Doxercalciferol Safely Suppresses PTH Levels in Patients With Secondary Hyperparathyroidism Associated With Chronic Kidney Disease Stages 3 and 4

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● *Background:* Calcitriol lowers parathyroid hormone (PTH) levels in patients with chronic kidney disease (CKD) stages 3 and 4, but its use is limited by a low therapeutic index and concerns regarding hypercalcemia and acceleration of kidney disease. We evaluated doxercalciferol (1α-hydroxyvitamin D$_2$) as an alternative therapy in a randomized, double-blinded, placebo-controlled, multicenter trial. *Methods:* Fifty-five adults with stage 3 or 4 CKD and an intact PTH (iPTH) level greater than 85 pg/mL (ng/L) completed 8 baseline weeks, followed by 24 weeks of oral therapy with doxercalciferol or placebo. Pretreatment demographics and biochemical features did not differ between groups. Dosages were increased gradually if iPTH level was not decreased by 30% or greater and serum calcium and phosphorus levels were stable. Regular monitoring included plasma iPTH, serum calcium and phosphorus, urinary calcium, bone-specific serum markers, and serum lα,25-dihydroxyvitamin D levels. Glomerular filtration rate (GFR) was measured before and after treatment. *Results:* Mean plasma iPTH level decreased by 46% from baseline after 24 weeks of doxercalciferol treatment (*P* <0.001), but was unchanged with placebo. After 6 weeks, iPTH level reductions with doxercalciferol treatment exceeded those with placebo at all subsequent intervals (*P* <0.001). No clinically significant differences in mean serum calcium or phosphorus or urinary calcium levels or incidence of hypercalcemia, hyperphosphatemia, or hypercalciuria were noted between groups. Serum C- and N-telopeptide and bone-specific alkaline phosphatase levels decreased with doxercalciferol treatment relative to both baseline and placebo (*P* <0.01). Adverse-event rates and changes in GFR did not differ between groups. *Conclusion:* Doxercalciferol is safe and effective in controlling secondary hyperparathyroidism of patients with CKD stages 3 and 4. *Am J Kidney Dis* 43:877-890.
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INDEX WORDS: Chronic kidney disease (CKD); secondary hyperparathyroidism; vitamin D; doxercalciferol (1α-hydroxyvitamin D$_2$); parathyroid hormone (PTH); moderate renal insufficiency.

THE DEVELOPMENT of progressive secondary hyperparathyroidism and renal osteodystrophy in patients with chronic kidney disease (CKD) involves complex interactions between phosphorus retention, reduction in serum calcium level, alterations in vitamin D metabolism, and other factors. Considerable evidence indicates that these abnormalities begin early in the course of CKD, often when kidney function is reduced to approximately 60 mL/min/1.73 m^2,[1-4] and there has been interest in reversing these abnormalities by treatment with active vitamin D sterols, as reviewed elsewhere.[5-7]

Several prospective placebo-controlled trials with oral calcitriol[8-11] or alfacalcidol[12] documented improvement in skeletal features of secondary hyperparathyroidism in patients with mild to moderate CKD. In most of these controlled trials,[8-12] patient selection was based only on level of renal function, and not degree of elevation in parathyroid hormone (PTH) level or severity of secondary hyperparathyroidism found on bone biopsy. Nevertheless, bone histomorphometric characteristics[8-10,12] or bone mineral density[11]

improved in these trials after treatment with calcitriol or alfacalcidol.

It was evident from early reports[13,14] and sub-

sequent trials[8,10,12] that therapeutic indices for calcitriol and alfacalcidol are low in patients with CKD. With calcitriol, doses escalating to 0.5 μg/d frequently were associated with hypercalcemia,[8,10] and 1 study using a dose of 1.0 μg/d found hypercalcemia and a reversible reduction in creatinine clearance.[13] In another controlled trial using a constant calcitriol dose of only 0.125 μg/d,[15] serum calcium and phosphorus levels were unchanged, as were levels of intact PTH (iPTH). However, there was partial prevention of a progressive increase in iPTH levels observed with placebo treatment. In a large, multicenter, placebo-controlled trial of alfacalcidol, the dose was titrated upward in 0.25-μg increments to increase serum calcium levels slightly within the normal range, and the dose was reduced if serum calcium level increased to greater than normal.[12] The maximum dose of alfacalcidol reached in this study averaged only 0.44 μg/d.

Three active vitamin D sterols have been introduced into clinical use that exert less calcemic action in experimental animals compared with calcitriol or alfacalcidol[16-19]; namely, paricalcitol,[20] doxercalciferol,[21,22] and maxicalcitol.[23] To date, clinical trials using these agents have been limited to patients with end-stage renal disease undergoing treatment with regular dialysis.

The present report describes results of a multicenter, double-blinded, placebo-controlled trial using oral doxercalciferol in patients with CKD with secondary hyperparathyroidism, defined as an iPTH level greater than 85 pg/mL (ng/L) and a glomerular filtration rate (GFR) ranging from 13 to 47 mL/min/1.73 m², estimated by means of the extended Modification of Diet in Renal Disease (MDRD) formula.[24] The trial showed a substantial reduction in iPTH levels during 24 weeks of doxercalciferol treatment. Moreover, a mean doxercalciferol dose as high as 1.62 μg/d was tolerated, with minimal increments in serum calcium levels, and almost all individual calcium values were within the normal range. Treatment with doxercalciferol caused no significant reduction in measured GFR and no increase in incidence of hypercalcemia and hypercalciuria compared with treatment with placebo. These results indicate that oral doxercalciferol can be administered safely and effectively to patients with stages 3 and 4 CKD.

METHODS

Study Design

Patients with mild to moderate chronic renal insufficiency, who would now be designated as having CKD stages 3 and 4 (GFR, 15 to 59 mL/min/1.73 m²),[25] and secondary hyperparathyroidism were enrolled in a multicenter, placebo-controlled, clinical trial. On enrollment, each subject was assigned at random in double-blinded fashion to 1 of 2 treatment groups. Both groups completed an 8-week baseline period (weeks −8 to 0) and entered a 24-week treatment period (weeks 1 to 24) to receive oral treatment with either doxercalciferol (1α-hydroxyvitamin D_2) or placebo. Subjects were administered no active vitamin D sterol other than doxercalciferol during the trial. When a local investigator considered that a phosphate-binding agent was needed, only calcium-based phosphate binders were administered. The protocol and consent forms were approved by the institutional review board at each study site, and informed consent was obtained from each patient at the time of screening for entry into the baseline period.

Plasma iPTH, serum calcium, and serum phosphorus levels and fasting spot urine samples for calcium-creatinine ratio (urine Ca-Cr ratio) were monitored monthly during the baseline period, biweekly during the first 2 months of the treatment period, and monthly thereafter. Routine blood chemistry and hematologic test results; 24-hour urinary calcium, phosphorus, and creatinine levels; levels of bone-specific serum markers, described later; and serum total 1α,25-dihydroxyvitamin D levels were monitored monthly during the baseline period and the first 2 months of the treatment period and bimonthly thereafter. Serum total 25-hydroxyvitamin D and GFR were measured before beginning the treatment period, and GFR was measured again at the last study visit.

Selection of Subjects

Patients were recruited from the West Los Angeles Veterans Affairs Healthcare Center, Los Angeles, CA; Diabetes and Glandular Disease Clinic, San Antonio, TX; Ochsner Clinic, New Orleans, LA; Joslin Diabetes Center, Boston, MA; Western New England Renal and Transplant Associates, West Springfield, MA; Evanston Northwestern Healthcare Research Institute, Evanston, IL; and Western Nephrology and Metabolic Bone Disease Clinics, Thornton and Lakewood, CO.

