A prospective, double-blind study of growth failure in children with chronic renal insufficiency and the effectiveness of treatment with calcitriol versus dihydrotachysterol

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Because controlled trials in adults have shown accelerated deterioration of renal function in a small number of patients receiving calcitriol for renal osteodystrophy, we initiated a prospective, randomized, double-blind study of the use of calcitriol versus dihydrotachysterol in children with chronic renal insufficiency. We studied children aged 1½ through 10 years, with a calculated glomerular filtration rate between 20 and 75 ml/min per 1.73 m^2, and with elevated serum parathyroid hormone concentrations. Ninety-four patients completed a mean of 8.0 months of control observations and were randomly assigned to a treatment period; 82 completed the treatment period of at least 6 months while receiving a calcitriol dosage (mean ± SD) of 17.1 ± 5.9 ng/kg per day or a dihydrotachysterol dosage of 13.8 ± 3.3 μg/kg per day. With treatment the height *z* scores for both calcitriol- and dihydrotachysterol-treated groups showed no differences between the two groups. In relation to cumulative dose, there was a significant decrease in glomerular filtration rate for both calcitriol and dihydrotachysterol; for calcitriol the rate of decline was significantly steeper ($p = 0.0026$). The treatment groups did not differ significantly with respect to the incidence of hypercalcemia (serum calcium concentration >2.7 mmol/L (>11 mg/dl)). We conclude that careful follow-up of renal function is mandatory during the use of either calcitriol or dihydrotachysterol because both agents were associated with significant declines in renal function. There was no significant difference between calcitriol and dihydrotachysterol in promoting linear growth or causing hypercalcemia in children with chronic renal insufficiency. Dihydrotachysterol, the less costly agent, can be used with equal efficacy. (J PEDIATR 1994;124:520-8)

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Chronic renal insufficiency in children is complicated by growth failure.[1-4] One of the major contributing factors to this growth failure is renal osteodystrophy.[5,6] Active metabolites of vitamin D have been effective in reversing this osteodystrophic process,[7] but concerns have been raised that the administration of vitamin D metabolites in renal failure may accelerate renal functional deterioration.[8-10] Such anecdotal findings, together with the uncontrolled observations of enhanced growth velocity in some children with renal osteodystrophy treated with 1,25-dihydroxycholecalciferol (calcitriol),[11,12] provide "a powerful rationale for a careful, prospective evaluation of the use of these metabolites in renal failure."[13] This is especially important during the period of rapid linear growth of the early childhood years. Because no single medical center had a sufficient number of pediatric patients to provide valid generalization, a multicenter, randomized, controlled, double-blind clinical trial was initiated with calcitriol and dihydrotachysterol as the alternative vitamin D metabolites. The use of a control group without vitamin D therapy was judged unacceptable for children with elevated parathyroid hormone concentrations associated with moderate chronic renal insufficiency.

METHODS

The study was directed from the administrative, statistical, and laboratory facilities at the Medical College of Virginia, Richmond. Twenty-five pediatric nephrology centers in the United States and Canada participated. All patients were observed during treatment for a minimum of 1 year to provide evaluation of linear growth, renal function, and the risk of hypercalcemia. Patient data files were initiated on Dec. 17, 1984, and closed on May 1, 1991. Informed consent was obtained from the parents before their children were enrolled in the study.

Entry criteria. Children between the ages of 18 months and 10 years with chronic renal insufficiency, documented by a calculated glomerular filtration rate[14,15] between 20 and 75 ml/min per 1.73 m^2, were eligible for entry into the control period. This age range was chosen to avoid the rapid growth periods before 18 months of age and during adolescence. Patients younger than 18 months of age were not included because recumbent length measurements used in infants were not comparable to the standing heights proposed in this study. In addition, the substantial changes in GFR characteristic of the first 18 months of life were avoided. The entry criterion of GFR $\leq$75 ml/min per 1.73 m^2 was justified to obtain prospective data on children with early chronic renal insufficiency during the control period.

Treatment with calcitriol or dihydrotachysterol was not initiated until the following conditions were fulfilled: (1) GFR $\leq$60 ml/min per 1.73 m^2, (2) elevation of serum parathyroid hormone concentration more than 1 SD above normal, documented during the control period, (3) patient at least 2 years of age, and (4) bone age $\leq$9 years. In children with chronic renal insufficiency, the bone age is usually less than the chronologic age; thus a bone age <9 years and a chronologic age <10 years were chosen. To minimize study losses, we set the lowest GFR acceptable for entry into the treatment period at 20 ml/min per 1.73 m^2, because it was anticipated that at least 1 year of data collection would be obtained before the patient required dialysis or transplantation. Furthermore, chronic renal insufficiency was expected to progress at a relatively stable rate when the GFR was between 20 and 75 ml/min per 1.73 m^2.

