CASE REPORT

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Effect of doxercalciferol (1α-hydroxyvitamin D_2) on PTH, bone turnover and bone mineral density in a hemodialysis patient with persistent secondary hyperparathyroidism post parathyroidectomy

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Key words
doxercalciferol – bone turnover – bone mineral density – hemodialysis

Abstract. The efficacy and safety of the vitamin D analog, doxercalciferol (1α-hydroxyvitamin D_2, $1\alpha D_2$) in the treatment of secondary hyperparathyroidism in hemodialysis patients has been previously reported. We report thse effect of 16-week $1\alpha D_2$ treatment on mineral metabolism and bone mineral density (BMD) in a hemodialysis patient with persistent secondary hyperparathyroidism post parathyroidectomy, resistant to previous calcitriol treatment. Levels of iPTH, bone-specific alkaline phosphatase and serum type I collagen C telopeptide were above normal at baseline and were substantially decreased with $1\alpha D_2$ treatment (–92%, –63% and –53%, respectively). BMD increased in all areas: total skeleton (+6.5%), lumbar spine (+6.9%) and total femur (+4.3%). The patient showed no hypercalcemia, and phosphorus levels remained between 3.3 and 6.2 mg/dl.

Introduction

Doxercalciferol (1α-hydroxyvitamin D_2, $1\alpha D_2$) is a vitamin D analog that has been reported to be effective in dialysis patients for decreasing the levels of parathyroid hormone (PTH) without causing undue increments on the serum calcium levels [Frazao et al. 1998, 2000, Maung et al. 2001, Tan et al. 1997].

We report the biochemical and bone densitometry response to $1\alpha D_2$ in a patient with persistent secondary hyperparathyroidism post parathyroidectomy.

Case report

A 42-year-old man having been on hemodialysis since 1993, was seen in our unit in August 2000, with chronic renal disease secondary to obstructive nephropathy due to renal tuberculosis. Renal tuberculosis was diagnosed in November 1987. After 1 year of 3 specific drug treatments, serial urine bacilloscopy was negative in November 1988. Secondary obstructive nephropathy was progressive, finally hemodialysis was started in March 1993.

Initial evaluation of the patient denoted severe back pain and impaired ambulation caused by a brown tumor located in L3. Two similar asymptomatic lesions of small size (on the posterior aspect of T12 and body of T10) and 1 lesion on the third right rib were found. All these lesions had the same MR imaging characteristics, suggesting a similar tissue composition.

The patient was admitted to the hospital and laminectomy was done with removal of the mass in L3 followed by gradual recuperation of ambulation and absence of pain. Level of intact PTH was 1,300 pg/ml (iPTH normal value (NV): 10 – 65), 25-OH-vitamin D 64 ng/ml (NV: 9 – 45), serum calcium 10.3 mg/dl (NV: 8.9 – 10.4), serum phosphorus 5.4 mg/dl (NV: 2.5 – 4.5), total alkaline phosphatase (AP) 1,353 IU/l (NV: 68 – 240) and bone-specific alkaline phosphatase 554 IU/l (NV: 31 – 95). Two weeks later a subtotal parathyroidectomy was performed (weight removed 5.3 g). After parathyroidectomy, iPTH levels remained elevated (iPTH: 1,000 pg/ml) and treatment with calcitriol (1,25-dihydroxyvitamin D) was started. The dose of oral calcitriol ranged between 0.5 and 4 μg/day adjusted to serum calcium and phosphorus