Inclusion criteria for entry of patients into the baseline period were age of 18 to 85 years; the presence of mild to moderate renal insufficiency, estimated by a serum creatinine level of 1.8 to 5.0 mg/dL (160 to 440 μmol/L) for men or 1.6 to 4.0 mg/dL (140 to 350 μmol/L) for women; and a plasma iPTH value greater than 85 pg/mL (>85 ng/L) at screening. A retrospective application of the extended MDRD equation showed that 1 enrolled subject had an estimated GFR of 13 mL/min/1.73 m²; all others had estimated GFRs ranging from 15 to 47 mL/min/1.73 m². Exclusion criteria included current alcohol or drug abuse; pregnancy or nursing; a history of nephrolithiasis; previous renal transplantation, hyperthyroidism, or sarcoidosis; active malignancy requiring treatment; various gastrointestinal diseases, such as malabsorption syndrome, surgery that might reduce intes-

tinal absorption, or ulcerative colitis; significant impairment of hepatic function; or any other condition that might place the patient at undue risk or preclude a patient from completing the study. Patients were excluded from entry if they had received treatment with anticonvulsants, glucocorticoids, bisphosphonates, fluoride, or lithium during the previous 12 months. Female patients who were receiving estrogen treatment before enrollment were maintained on the same estrogen regimen throughout the study. An enrolled subject was withdrawn and did not enter the treatment period if, during the baseline period, urinary protein excretion was 4.0 g/24 h or greater combined with a serum albumin level of 3.5 g/dL or less (≤35 g/L), urinary calcium excretion exceeded 150 mg/24 h (>3.74 mmol/24 h), or serum creatinine level exceeded 5.0 mg/dL (>440 μmol/L) for men or 4.0 mg/dL (>350 μmol/L) for women. Enrolled subjects who initiated dialysis therapy or underwent renal transplantation were withdrawn from the study.

Patient Screening and Enrollment

Of 133 patients initially screened, 72 patients (54%) entered the baseline period. The 61 screened patients who did not enter the baseline period included 40 patients with iPTH levels of 85 pg/mL or less (≤85 ng/L), 9 patients with serum creatinine levels outside the allowed ranges, 3 patients who had received therapy with glucocorticoids, 1 patient who had received anticonvulsant therapy, and 1 patient who was found to have idiopathic calcium stone disease. One patient died before enrollment, 5 patients declined to participate and withdrew their consent, and 1 patient was found to reside too far from the study site for 6 months of each year.

Subjects Discontinuing During Baseline

Fifty-five of 72 subjects (76%) who enrolled in the baseline period qualified for entry into the treatment period. The 17 subjects who terminated or were disqualified during the baseline period included 8 patients with urinary protein excretion of 4 g/24 h or greater combined with a serum albumin level of 3.5 g/dL (35 g/L), 3 patients with serum creatinine levels greater than the allowed limit at 1 of the first 2 washout visits (weeks −8 or −4), and 1 patient with a serum creatinine level less than the inclusion limit. Three subjects withdrew their consent to participate, and 2 patients were hospitalized for serious illnesses that precluded further participation in the study.

Randomization

Random assignment of subjects to either treatment group, doxercalciferol or placebo, was completed in subgroups of 10, with 5 subjects assigned to each group. An independent statistician using the Statistical Analysis System (SAS Institute, Cary, NC) prepared the randomization code.

Drug Formulation

Doxercalciferol was formulated in soft gelatin capsules, each containing 0.5 μg. Identical-appearing capsules containing either doxercalciferol or placebo were packaged, 50 capsules/bottle, in polyethylene bottles with tamper-evident seals and reusable child-resistant caps.

Dosing

The initial dose was 2 capsules/d, taken before breakfast; this provided 1.0 μg/d for those assigned to doxercalciferol treatment. The dosage was increased by 1 capsule/d at monthly intervals if plasma iPTH level was not reduced by at least 30% from baseline value and providing serum calcium level was 9.6 mg/dL or less (≤2.4 mmol/L), serum phosphorus level was 5.0 mg/dL or less (≤1.6 mmol/L), 24-hour urinary calcium level was 200 mg or less (≤5.0 mmol), and fasting urine Ca-Cr ratio was 0.25 mg/mg or less (≤0.71 mmol/mmol). The maximum dosage permitted was 10 capsules/d, which would provide 5.0 μg/d, or 35.0 μg/wk, of doxercalciferol.

During the treatment period, subjects suspended treatment temporarily if they developed low iPTH levels (<15.0 pg/mL [ng/L]); moderate hypercalcemia, defined as corrected serum calcium level greater than 10.7 mg/dL (>2.7 mmol/L); hypercalciuria, defined as urinary calcium level greater than 200 mg/24 h (>5.0 mmol/24 h); or a fasting urine Ca-Cr ratio greater than 0.25 mg/mg (>0.71 mmol/mmol). They were then monitored weekly until serum calcium and urine calcium levels normalized (≤10.2 mg/dL [≤2.5 mmol/L] for serum calcium, ≤150 mg/24 h [≤3.7 mmol/24 h] for urinary calcium, and ≤0.25 mg/mg [≤0.71 mmol/mmol] for urine Ca-Cr ratio). Then they resumed the test drug at a dose reduced by 1 capsule/d. If appropriate, they also reduced the dose of a calcium-based phosphate-binding agent. If mild hypercalcemia, defined as a serum calcium level of 10.3 to 10.7 mg/dL (2.6 to 2.7 mmol/L), or hyperphosphatemia, defined as a serum phosphorus level greater than 5.0 mg/dL (>1.6 mmol/L), occurred, patients adjusted their consumption of calcium-based phosphate binders and/or reduced the dosage of test drug. At the discretion of each local investigator, the prescribed dosage of calcium-based phosphate binder could be increased in those who developed hypocalcemia (serum calcium ≤ 9.0 mg/dL [≤2.2 mmol/L]). If a specific constant daily dosage of doxercalciferol was not optimal in maintaining a decrease in plasma iPTH levels of 30% or greater from baseline, the local investigator could vary the daily dosage according to a defined schedule (eg, alternating the daily dose from 1 to 2 capsules, or 0.5 μg to 1.0 μg) to optimize the weekly dose for the requirements of an individual subject.

Laboratory Procedures

Blood samples collected at each local site were shipped on cold packs by overnight delivery to LifeChem Laboratory Services (now SpectraEast Laboratory), Rockleigh, NJ, for analysis. Plasma iPTH levels were determined by using a first-generation 2-site immunoradiometric assay. Aliquots of 24-hour urine were acidified to a pH less than 2.0 by using 6 mol/L of HCl for the determination of calcium, phosphorus, and creatinine levels. Serum samples for determination of osteocalcin, bone-specific alkaline phosphatase (BSAP), C-telopeptide, N-telopeptide, and total 25-hydroxyvitamin D levels were divided into multiple 1-mL aliquots, stored frozen at −70°C in polypropylene tubes, and subsequently shipped on dry ice to Pacific Biometrics Inc, Seattle, WA, for analysis without previous thawing. All samples obtained from the same subject for each specific parameter were

Table 1.   Demographic Profile of Enrolled Subjects at Baseline, by Treatment Group

Characteristic	Active (n = 27)	Placebo (n = 28)	Difference (P)
Age (y)	64.1 ± 12.6	65.0 ± 12.1	0.79
Sex			
Male	21	24	0.50
Female	6	4	
Race			
African American	12	10	0.60
Caucasian	13	15	
Hispanic	1	3	
Other	1	0	
Weight (kg)	84.3 ± 20.0*	85.9 ± 18.2	0.76
Measured GFR (mL/min)	33.5 ± 15.4	36.9 ± 17.2	0.45
Calculated GFR (mL/min/1.73 mm^2)†	25.2 ± 9.3	24.7 ± 7.2	0.78
Previous use of calcitriol			
Yes	1	2	1.00
No	26	26	
Previous use of calcium-based phosphate binders			
Yes	6	10	0.38
No	21	18	

NOTE. Values expressed as mean ± SD or number of patients.

