EFFECTS OF SUBCUTANEOUS CALCITRIOL ADMINISTRATION ON PLASMA CALCIUM AND PARATHYROID HORMONE CONCENTRATIONS IN CONTINUOUS AMBULATORY PERITONEAL DIALYSIS UREMIC PATIENTS

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Objective: To ascertain whether the parathyroid hormone (PTH) secretion of continuous ambulatory peritoneal dialysis (CAPD) uremic patients could be suppressed by repeated subcutaneous injections of calcitriol (CLT).

Design: Nonrandomized prospective study with weekly evaluation.

Setting: Hospital CAPD clinic.

Patients: Seven uremic CAPD patients with signs of severe hyperparathyroidism.

Interventions: Patients were treated with CLT (2 μg), injected subcutaneously three times a week, on alternate days over a period of 8 weeks.

Measurements: Plasma PTH, ionized calcium (Ca), serum phosphate (Pi), and alkaline phosphatase (AP) were assayed before the start of CLT therapy and weekly thereafter.

Results: The average basal PTH was 349±26 pg/mL (mean ±SD). It fell significantly by the fifth week to 158±20, then leveled off. Analysis of the individual data, however, revealed that only 5 of 7 patients had a significant decrease in plasma PTH. Basal Ca was ±.02 mmol/L; it increased continuously throughout the study, significantly by the fourth week, reaching a level of 1.33±0.3 mmol/L at the sixth week, then declined slightly. In those patients with significantly decreased PTH, there was an inverse correlation between PTH and the corresponding Ca levels.

Conclusions: In some CAPD patients subcutaneous administration of CLT significantly suppresses PTH. This effect is mainly mediated via an increase in ionized calcium, but a direct inhibitory effect of the vitamin on parathyroid glands cannot be excluded.

KEY WORDS: Calcitriol; parathyroid hormone; ionized calcium.

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being treated with 4 x 2L exchanges/day, using standard dialysate containing 3.5 mEq of Ca/L. All had been treated for at least 6 months with oral CLT at doses of 0.25-0.50 μg/day, since they had radiographic findings of osteitis fibrosa of the fingers and persistently high plasma intact PTH, ranging from 280 to 880 pg/mL. Drug use, however, was erratic, since it needed to be frequently discontinued owing to the recurrence of hypercalcemia, hyperphosphatemia, or both. Oral CLT was therefore stopped and substituted with injectable CLT after at least two weeks of "wash-out." Injectable CLT (Calcijex, Abbott Laboratories, North Chicago, IL), 2 μg in water suspension, was administered subcutaneously in the deltoid area, three times a week on alternate days, over a period of 8 weeks.

In order to ensure the patients’ compliance with the drug, the injection was given by a nurse at our CAPD clinic for at least the first 4 weeks after the start of the therapy. Patients’ complaints and skin reactions to the injection were recorded and referred to the medical staff. Patients were then allowed to continue the therapy at home, where the drug was administered by a previously trained relative.

All subjects were taking calcium carbonate as phosphate binders. To avoid the onset of hypercalcemia, however, only a dose up to a maximum of 4 g/day was allowed, and when necessary (plasma Pi >5.5 mg/dL) aluminum-containing drugs were also prescribed, up to a maximum of 1.5 g/day and for only 15 days. Plasma PTH and ionized calcium, serum phosphate (Pi), and alkaline phosphatase (AP) were measured prior to the start of CLT therapy and weekly thereafter.

The blood samples for intact immunoreactive PTH were collected with heparinized plastic syringes. Immediately after collection, the samples were transferred into chilled tubes, centrifuged, and the plasma was stored at -70°C until assay. All samples were assayed together using fresh radioimmunoassay kits with an antiserum that identified the intact hormone (RIA Allegro, Nichols Institute, TX). With this method normal values in our laboratory range from 10 to 65 pg/mL.

To assess the reproducibility of the PTH assay, plasma PTH was determined for 20 hemodialyzed uremic patients from whom blood was drawn twice within 20 minutes. Interassay variability for the PTH assay was defined as the difference between the two measurements expressed as a percentage of the first. These percentage variations were averaged, the standard deviation calculated, and a 95% confidence limit (mean±plusmn;2SD) was obtained. Ionized calcium was measured with the ICAI ionized calcium analyzer (RadiometerA/S, Copenhagen, Denmark). Pi and AP were assayed by routine laboratory methods. Results are given as mean±plusmn;SD.

Within-group comparisons were made by analysis of variance for repeated measures (ANOVA). If the F statistic was significant, then the Student’s t-test for paired data was used. Changes in plasma PTH for each patient were considered to be significant only if they exceeded the 95% confidence limit for PTH interassay variability. Linear correlations were calculated by the least squares method.

RESULTS

No local reactions or adverse effects were recorded when CLT was administered at our outpatient CAPD clinic. Only one patient complained at times of some mild feeling of pain following skin puncture. All patients were aware of the seriousness of their disease and were willing to continue the therapy at home. One of 7 patients stopped the treatment after 4 weeks because of the appearance of hypercalcemia (Ca > 1.38 mmol/L), but resumed the therapy 2 weeks later and continued the blood sampling in the mean time.