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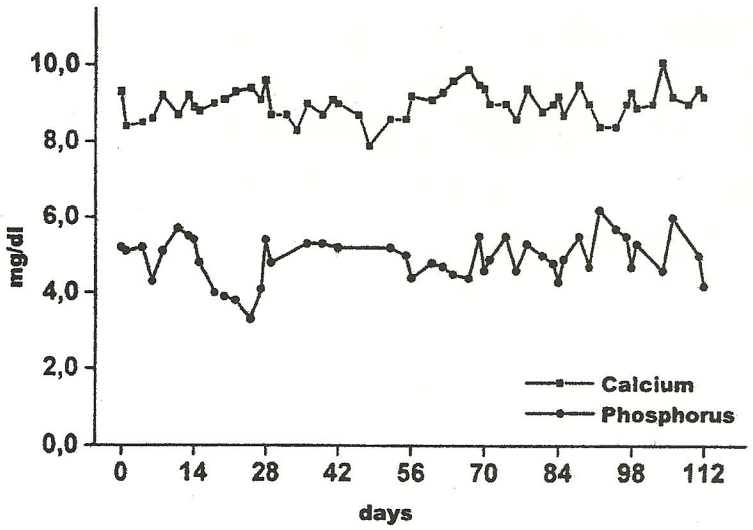

Figure 1. Serum calcium and phosphorus levels during 16 weeks of $1\alpha D_2$ treatment.

levels. During calcitriol treatment, 2 – 6 g of elemental calcium (as carbonate) were administered daily as a phosphate binder. Values of iPTH ranged between 1,000 and 1,600 pg/ml, bone AP between 189 and 539 IU/l, serum calcium between 8.4 and 10.6 mg/dl and serum phosphorus levels between 3.9 and 7.8 mg/dl. However, after 11 months, iPTH levels remained elevated and calcitriol treatment was discontinued due to hyperphosphatemia. After calcitriol treatment, the patient received 3 g of elemental calcium (as carbonate) daily as a phosphate binder. During the next 9 months the patient was monitored and biochemical determinations were performed monthly. Values of iPTH ranged between 1,200 and 1,970 pg/ml, bone AP between 344 and 505 IU/l, serum calcium between 8.8 and 10.0 mg/dl and serum phosphorus levels between 3.1 and 5.5 mg/dl.

Treatment with $1\alpha D_2$

Oral $1\alpha D_2$ therapy was begun 20 months post parathyroidectomy due to persistent iPTH elevation (> 1,500 pg/ml). It was given 3 times per week (4 capsules of 2.5 µg post dialysis) for a total of 30 µg per week for 16 weeks. The patient used 3 – 6 g of elemental calcium (as carbonate) daily as a phosphate binder. During the period of doxercalciferol treatment, dialysate calcium was maintained at the same concentration (2.5 mEq/l).

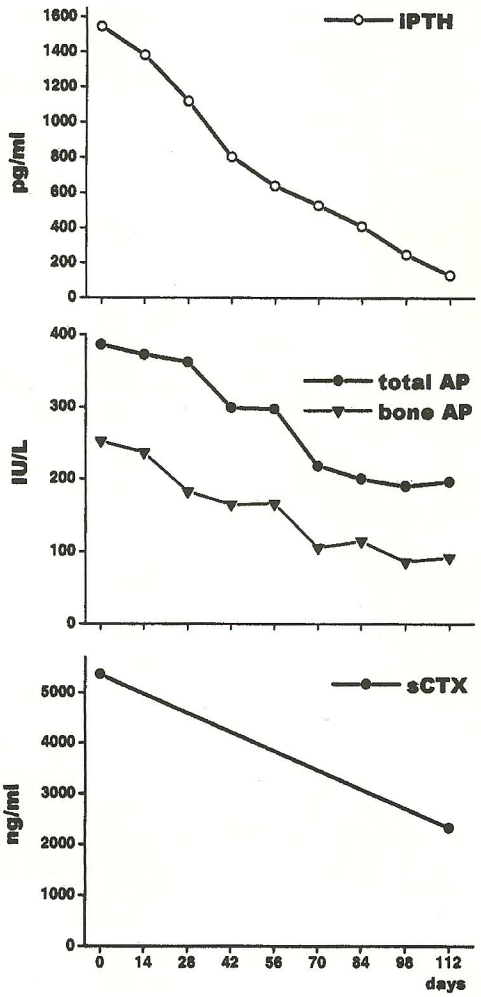

Figure 2. Serum intact parathormone (iPTH), total alkaline phosphatase (total AP), bone alkaline phosphatase (bone AP) and type I collagen C telopeptide (sCTX) levels during 16 weeks of $1\alpha D_2$ treatment.