*A baseline weight was not obtained for 2 subjects in the active-treatment group.

†By MDRD Study equation.

analyzed together in the same batch. Serum samples for total 1α,25-dihydroxyvitamin D were frozen at $-70°C$ in polypropylene tubes and shipped on dry ice to Esoterix Inc, Calabasas Hills, CA. Serum samples from each subject were analyzed batch-wise by using a radioreceptor assay preceded by high-performance liquid chromatography, which measured both 1α,25-dihydroxyvitamin D$_2$ and 1α,25-dihydroxyvitamin D$_3$. GFR was determined during baseline and on completion of the treatment period by means of a method using either technetium-labeled diethylene triamine pentacetic acid or 125 iodine–labeled iothalamate. The same standardized method for GFR determination was used in all subjects at each individual study site. Serial blood and urine samples collected for GFR determination were analyzed on site or, if not possible, sent on ice for analysis at the Cleveland Clinic, Cleveland, OH.

Analysis of Data

In patients with serum albumin levels less than 4.0 g/dL (<40 g/L), corrected serum calcium level was calculated by using the following formula:

Corrected serum calcium (mg/dL)

$$= \text{measured serum calcium (mg/dL)} + (0.8 \times [4.0$$
$$- \text{measured serum albumin (mg/dL)}])$$

Baseline serum calcium values were corrected in 17 subjects (10 subjects assigned to active treatment, 7 subjects assigned to placebo) for reduced serum albumin levels that ranged from 3.40 to 3.95 g/dL (34.0 to 39.5 g/L). Week 24, serum calcium values were corrected in 16 subjects (7

patients, active treatment; 9 patients, placebo) for serum albumin levels ranging from 3.60 to 3.90 g/dL (36.0 to 39.0 g/L). Mean serum albumin levels in these subjects at baseline and week 24 were 3.81 ± 0.19 and 3.77 ± 0.11 g/dL (38.1 ± 1.9 and 37.7 ± 1.1 g/L) in the active group and 3.75 ± 0.19 and 3.82 ± 0.11 g/dL (37.5 ± 1.9 and 38.2 ± 1.1 g/L) in the placebo group.

Baseline values for all parameters are defined as the mean of data collected during weeks -4 and 0 of the baseline period. A positive response is defined as a reduction in mean plasma iPTH levels at weeks 20 and 24 that was at least 30% less than the baseline value. At each time, descriptive statistics were calculated, including number, mean, SD, and SE. Also, the significance of the mean difference from baseline at each time was assessed by means of paired t-test using the Bonferroni method to correct for multiple comparisons. Treatment groups were compared at baseline and each subsequent time, and the significance of differences between means was assessed by means of 2-sample t-test. For selected parameters, such as iPTH level, absolute data also were expressed as a percentage of baseline or absolute change from baseline, and the analysis was repeated on these relative values. These analyses were completed on data from all subjects administered any test drug.

RESULTS

Study Population

Demographic and baseline biochemical profiles of 55 subjects who entered the treatment period are listed according to treatment group in

Table 2. Biochemical Profile of Enrolled Subjects at Baseline by Treatment Group

Characteristic	Active (n = 27)	Placebo (n = 28)	Difference (P)
Plasma PTH (pg/mL or ng/L)	219.1 ± 116.0	171.4 ± 75.8	0.08
Serum calcium (mg/dL)	8.79 ± 0.63	8.87 ± 0.67	0.67
Serum phosphorus (mg/dL)	4.02 ± 0.78	3.89 ± 0.69	0.51
Serum creatinine (mg/dL)	3.02 ± 0.97	3.06 ± 0.83	0.88
Serum urea nitrogen (mg/dL)	47.8 ± 18.5	48.4 ± 17.0	0.91
Urine calcium (mg/24 h)	26.2 ± 26.0	29.9 ± 28.8	0.61
Urine phosphorus (mg/24 h)	623.2 ± 217.3	610.4 ± 210.9	0.83
Spot fasting urine Ca-Cr ratio (mg/mg)	0.019 ± 0.031	0.019 ± 0.018	0.98
Serum total 1α, 25-dihydroxyvitamin D (pg/mL)	33.9 ± 15.1	34.9 ± 19.5	0.83
Reference range, 21-65			
Serum total 25-hydroxyvitamin D (ng/mL)	18.5 ± 9.6	18.4 ± 6.6	0.97
Reference range, 9.0-37.6			
Serum total alkaline phosphatase (U/L)	113.9 ± 88.9	106.9 ± 57.3	0.73
Reference range, 39-117			
BSAP (U/L)	38.9 ± 42.0	29.7 ± 14.3	0.28
Reference ranges			
Men (≥25 y), 15.0-41.3			
Women (25-44 y), 11.6-29.6			
Women (≥ 45 y), 14.2-42.7			
Serum osteocalcin (ng/mL or μg/L)	87.0 ± 61.0	77.1 ± 46.9	0.50
Reference ranges			
Men, 11-46			
Women (premenopausal), 12-41			
Women (postmenopausal), 20-48			

NOTE. Values expressed as mean ± SD. To convert serum calcium in mg/dL to mmol/L, multiply by 0.2495: serum phosphorus in mg/dL to mmol/L, multiply by 0.3229; serum creatinine in mg/dL to μmol/L, multiply by 88.4; serum urea nitrogen in mg/dL to mmol/L, multiply by 0.357; urine calcium in mg/24 h to mmol/24 h, multiply by 0.02495; urine phosphorus in mg/24 h to mmol/24 h, multiply by 0.03229; urine Ca-Cr ratio in mg/mg to mmol/mmol, multiply by 2.822; serum 1α, 25-dihydroxyvitamin D in pg/mL to pmol/L, multiply by 2.6; serum total 25-hydroxyvitamin D in ng/mL to nmol/L, multiply by 2.496.

Tables 1 and 2, respectively. Subjects most commonly were middle-aged men, with ages ranging from 36 to 84 years. Comparison of subjects assigned to doxercalciferol treatment with those assigned to placebo showed no significant differences for any of the parameters listed in these tables.

Plasma iPTH

All subjects had an iPTH level greater than 85 pg/mL (ng/L) on screening, and ranges of iPTH values at baseline were 75 to 583 pg/mL (ng/L) in the active group and 62 to 330 pg/mL (ng/L) in the placebo group. Changes in plasma iPTH levels during the 24-week treatment period are shown in Fig 1. In the doxercalciferol group, mean iPTH level decreased from a baseline value of 219 ± 22 (SE) pg/mL (ng/L) by 46.3% ± 7.6% to 118 ±17 pg/mL (ng/L) at week 24 (P <0.001). Conversely, mean iPTH level in the

placebo group did not change significantly from a baseline value of 171 ± 14 pg/mL (ng/L) to 167 ± 15 pg/mL (ng/L) at week 24. At weeks 16, 20, and 24, mean iPTH levels in the doxercalciferol group were significantly lower than those in the placebo group (P <0.05). Moreover, mean percentages of reduction in iPTH levels in the doxercalciferol group exceeded mean changes observed in the placebo group (P <0.05) at all treatment weeks except week 6 (Fig 1). Ranges of iPTH values at week 24 were 10 to 386 pg/mL (ng/L) in the active group and 43 to 257 pg/mL (ng/L) in the placebo group.

