so-called iPTH (1–84) ratio or bAP. However, the difference in the time-courses of the changes in serum calcium concentration between the two groups was significant, although, the effect of both drugs on serum calcium concentration were similar after 12 months of treatment. Since our study included patients with mild hyperparathyroidism, we also analysed the data in the subgroups with higher basal iPTH levels, but the changes in PTH levels and the maximal inhibition rates of iPTH in these subgroups also were not significantly different between the treatments groups. The effects of each drug on serum calcium, phosphate and bAP in these subgroups were also similar between the two groups.

The iPTH levels adopted for the enrollment criteria and the first end point of this study were relatively low compared with the recommendation of K/DOQI [15]. We chose those criteria and end point based on the results of three previous studies with calcitriol and maxacalcitol [10,11,13], which were conducted in Japan. Furthermore, it has been reported [16] that normal bone histology was observed in patients with iPTH levels of up to 2.5 times the upper limit of normal (~100–150 pg/ml). In the previous study on the treatment of mild secondary hyperparathyroidism also, the same enrollment criteria were used to compare the effects of calcium carbonate and oral calcitriol [17]. Since our study was conducted before the publication of the K/DOQI guidelines, we used the criteria and end point described in the methods. However, it should be noted that our end point, iPTH <150 pg/ml, may increase the risk of adynamic bone disease.

Calcitriol has been used to treat renal osteodystrophy and secondary hyperparathyroidism in patients on chronic HD, and although calcitriol has been demonstrated to be effective in managing these complications, hypercalcaemia and hyperphosphataemia have been unavoidable complications of calcitriol therapy. It has also been suggested that calcitriol induces adynamic bone disease in patients with renal bone disease [4]. Several analogues of vitamin D have been developed to separate its effects on the parathyroid gland from its effects on bone and the intestine [5]. Maxacalcitol was developed by Chugai Pharmaceutical Company for this purpose and has been reported to suppress PTH secretion in normal rats and a rat model of chronic renal failure with only minor changes in serum calcium levels [6–9]. Long-term studies of maxacalcitol were conducted in patients with secondary hyperparathyroidism and it demonstrated its effectiveness in reducing PTH [11,18]—although serum calcium significantly increased during maxacalcitol therapy, in contrast to animal studies. Since those previous studies were not conducted to identify differences between the effects of calcitriol and maxacalcitol, we planned a randomized prospective multicentre trial. Consistent with the results of previous clinical trials [11,13,18], both maxacalcitol and calcitriol significantly decreased PTH levels, and the suppressive effect of maxacalcitol and calcitriol on PTH secretion did not significantly differ under the conditions of our study. The assessment of the effects of the two drugs on serum electrolyte concentration showed similar changes in serum phosphate concentration and the Ca × IP products with either drug, but the changes in serum calcium concentration were significantly different between the two.

The changes in adjusted calcium concentrations in each group were consistent with the results of previous studies [11,13], but the incidence of hypercalcaemia seemed lower than in previous studies. It is possible that the participating physicians were already used to both drugs and decreased their doses prophylactically. The difference in changes in calcium concentrations was significant between the two treatment groups, but the difference was observed only in the early phase of treatment, and may not be important clinically. On the other hand, the data suggest that their effects on the intestinal absorption of calcium and phosphate did not differ between the groups.

In this study we also examined the effects of maxacalcitol and calcitriol on PTH metabolism. Recent studies have reported that the so-called iPTH...
assay may detect not only real iPTH and PTH(1–84) but also its metabolites, including PTH(7–84) [14]. A new assay that specifically detects real iPTH, PTH (1–84), has been developed [14], and it has revealed that more than half of the so-called iPTH in some patients were PTH metabolites, mainly PTH(7–84) fragments. Interestingly, it has also been reported that PTH(7–84) inhibits the effects of PTH(1–84) on bone metabolism [19], and that lower whole PTH/non-PTH(1–84) ratios may predict low-turnover bone disease in patients on chronic HD [20,21]. In the present study, we compared the effects of calcitriol and maxacalcitol on PTH metabolism, but as shown in Figure 2, there were no significant differences in PTH metabolism between the two treatment groups.

The effects on bone metabolism markers in the two groups were also similar. Several bone markers, including bAP, tartrate-resistant acid phosphatase, and procollagen type I C-terminal extension peptide, have been reported to be useful in predicting low- or high-turnover bone diseases [22,23]. Since bone-specific alkaline phosphatase has been the most extensively studied of the markers and its usefulness in the study of bone metabolism has been established, we chose to use it in this study as a marker of bone metabolism. In the late phase of the treatment period, bAP significantly decreased in both the maxacalcitol group and the calcitriol group, except at 12 months of treatment in the calcitriol group. These results for bAP are consistent with results reported previously, that calcitriol significantly decreases bAP [13]. Since the decreases in bAP, iPTH and whole PTH levels were comparable in the two groups after treatment, both drugs are expected to suppress bone turnover similarly.

In conclusion, we performed a randomized prospective study to determine whether or not the effects of maxacalcitol and calcitriol on PTH and bone metabolism are different. The results showed that the effects of the two drugs on PTH metabolism were similar, as were their effects on serum electrolytes and bone metabolism. This study did not demonstrate that maxacalcitol is superior to calcitriol in the treatment of hyperparathyroidism in patients on chronic HD in terms of its ability to suppress PTH or in terms of its side effects, such as hypercalcaemia, although these conclusions need to be confirmed by bone histological studies.

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