For the group as a whole, plasma Ca increased continuously (Figure 1), significantly between the third and sixth weeks, then tended to decrease, although not significantly until the end (Ca at the sixth week = 1.33±0.33 mmol/L; Ca at eighth week = 1.31±0.1; t=1.6; p=0.17).

The mean pretreatment value for i-PTH was 349±26 pg/mL. It had decreased significantly (F=5.17; p<0.04, ANOVA) by the fifth week to 158±20, then leveled off until the eighth week (Figure 1).

Figure 2 shows the individual percent changes in plasma PTH and the 95% confidence limits of the inter assay variability for PTH assay (from -14% to 22%). From this figure it can be seen that 5 subjects had declines in plasma PTH to below the lower limit of variability of PTH assay, while 2 did not have significant changes.

Overall, the plasma levels of Ca were unrelated to the corresponding values of plasma PTH. On the other hand, if we consider only those patients who...
had significant decreases in plasma PTH, there was a significant inverse relationship between plasma PTH and time-related plasma Ca levels (r=0.43, n=44, p <0.01; graph not shown).

Analysis of the individual data for the two patients whose plasma PTH did not decrease revealed that their plasma calcium did increase, since the plot of Ca versus time was statistically significant for one case (r=0.67, n=9, p=0.46), and there was a trend toward a statistical association in the other (r=0.57).

The basal level of AP was 513±248 U/L (normal laboratory value, 98-279 U/L) and the level tended to decrease, although not significantly, after 8 weeks (261±98 U/L). Resting plasma Pi were 5±0.5 mg/dL and tended to increase continuously although insignificantly throughout (5.5±0.6 mg/dL, after 8 weeks).

**DISCUSSION**

Persistent hyperparathyroidism remains a substantial clinical problem in many CAPD patients (1-3). Attempts to attenuate the oversecretion of PTH in dialyzed uremics by avoidance of negative external calcium balance are often hindered by the onset of hypercalcemia (9). Injectable CLT, however, might be a suitable adjunctive therapy for these subjects, lessening PTH release and thus avoiding excessive threatening hypercalcemia (4). Intravenous injection of CLT, in fact, is thought to have at least in part a direct inhibitory effect on parathyroid glands, independent of the increase in ionized calcium (5). However, because CAPD patients do not have the arterio-venous fistula, they cannot easily take advantage of this simple therapy.

We decided, therefore, to administer the drug subcutaneously in an attempt to limit PTH secretion in a group of CAPD patients in whom previous therapy with oral CLT was either ineffective or very difficult to handle due to the frequent recurrence of either hypercalcemia or hyperphosphatemia. In this study none of the patients had evidence of clinically significant hyperphosphatemia, while the occurrence of hypercalcemia was limited to only one of them. Thus parenteral CLT seems to have some clinical advantage over the oral form, whose administration is so often hindered by the occurrence of both hyperphosphatemia and hypercalcemia.

In our patients repeated subcutaneous administration ofCLT, 2 μg, three times a week over a period of 8 weeks, resulted in an average 55% decrease in plasma PTH concentrations. On the other hand, 2 of 7 patients had nonsignificant changes in plasma PTH. Analysis of the individual data of these subjects demonstrated that their plasma calcium concentrations did increase throughout the entire study period. Furthermore, these subjects, like the others enrolled in this study, were well-motivated patients, since they were aware that they were undergoing the last "pharmacological attempt" before entering a program of surgical parathyroidectomy. We have no doubts, therefore, regarding their compliance with the therapy, and we are confident that they were continuing to take subcutaneous CLT at home with the same schedule and procedure with which they were familiarized at the CAPD outpatient clinic.

Finally, the CLT we used was dispensed in an aqueous vehicle which would provide uniform and predictable absorption of the drug. Therefore, we must conclude that subcutaneous CLT was indeed taken, but that it failed to suppress PTH secretion in these subjects.

In those subjects whose plasma PTH significantly decreased, the changes in the circulating levels of the hormone were related to and clearly followed increases in plasma ionized calcium concentrations. On the other hand, from the sixth week onward, the changes in plasma Ca and PTH tended to be disconnected from each other, since the former tended to decrease and the latter tended to remain unchanged. Thus we cannot exclude that if we were to continue the experiment for more than 8 weeks, the calcium might come back toward baseline at a time when the PTH might still be decreased. Therefore, one might think that subcutaneous CLT injections, unlike p.o. and intraperitoneal administration (4,6), might have some direct effect on PTH secretion other than that simply mediated by an increase in ionized calcium.

The postulated inhibitory effects of CLT on the parathyroid gland seem to occur only when there have been brief peak increases in the sterol, such as those observed after direct intravenous infusions (4). On the other hand, oral and intraperitoneal administration of CLT result in sluggish and prolonged increases of the circulating levels of the drug (8).

Whether this is also true after subcutaneous administration cannot be answered at this time, since in this study we neither measured circulating levels of the sterol nor determined its pharmacokinetic behavior.

In conclusion, repeated subcutaneous CLT administration to a group of uremic patients significantly
decreased circulating PTH in most of them without inducing hyperphosphatemia or recurrent life threatening hypercalcemia. The short study period, the small number of patients, and the lack of knowledge of the pharmacokinetic CLT behavior do not allow us to ascertain to what extent this PTH suppressive effect was due to the increase in plasma calcium and to what extent it was also induced by direct inhibition of the parathyroid glands by the vitamin.

REFERENCES