Twenty of 27 subjects (74%) treated with doxercalciferol achieved 30% or greater reductions in mean iPTH levels from baseline values during weeks 20 through 24. Conversely, only 2 of 28 subjects (7%) treated with placebo achieved an equivalent reduction in plasma iPTH levels.
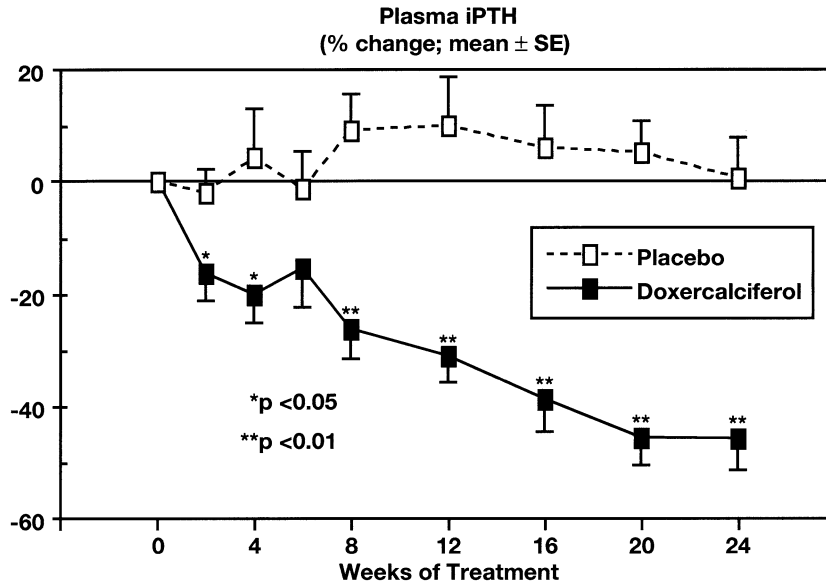
Plasma iPTH
(% change; mean ± SE)

Fig 1. Changes in plasma iPTH levels, shown as percentage of baseline value, in subjects administered doxercalciferol compared with those administered placebo. iPTH levels had decreased significantly by 2 weeks of doxercalciferol treatment and continued to decrease thereafter.

Of 7 subjects in the doxercalciferol group who failed to achieve 30% or greater iPTH suppression during weeks 20 through 24, a total of 4 subjects completed all 24 weeks of therapy and 3 subjects terminated treatment prematurely. During weeks 20 and 24, mean iPTH level reductions in the former group of 4 subjects were −24%, −24%, −20%, and +3.9%. The last subject was administered only low doses of doxercalciferol because of 2 episodes of hypercalcemia. The other group of 3 subjects prematurely terminated doxercalciferol treatment at weeks 5,

8, and 15 when they showed iPTH level changes of +23%, −28%, and −44%, respectively.

Serum Calcium and Phosphorus

Mean values for corrected serum calcium and serum phosphorus levels during the treatment period are shown in Fig 2. Baseline mean corrected serum calcium levels were 8.79 ± 0.12 (SE) mg/dL (2.19 ± 0.030 mmol/L) in the doxercalciferol group and 8.87 ± 0.13 mg/dL (2.21 ± 0.32 mmol/L) in the placebo group (P = not significant [NS]). At week 24, mean corrected
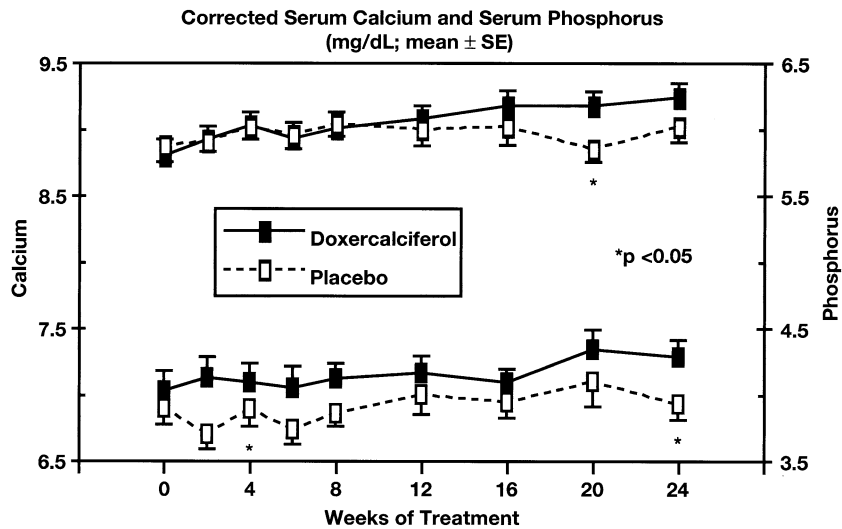
Fig 2. Corrected serum calcium (top) and serum phosphorus (bottom) levels in subjects administered doxercalciferol compared with those administered placebo. As listed in Table 3, the majority of values for both calcium and phosphorus were within the normal range. To convert serum calcium in mg/dL to mmol/L, multiply by 0.2495; serum phosphorus in mg/dL to mmol/L, multiply by 0.3229.

Corrected Serum Calcium and Serum Phosphorus
(mg/dL; mean ± SE)

Spot Urine Calcium/Creatinine Ratio
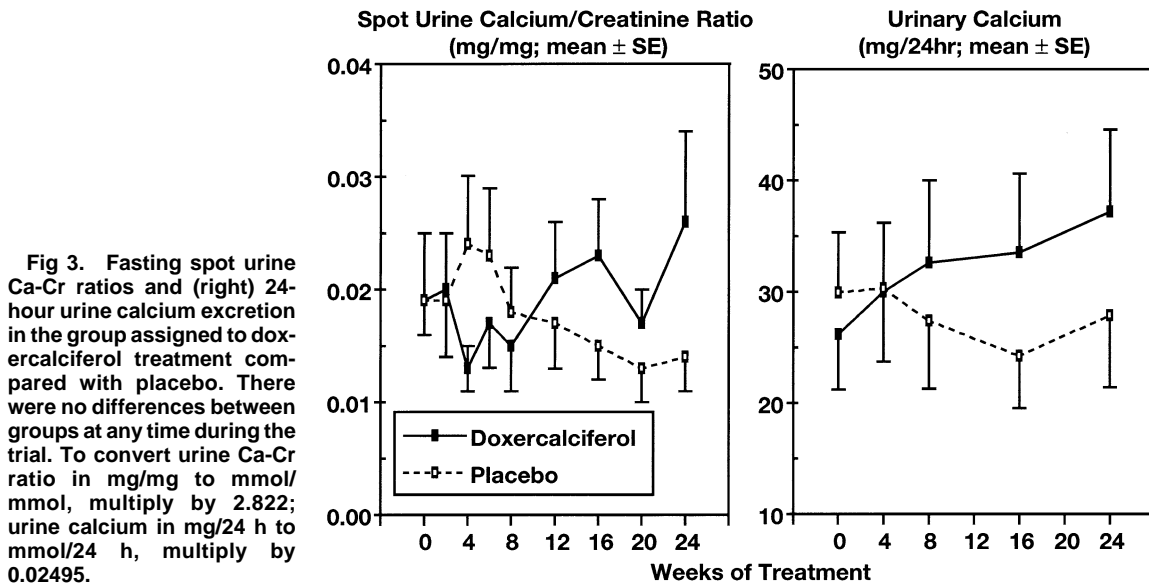**(mg/mg; mean ± SE)**

Urinary Calcium
(mg/24hr; mean ± SE)

Fig 3. Fasting spot urine Ca-Cr ratios and (right) 24-hour urine calcium excretion in the group assigned to doxercalciferol treatment compared with placebo. There were no differences between groups at any time during the trial. To convert urine Ca-Cr ratio in mg/mg to mmol/mmol, multiply by 2.822; urine calcium in mg/24 h to mmol/24 h, multiply by 0.02495.