Materials and methods

Blood determinations included serum calcium, phosphate, iPTH, both total and bone-specific alkaline phosphates (AP) (selective wheat germ lectine precipitation) and serum type I collagen C telopeptide (sCTX) (competitive enzyme immunoassay method, Crosslaps Osteometer, Rodrove, Denmark). All samples were collected during midweek treatment. Bone mineral density (BMD in g/cm^2) was measured at lumbar spine, total proximal femur and total skeleton, using the same dual energy x-ray absorptiometry (DEXA). The coefficients of variation (CV) determined in our laboratory were: 0.4% (total skeleton), 1.5% (lumbar spine) and 1.5% (total femur) [Bagur et al. 1994].

Table 1. Biochemical values before and after 16 weeks of $1\alpha D_2$ treatment in a weekly dose of 30 μg.

	Calcium mg/dl (8.9 – 10.4)	Phosphorus mg/dl (2.5 – 4.5)	Total AP IU/l (68 – 240)	Bone AP IU/l (31 – 95)	iPTH pg/ml (10 – 65)	sCTX ng/ml (14 – 450)
Baseline	9.3	5.2	386	252	1,544	5,360
16 weeks	9.2	4.2	196	92	128	2,320
% change			–49	–63	–92	–53

Normal values in parentheses; iPTH = intact parathormone, total AP = total alkaline phosphatase, bone AP = bone alkaline phosphatase, sCTX = serum type I collagen C telopeptide.

Table 2. Bone mineral density (BMD) at baseline and after 16 weeks of $1\alpha D_2$ treatment.

BMD (g/cm^2)		Baseline	16 weeks	Change (%)
Total skeleton		1.185	1.262	+6.5
	Head	2.901	3.222	+11.1
	Arms	0.884	1.011	+14.3
	Ribs	0.778	0.811	+4.2
	Spine	1.096	1.276	+16.4
	Pelvis	1.045	1.103	+5.5
	Legs	1.158	1.181	+2.0
Lumbar spine		1.058	1.131	+6.9
Total femur		0.969	1.011	+4.3

Results

At baseline, levels of iPTH, total and bone AP and sCTX were markedly above the normal range (Table 1). BMD was diminished compared to age- and sex-matched controls, Z scores were: total skeleton –0.4 SD, total femur –0.6 SD and lumbar spine –1.5 SD.

During $1\alpha D_2$ administration the patient showed no hypercalcemia, and phosphorus levels remained between 3.3 and 6.2 mg/dl (Figure 1). After 4 months of treatment, iPTH values decreased 92%, total AP 49%, bone AP 63% and sCTX 53% (Figure 2, Table 1). PTH and both total and bone AP reached normal range. $1\alpha D_2$ treatment increased BMD in all areas: total skeleton (+6.5%), lumbar spine (+6.9%) and total femur (+4.3%). Within the subareas of the total skeleton DEXA scan, the greatest increment was observed on the combined dorsal and lumbar spine (+16.4%) (Table 2).

After 120-day treatment, doxercalciferol treatment was stopped due to low iPTH values (128 pg/ml) to make adjustment in the dose. Seventy-five days later, serum biochemical determinations were done: iPTH 1,106 pg/ml, calcium 8.7 mg/dl, phosphorus 4.2 mg/dl, total AP 192 IU/l, bone AP 104 IU/l. Due to the rise of the iPTH, doxercalciferol treatment was reinitiated at the same dose (3 times per week (4 capsules of 2.5 μg post dialysis)), and 4 g of elemental calcium (as carbonate) daily as a phosphate binder. After 8 weeks of the new period of treatment, serum calcium values ranged between 6.6 and 9.7 mg/dl, and serum phosphorus between 3.5 and 6.1 mg/dl, the levels of iPTH decreased to 486 pg/ml.