Weeks of Treatment

serum calcium levels were 9.23 ± 0.11 mg/dL (2.30 ± 0.03 mmol/L) in the doxercalciferol group and 9.01 ± 0.12 mg/dL (2.25 ± 0.04 mmol/L) in the placebo group ($P = $ NS). Mean levels differed between the 2 treatment groups only at week 20 ($P < 0.05$). The largest mean increment in serum calcium level in the doxercalciferol group from baseline was $+0.47 \pm 0.11$ mg/dL (0.12 ± 0.01 mmol/L) at week 24 ($P = 0.012$).

At baseline, mean serum phosphorus levels were 4.02 ± 0.15 (SE) mg/dL (1.30 ± 0.05 mmol/L) in the doxercalciferol group and 3.89 ± 0.13 mg/dL (1.26 ± 0.04 mmol/L) in the placebo group ($P = $ NS). At week 24, mean serum phosphorus levels were 4.27 ± 0.13 mg/dL (1.38 ± 0.04 mmol/L) in the doxercalciferol group and 3.92 ± 0.12 mg/dL (1.27 ± 0.04 mmol/L) in the placebo group ($P = 0.047$). Mean serum phosphorus levels did not change significantly from baseline values with doxercalciferol treatment, but they were slightly greater than in the placebo group at weeks 2 and 24 ($P < 0.05$).

Serum calcium $\times$ serum phosphorus product ranged from 20.0 to 61.6 mg^2/dL^2 (1.61 to 4.96 mmol^2/L^2) in subjects treated with doxercalciferol and 25.0 to 71.0 mg^2/dL^2 (2.01 to 5.72 mmol^2/L^2) in subjects treated with placebo. Mean product values in subjects assigned to doxercalciferol treatment were 35.1 ± 1.3 (SE) mg^2/dL^2

(2.83 ± 0.10 mmol^2/L^2) at baseline and 39.2 ± 1.4 mg^2/dL^2 (3.16 ± 0.11 mmol^2/L^2) at week 24 ($P < 0.01$). Mean values in subjects assigned to placebo treatment were 34.1 ± 1.0 mg^2/dL^2 (2.75 ± 0.08 mmol^2/L^2) at baseline and 35.0 ± 1.0 mg^2/dL^2 (2.82 ± 0.08 mmol^2/L^2) at week 24 ($P = $ NS). The mean product value was greater in the group treated with doxercalciferol at weeks 2 and 24 ($P < 0.05$).

Urine Calcium

Mean 24-hour urinary calcium excretion rates and mean fasting urine Ca-Cr ratios did not differ between the doxercalciferol- and placebo-treated groups at any time during the treatment period (Fig 3). In subjects treated with doxercalciferol, the mean urinary calcium level of 26.2 ± 5.0 (SE) mg/24 h (0.65 ± 0.12 mmol/24 h) at baseline (range, 5.0 to 114.0 mg/24 h [0.12 to 2.84 mmol/24 h]) increased slightly ($P < 0.05$) to 37.2 ± 7.4 mg/24 h (0.93 ± 0.18 mmol/24 h) at week 24 (range, 4.9 to 134.0 mg/24 h [0.12 to 3.34 mmol/24 h]). The highest 24-hour urinary calcium excretion during doxercalciferol treatment was 176 mg/24 h (4.39 mmol/24 h) when the corresponding corrected serum calcium level was 8.2 mg/dL (2.05 mmol/L). The highest 24-hour urine calcium excretion during placebo treatment was 171 mg/24 h (4.27 mmol/24 h) when the corresponding corrected serum calcium was 8.6 mg/dL (2.15 mmol/L).

Table 3. Comparison of Elevated Values of Corrected Serum Calcium, Serum Phosphorus, 24-Hour Urine Calcium, and Fasting Spot Urine Ca-Cr Ratio During Treatment With Doxercalciferol and Placebo

Parameter	Active (n = 27)	Placebo (n = 28)	Difference (P)
Corrected serum calcium	n = 227	n = 215	
>10.5 mg/dL (%)	2.6	1.9	0.27
>10.2 mg/dL (%)	4.9	1.9	0.35
Serum phosphorus	n = 227	n = 215	
>6.5 mg/dL (%)	0.4	0.5	0.50
>6.0 mg/dL (%)	2.6	0.5	0.15
>5.0 mg/dL (%)	8.8	6.5	0.47
24-Hour urine calcium	n = 125	n = 125	
>200 mg (%)	0.0	0.0	NA
>150 mg (%)	1.6	1.6	0.61
>100 mg (%)	7.2	4.8	0.59
Fasting spot urine Ca-Cr ratio	n = 227	n = 215	
>0.15 (%)	1.6	0.0	0.47
>0.10 (%)	4.0	3.2	0.99

NOTE. To convert serum calcium in mg/dL to mmol/L, multiply by 0.2495; serum phosphorus in mg/dL to mmol/L, multiply by 0.3229; urine calcium in mg/24 h to mmol/24 h, multiply by 0.02495; urine Ca-Cr ratio in mg/mg to mmol/mmol, multiply by 2.822.
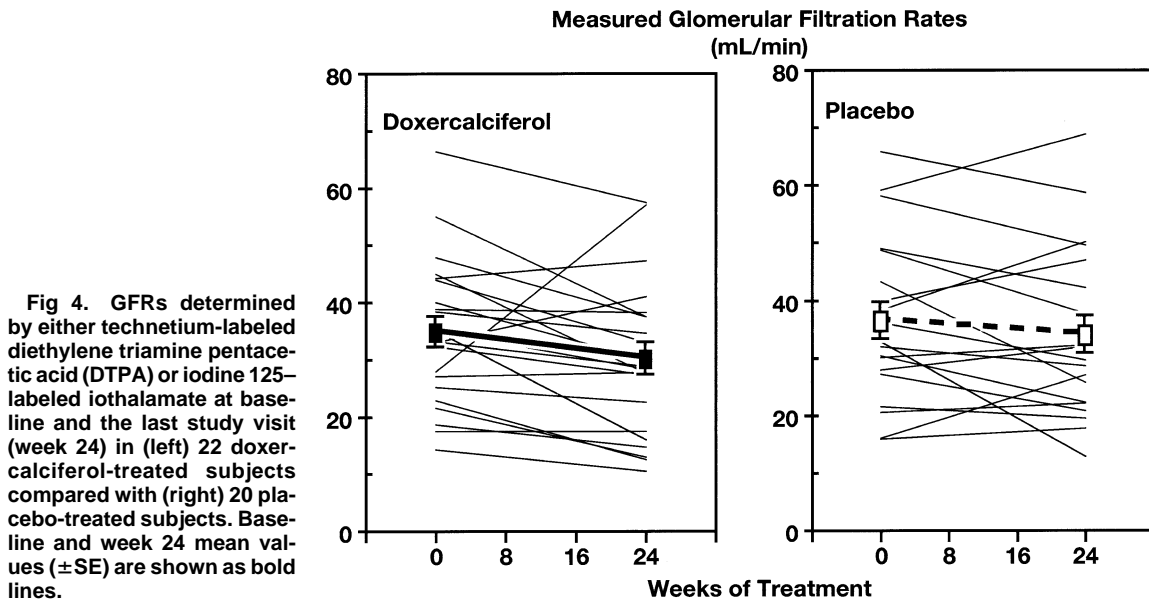
Side Effects

The prevalence of elevated values at various limits for serum calcium, serum phosphorus, 24-hour urinary calcium excretion, and urine Ca-Cr ratio are listed in Table 3. There were no differences between the doxercalciferol and placebo groups with regard to percentages of serum calcium determinations greater than 10.2 mg/dL (>2.54 mmol/L), greater than 10.5 mg/dL (>2.62 mmol/L), or greater than 11.0 mg/dL (>2.74 mmol/L); percentages of serum phosphorus measurements greater than 5.0 mg/dL (>1.61 mmol/L), greater than 5.5 mg/dL (>1.78 mmol/L), or greater than 6.0 mg/dL (>1.94 mmol/L); or percentages of 24-hour urinary calcium measurements or urine Ca-Cr ratios greater than any of the limits listed in Table 3. Two separate episodes of hypercalcemia, defined as corrected serum calcium level exceeding 10.7 mg/dL (>2.67 mmol/L), occurred in 1 doxercalciferol-treated subject who was administered the lowest mean dose of doxercalciferol (0.35 μg/d) and who showed values as high as 10.7 mg/dL (2.67 mmol/L) during the baseline period. Maximum serum calcium levels recorded during these 2 episodes were 10.9 mg/dL (2.72 mmol/L) and 11.0 mg/dL (2.74 mmol/L). There was 1 episode of hypercalcemia, with a maximum calcium level of 10.9 mg/dL (2.72 mmol/L) at week 12, in a subject administered placebo. As listed in Table 3, there was no difference in frequency of hyperphosphatemia between the 2 treatment groups regardless of the limit used to define hyperphosphatemia. There was a single episode of a serum calcium-phosphorus product greater than 65 mg^2/dL^2 (>5.24 mmol^2/L^2) in a subject assigned to placebo. One subject showed an iPTH value less than 15.0 pg/mL (ng/L) at week 24 of doxercalciferol treatment.

Renal Function

The effect of treatment on GFR, measured at baseline and end of the treatment period, is shown for individual subjects in Fig 4. Five subjects in the doxercalciferol group (19%) and 8 subjects in the placebo group (29%) failed to have a second measurement of GFR on either premature or scheduled termination of treatment. Among 42 subjects with GFR measurements both before and after treatment, baseline GFRs averaged 34.7 ± 2.7 (SE) mL/min in the doxercalciferol group (n = 22) and 36.4 ± 3.2 mL/min in the placebo group (n = 20). At week 24, GFRs averaged 30.0 ± 2.9 mL/min in the doxercalciferol group and 33.9 ± 3.3 mL/min in the placebo group. Mean GFRs in the 2 treatment groups at baseline or week 24 and changes in GFR from baseline to end of the treatment period in either treatment group did not differ significantly.

There was an increase in mean serum urea nitrogen level in the doxercalciferol-treatment group at week 24 (P <0.05), but changes in serum urea nitrogen levels from baseline did not differ between groups. Mean serum creatinine levels increased during doxercalciferol treatment (up to 0.4 mg/dL) compared with baseline values at weeks 8, 16, and 24 (P <0.05), but not in comparison to changes during placebo treatment. Creatinine clearances, calculated from 24-hour urine creatinine excretion, in doxercalciferol-treated subjects were 28.4 ± 2.11 (SE) mL/min (0.473 ± 0.035 mL/s) at baseline and 27.4 ± 2.18 mL/min (0.458 ± 0.0363 mL/s) at the end of treatment. Mean percentage of change in creatinine clearance was +1.03% ± 7.34% (P = NS). Corresponding values in the placebo group

**Measured Glomerular Filtration Rates
(mL/min)**

Fig 4. GFRs determined by either technetium-labeled diethylene triamine pentacetic acid (DTPA) or iodine 125–labeled iothalamate at baseline and the last study visit (week 24) in (left) 22 doxercalciferol-treated subjects compared with (right) 20 placebo-treated subjects. Baseline and week 24 mean values (±SE) are shown as bold lines.

were 28.8 ± 2.41 mL/min (0.480 ± 0.040 mL/s) at baseline and 28.0 ± 2.43 mL/min (0.467 ± 0.041 mL/s) at end of treatment. Mean percentage of change in creatinine clearance was −1.81% ± 4.73% (P = NS). Percentages of change in creatinine clearances did not differ between the 2 treatment groups.

Intake of Calcium-Containing Phosphate Binders

At week 0, 6 subjects assigned to doxercalciferol treatment (22%) and 10 subjects assigned to placebo treatment (36%) were prescribed calcium-based phosphate binders. At the end of treatment, 12 subjects in the doxercalciferol group (44%) and 11 subjects in the placebo group (39%) were prescribed binders. All subjects prescribed binders were administered calcium carbonate, except for 1 or 2 subjects per treatment group who were administered calcium acetate. In subjects prescribed binders, quantities at week 0 were 641 ± 325 (SD) mg/d of elemental calcium in the doxercalciferol group and 775 ± 498 mg/d in the placebo group. At the end of treatment, prescribed quantities were 683 ± 220 mg/d in the doxercalciferol group and 707 ± 355 mg/d in the placebo group. Analysis of the percentage of reductions in iPTH levels in doxercalciferol-treated subjects prescribed calcium-based binders compared with those not prescribed such agents showed no significant differences (data

not shown). Similarly, prescription of calcium-based binders had no effect on changes in serum calcium levels.

Routine Chemistry and Hematology Tests

Mean total alkaline phosphatase levels decreased with doxercalciferol treatment from a baseline value of 113.9 ± 17.1 U/L by 9% and 12% at weeks 16 and 24, respectively (P <0.05). Conversely, mean alkaline phosphatase levels in the placebo group remained unchanged. No other changes of clinical importance were observed from baseline or between groups for other routine biochemical or hematologic parameters. Serum albumin levels, used to correct serum calcium values, were unchanged from baseline in both groups during the treatment period ($P ≥$ 0.13).

*Serum Bone-Specific Markers and
1α,25-Dihydroxyvitamin D*

Among patients in the doxercalciferol group, reductions from baseline level in serum BSAP were 19.7% ± 3.7% and 27.9% ± 4.6% at weeks 16 and 24, respectively (P <0.001). BSAP level reductions from baseline were not significant at any treatment week in the placebo group. Differences in BSAP level reductions were significant between the 2 treatment groups from week 8 to week 24 (P <0.05). Similar reductions were observed in serum N- and C-telopeptide levels

during doxercalciferol treatment. Mean serum osteocalcin level declined from baseline by 22% at week 24 (P <0.001) with doxercalciferol treatment. This decrease differed significantly from the corresponding change observed in the placebo group (P <0.01). In the doxercalciferol group, mean increments in serum total $1\alpha,25$-dihydroxyvitamin D levels from baseline increased gradually to reach 48.8% ± 18.2% (SE) by week 24 (P = 0.025); no changes were observed in the placebo group. During the treatment period, changes in serum total $1\alpha,25$-dihydroxyvitamin D levels differed between the 2 treatment groups (P <0.05) from weeks 4 to 24.