Discussion

Low levels of serum calcitriol play a major role in the initiation and maintenance of secondary hyperparathyroidism. Calcitriol treatment can be effective in controlling secondary hyperparathyroidism. However, side effects, including increased intestinal absorption of calcium and phosphate, often complicate therapy causing hypercalcemia and/or hyperphosphatemia. In the patient described in this report, oral calcitriol treatment did not effectively suppress iPTH levels (Figure 3) and treatment was discontinued due to hyperphosphatemia.

Other vitamin D compounds that produce suppression of PTH secretion but have minimal calcemic action are theoretically ideal for the management of secondary hyperparathyroidism in hemodialysis patients. Studies

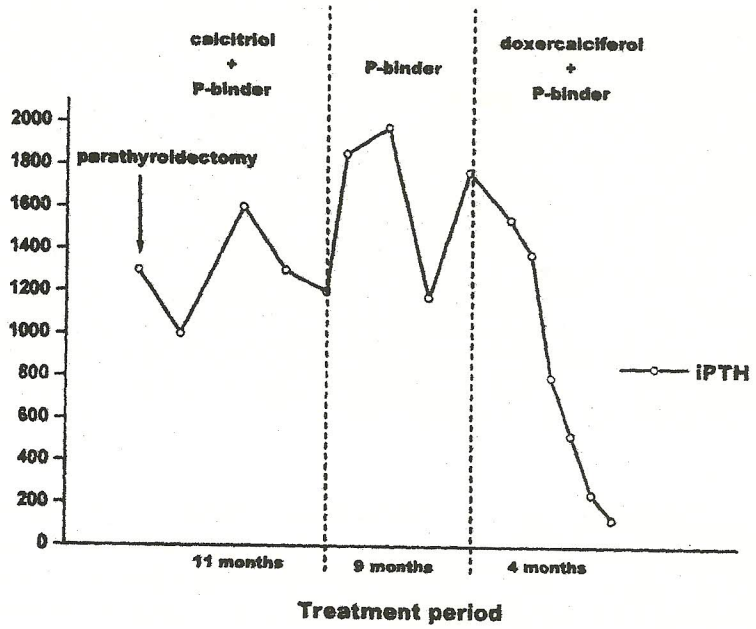

Figure 3. Serum intact parathormone (iPTH) levels during the 3 periods of treatment: with calcitriol plus phosphate binder, phosphate binder alone and doxercalciferol plus phosphate binder. The arrow shows the time of parathyroidectomy.

in experimental animals provided good evidence that $1\alpha D_2$ causes less hypercalcuria and hypercalcemia compared to $1\alpha D_3$ [Sjöden et al. 1985a, b]. Previously reported data showed that oral and intravenous treatment with $1\alpha D_2$ in hemodialysis patients with secondary hyperparathyroidism was safe and effective in suppressing iPTH levels with low incidence of mild hypercalcemia and hyperphosphatemia [Frazao et al. 1998, 2000, Maung et al. 2001, Tan et al. 1997].

Levels of iPTH were substantially decreased (–92%) with $1\alpha D_2$ treatment in this patient.

Also, studies have shown that $1\alpha D_2$ produces at least as much improvement in bone as the other vitamin D sterols in several animal models of "bone disease" [Erben et al. 1994, Sjöden et al. 1985a, b]. No report has been published about the effect of $1\alpha D_2$ on BMD and bone turnover in hemodialysis patients with secondary hyperparathyroidism.

We observed a substantial reduction in sCTX levels (–53%), and both total and bone AP levels (–49% and –63%, respectively) in the present patient after 16 weeks of $1\alpha D_2$ treatment. This reduction in bone turnover was concomitant with a marked increase in the BMD, suggesting an effect of treatment.

During follow-up the patient showed no hypercalcemia and the maximum serum phosphorus level was 6.3 mg/dl. However, the lack of significant rise of serum calcium and phosphorus could have been, in part, due to the remineralization of the skeleton.

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