Premature Terminations

Nine subjects failed to complete the full 24-week treatment period; 3 subjects in the doxercalciferol group and 6 subjects in the placebo group. One doxercalciferol-treated subject withdrew during week 5 because of congestive heart failure; another withdrew during week 8 on the recognition of a previously existing disorder causing intestinal malabsorption; this problem had not been recognized during screening. The third doxercalciferol-treated subject withdrew when hemodialysis therapy was initiated during week 15. Three placebo-treated subjects withdrew prematurely because of adverse events: 1 subject had a myocardial infarction during week 12, 1 subject died at home with a presumed cardiac arrest during week 15, and the third subject developed neuromuscular symptoms and withdrew during week 16. Three additional placebo-treated patients withdrew: 1 subject was "unable to tolerate" the test drug during week 3, another subject moved away from the study area during week 14, and another subject was withdrawn when hemodialysis therapy was started during week 20.

Dosing Compliance

Compliance to the prescribed doses averaged greater than 98% and exceeded 80% in 52 of 55 treated subjects. Dosing compliance was 71% in 1 subject randomly assigned to placebo and 79% in another subject randomly assigned to doxercalciferol. A third subject, assigned to doxercalciferol, achieved only 67% dosing compliance before he withdrew because of congestive heart

failure at week 5; this patient had an increase in iPTH levels by week 4 (+23%), as noted.

Prescribed Dosages

As specified by the protocol, the prescribed dosage of test medication of 2.0 capsules/d (1.0 μg/d for those administered doxercalciferol) was constant in all subjects during the first 4 weeks of treatment. Thereafter, the mean dose in the doxercalciferol group increased progressively and reached a plateau of 1.62 ± 0.20 (SE) μg/d by week 20 (range of peak dose, 1.0 to 3.5 μg/d). Mean dose in the placebo group increased more rapidly and reached a maximum of 5.13 ± 0.49 capsules/d by week 24 (range of peak dose, 2 to10 capsules/d). The average prescribed number of capsules differed significantly between the 2 treatment groups from weeks 12 through 24 (P <0.05). Dosages of test medication were reduced in 4 doxercalciferol-treated subjects. In 1 subject, the dosage was reduced temporarily from 1.5 to 0.5 μg/d after 8 weeks of treatment because plasma iPTH level decreased to 53 pg/mL (ng/L) from the baseline value of 172 pg/mL (ng/L). During week 15, the dosage was restored to 1.0 μg/d after plasma iPTH level increased to 90 pg/mL (ng/L) at the end of week 12. Plasma iPTH levels then ranged from 90 to 124 pg/mL (ng/L) while the dosage was continued at 1.0 μg/d during the final weeks of treatment. In a second subject, the dosage was reduced from 1.5 to 1.0 μg/d after 20 weeks of treatment when plasma iPTH level decreased to 39 pg/mL (ng/L) from the baseline value of 285 pg/mL (ng/L); subsequently, plasma iPTH level increased to 71 pg/mL (ng/L) after 4 weeks on the reduced dosage. In a third subject, the dosage was reduced from 2.0 to 1.5 μg/d during week 9 after the plasma iPTH level decreased to 69 pg/mL (ng/L) from a baseline value of 231 pg/mL (ng/L). Plasma iPTH levels stabilized at 96 pg/mL (ng/L) during weeks 20 through 24 at this reduced dosage. Doxercalciferol treatment was suspended because of hypercalcemia twice in 1 doxercalciferol-treated subject, as noted.

DISCUSSION

The present randomized, double-blinded, placebo-controlled clinical trial shows that doxercalciferol (1α-hydroxyvitamin D_2) is highly effective in reducing elevated iPTH levels in patients

with secondary hyperparathyroidism associated with mild to moderate renal insufficiency. This trial differs from previous studies that evaluated either calcitriol[8,10,11,15,26,27] or alfacalcidol (1α-hydroxyvitamin D_3)[12] in that the dosage of doxercalciferol was adjusted according to changes in plasma iPTH levels, with increments in serum calcium and phosphorus levels considered side effects. In trials using calcitriol, doses were either constant[11,15,26,27] or the dosage was increased gradually until hypercalcemia appeared.[8,10] In a large trial using alfacalcidol, the dose was increased until serum calcium levels increased "slightly within the normal range," but was reduced when hypercalcemia appeared.[12]

In the present trial, a decrease in iPTH levels of 30% or greater from baseline was chosen as the minimal clinically meaningful reduction. However, mean percentage of iPTH level reduction actually achieved was considerably larger, averaging more than 46% during the last 4 weeks of the study. The incidence of side effects, assessed from various degrees of elevation of serum calcium or serum phosphorus levels or different increments in urinary calcium levels, did not differ between the placebo- and doxercalciferol-treated groups.

In mild to moderate renal insufficiency, serum total 1,25-dihydroxyvitamin D levels usually are low or in the lower portion of the normal range.[2,3,28,29] Such low or low-normal 1,25-dihydroxyvitamin D levels often are associated with elevated PTH levels, and levels of the former ordinarily would increase, except for the failure of renal tubular cells to respond to the greater PTH levels. Therapy with an active vitamin D sterol would be useful in such patients. However, therapy with calcitriol or alfacalcidol is used infrequently because of overriding concerns regarding the risk for side effects.

To evaluate doxercalciferol as an alternate therapy for secondary hyperparathyroidism in patients with CKD stages 3 and 4, we compare doxercalciferol, in the following paragraphs, with calcitriol and alfacalcidol, with a focus on the effects of these agents in controlled trials on: (1) serum and urine calcium levels, and (2) creatinine clearances and GFR. Ideally, there should be trials that directly compare these vitamin D sterols, but such trials are not available.

In the present trial, the final mean serum calcium level in doxercalciferol-treated patients did not differ from that of the placebo group. The maximum absolute increment in mean serum calcium level was small ($+0.47$ mg/dL [0.12 mmol/L]) despite the escalation in doxercalciferol dose to an average of 1.62 ± 0.20 (SE) µg/d and a mean prescribed dose of elemental calcium from phosphate binders of 683 ± 220 (SD) mg/d in 45% of subjects. Moreover, doxercalciferol dosage was reduced in only 1 subject because of hypercalcemia. This subject had a prior history of hypercalcemia when not treated with active vitamin D sterols. These observations contrast sharply with reported dosage reductions in a substantial fraction of subjects who developed hypercalcemia during controlled trials using calcitriol doses titrated upward from 0.25 µg/d.[8,10] In the study of Nordal and Dahl,[8] calcitriol dosage averaged only 0.32 µg/d. Bianchi et al[27] noted that mean serum calcium level increased from a baseline value of 8.5 ± 0.3 mg/dL (2.12 ± 0.07 mmol/L) to 9.3 ± 0.2 mg/dL (2.32 ± 0.05 mmol/L; $P < 0.05$) and then to 9.9 ± 0.2 mg/dL (2.47 ± 0.05 mmol/L; $P < 0.01$) with use of a constant calcitriol dosage of 0.25 µg/d, with calcium carbonate providing 500 mg/d of elemental calcium. Ritz et al[15] administered calcitriol in a dose of 0.125 µg/d and detected no change in serum calcium levels; however, there was no reduction in iPTH levels.

Comparison of doxercalciferol and alfacalcidol is of special interest because both sterols undergo hepatic hydroxylation before exerting their effects. In a large placebo-controlled trial, Hamdy et al[12] reported that alfacalcidol increased mean serum calcium level to 9.76 mg/dL (2.44 mmol/L) compared with 9.44 mg/dL (2.36 mmol/L) in placebo patients after 6 months of treatment ($P < 0.05$). The increment in serum calcium levels from baseline of $+0.32$ mg/dL (0.08 mmol/L) did not differ from the maximum increment of 0.47 mg/dL (0.12 mmol/L) observed in the present study with doxercalciferol. However, average doxercalciferol dosage at the end of the present trial was 4-fold greater than the alfacalcidol dose: 1.62 µg/d versus 0.42 µg/d, respectively. Furthermore, patients who entered the present study had greater pretreatment iPTH levels than those administered alfacalcidol by Hamdy et al[12] (219 ± 22 versus 96.8 ± 16.3 pg/mL, respectively), and the percentage of

suppression at 6 months with doxercalciferol was 46% compared with 28% with alfacalcidol. These observations suggest that doxercalciferol may have a greater margin of safety than alfacalcidol, but direct comparisons of the sterols are necessary to establish such a difference.

Data in experimental animals indicate that doxercalciferol is less calcemic than either calcitriol or alfacalcidol. Observations show that small, but equal, low doses of doxercalciferol and alfacalcidol have the same potencies in promoting healing of rickets in vitamin D–deficient rats[30]; however, at larger doses, doxercalciferol has far less calcemic and calciuric actions.[18,19,31]

Similar data are available from clinical studies. A trial of osteoporotic women that used doxercalciferol doses up to 10.0 μg/d found only modest increments in urine calcium levels without hypercalciuria with doses as high as 5.0 μg/d.[32] This compares with the substantial hypercalciuria observed in healthy subjects administered lower doses of either alfacalcidol[33] or calcitriol.[34] Baker et al[10] observed a mean increment in urine calcium level of 61 mg/24 h (1.52 mmol/24 h), which was 125% of the baseline value, in patients administered calcitriol at doses of 0.25 to 0.5 μg/d for 24 weeks. With alfacalcidol, Hamdy et al[12] found a mean increment in 24-hour urinary calcium level of 19 $\pm$ 7.6 mg/24 h (0.47 $\pm$ 0.19 mmol/24 h) after 6 months of therapy. This compares with the increment in urinary calcium level of 11 $\pm$ 4.7 mg/24 h (0.27 $\pm$ 0.12 mmol/24 h) after 24 weeks of treatment with doxercalciferol in substantially larger doses than those of alfacalcidol. Data from the present trial show no difference in frequency of hypercalciuric events in doxercalciferol- compared with placebo-treated patients. Thus, comparison of the current data with those from controlled trials using either calcitriol or alfacalcidol suggests there may be a reduced tendency for doxercalciferol to increase urinary calcium levels despite use of larger doses.

One concern limiting the use of active vitamin D sterols has been their potential effect to reduce renal function and accelerate progression of CKD. Such an effect would not be surprising if severe or prolonged hypercalcemia were to develop.[35] In an early trial with calcitriol, 1.0 μg/d, there was an increase in serum creatinine level in conjunction with an increase in serum calcium

level[13]; both resolved after calcitriol therapy was discontinued. Another trial that used calcitriol, 0.5 μg/d, in osteoporotic women noted significant increments in serum creatinine levels in comparison to results in placebo-treated patients.[14] One study of subjects with moderately severe CKD[36] and another study of patients with psoriasis and normal kidney function[37] showed that calcitriol in doses of 0.5 μg/d or greater caused a reduction in creatinine clearance; however, there was no effect on GFR measured by means of inulin clearance.[36,37] Such findings are consistent with calcitriol exerting an action to inhibit renal tubular secretion of creatinine without affecting GFR. In calcitriol trials that used lower doses of 0.125 μg/d[15] or 0.25 μg/d,[26,27,38] increments in serum creatinine levels and/or reductions in creatinine clearances were not observed. These data suggest that the effect of calcitriol on serum creatinine level may be dose dependent. In the present trial, slight increments in serum creatinine levels occurred in subjects administered doxercalciferol, but these changes did not differ from those observed in the placebo group, and no differences in measured GFRs or creatinine clearances were detected between treatment groups.

It is unknown what iPTH level indicates secondary hyperparathyroidism of a magnitude that warrants therapy with an active vitamin D sterol. In early studies of patients with CKD stages 3 and 4, pretreatment bone biopsy specimens showed features of secondary hyperparathyroidism in a large fraction of subjects who were enrolled solely on the basis of stable renal disease without consideration of PTH levels.[8-10] Unfortunately, a retrospective comparison of PTH levels in these early studies compared with more recent reports is thwarted because the antiserum used for PTH measurements in the early studies[8-10] cannot be compared with the widely used "iPTH" assay used in several more recent reports[11,12,15,27] and in the present study.

In pretreatment bone biopsies, Bianchi et al[27] found highly abnormal histomorphometric parameters consistent with secondary hyperparathyroidism in patients with a mean iPTH level of 142 pg/mL (range, 39 to 220 pg/mL). In their large study, Hamdy et al[12] found histomorphometric abnormalities, almost entirely those of hyperparathyroidism, in the pretreatment bone biopsy speci-

men in 76% of patients assigned to alfacalcidol treatment and 73% of those assigned to placebo. Mean iPTH levels in these 2 groups were 97 $\pm$ 149 (SD) and 60 $\pm$ 43 pg/mL (ng/L), respectively. Two years later, skeletal abnormalities were present in 86% of bone biopsy samples from the placebo group when mean iPTH level had doubled. No individual biopsy data were reported from either study, which might indicate the iPTH level at which skeletal features of secondary hyperparathyroidism exist in patients with CKD stages 3 or 4. Also, it is not possible to characterize the relationship between severity of bone biopsy specimen abnormalities and iPTH levels, as reported in patients with ESRD by Quarles et al[39] and Sherrard et al.[40] The present trial excluded patients with iPTH levels less than 86 pg/mL (ng/L), and the severity of secondary hyperparathyroidism, judged by iPTH levels, was considerably greater than that reported in the trials that used a similar iPTH assay (IRMA).[12,27] Early studies of patients with moderate to severe renal insufficiency showed a reduced calcemic response to a standardized infusion of parathyroid extract,[41] and it was suggested that skeletal resistance to the calcemic action of PTH occurs in the early phases of renal insufficiency. However, data on bone histological characteristics evaluated without regard to PTH levels[8,10,12,27,42] suggest that histological features of secondary hyperparathyroidism are common and occur with only modest elevations in iPTH levels in patients with CKD stages 3 and 4.

Thus, the present double-blinded placebo-controlled trial indicates that oral doxercalciferol administered in daily doses that averaged slightly greater than 1.5 μg/d is highly effective in reducing iPTH levels in adult patients with estimated GFRs ranging from 13 to 43 mL/min/1.73 mm^2. Moreover, serum calcium levels were minimally affected, and dosage reduction was necessary in only 1 of 27 subjects because of hypercalcemia. Additional trials for more prolonged periods and with bone biopsies are needed to define the long-term role and actions of doxercalciferol in CKD stages 3 and 4.

ACKNOWLEDGMENT

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