Exclusion and exit criteria. The following conditions that could affect linear growth excluded patients from enrollment: nephrotic syndrome, lupus erythematosus or other nephropathies in which steroid treatment had been or was expected to be used, vitamin D–dependent rickets, hypophosphatemic rickets, hypoparathyroidism and pseudohypoparathyroidism, primary renal tubular acidosis, and other exclusion criteria as previously described.[13] Children who had already been treated with calcitriol, dihydrotachysterol, or any form of vitamin D (except that in multivitamin supplements) were also excluded from the study. Exit criteria included initiation of dialysis or transplantation, patient's or parent's decision to leave the study, or physician's decision to withdraw the patient.

GFR	Glomerular filtration rate
z Score	Standard deviation score

Control protocol. Each eligible patient entered a control period for baseline observations with an initial visit and three follow-up clinic visits at 2-month intervals to provide four sets of anthropometric measurements and three serum chemistry profiles. Parathyroid hormone values were measured at the initial and third follow-up visits. Random assignment to calcitriol or dihydrotachysterol treatment was made at the end of the control period.

The medications used to regulate and stabilize other variables, to permit evaluation of the effects of the vitamin D therapies, consisted of calcium carbonate (to maintain serum phosphorus concentrations between 1.3 and 1.8 mmol/L [4.0 and 5.5 mg/dl]), and sodium bicarbonate (to maintain serum total carbon dioxide content $\geq$18 mmol/L).[13] Thus compounding variables were controlled or maintained at a steady level to permit the effects of the two treatment arms to be evaluated more accurately.

Treatment protocol. Patients randomly assigned to receive calcitriol ingested a combination of active calcitriol and placebo dihydrotachysterol; those randomly assigned to receive dihydrotachysterol ingested a combination of active dihydrotachysterol and placebo calcitriol. Thus patients received, by appearance, identical regimens.

The dose of calcitriol was started at 20 ng/kg per day, and administration of dihydrotachysterol was started at 15 μg/kg per day, with adjustments as necessary for weight

changes every 6 months, and monthly for hypercalcemia or elevated alkaline phosphatase values. The 30-day medication package (Remind-A-Pac Inc., Southfield, Mich.) of medication and placebo and the "backup" supply have been described previously.[14, 15]

During the treatment period, monthly fasting serum calcium and phosphorus concentrations[14] were determined. Heights were measured according to standardized procedures[14] with a Holtain stadiometer (Seritex; Carlstadt, N.J.) provided at each center. All personnel taking this measurement were trained at the initial, and annual workshops.[14] Interlaboratory variations were avoided by central analysis of serum creatinine and parathyroid hormone.[14] By special arrangement with BioScience Labs (Van Nuys, Calif.), all parathyroid hormone analysis was done with C-terminal antibodies (the contemporary method when the study was initiated in 1984) and continued throughout the subsequent 7 years of the study.[14] Hematocrit values and blood concentrations of sodium, potassium, chloride, total carbon dioxide, blood urea nitrogen, total protein, albumin, alkaline phosphatase, and hemoglobin were determined monthly for the first 3 months after randomization and every 6 months thereafter.[14] If hypercalcemia (>2.7 mmol/L [11 mg/dl]) occurred, the medication was discontinued until normal levels of calcium (2.2 to 2.6 mmol/L [9 to 10.5 mg/dl]) were reestablished; treatment with the medication was then restarted at 75% of the previous dose.

Data collection. Each member of the team was required to pass a comprehensive examination to be certified for proficiency and uniformity in data collection.[15] Additional workshops were given annually to provide retraining and to accommodate any changes in personnel.

Safety monitoring. An external advisory committee, independently appointed by the National Institutes of Health, monitored the conduct of this clinical trial.[13-16] The committee was empowered to discontinue the study if the benefits of one treatment arm were markedly superior or if the risks of renal functional deterioration and hypercalcemia were unacceptably high.

Compliance monitoring. The patient medication packages were designed with each day's dose sealed in transparent pockets. Each pocket was opened by the parent to deliver the daily dose. All patient medication packages and 20-day "backup" packages were to be brought to each clinic visit to be inspected by the investigator for compliance.

Statistical analysis. Changes in height and weight were converted to scores z scores (standard deviation scores)[17] on the basis of National Center for Health Statistics percentile tables.[18] A z score for a particular subject represents the distance in standard deviations from the 50th percentile for subjects of the same age and gender.[17]

The linear height z scores, the weight z scores, and the GFRs were analyzed with a longitudinal data analysis.[19, 20] This method of analysis is basically a repeated measurements analysis of variance that allows for unbalanced data (i.e., unequal duration of patient follow-up). The purpose of the longitudinal data analysis is to compare average changes within individuals. In a cross-sectional study, the response is measured only once and typically has a large variability, whereas changes with time for individual subjects usually display less variability. Thus longitudinal studies typically provide more precise estimates of treatment effects. A longitudinal data analysis provides an average change for each treatment group, and the average changes of the groups can be compared. Vonesh and Carter[20] developed a statistical method for the analysis of longitudinal data that incorporates random effects; it was applied to the longitudinal data in this study with their software.

For each treatment group the longitudinal model consisted of a slope (in years) for the control period, an intercept representing the mean response at the end of the control period (time = 0), and a slope (in years) for the treatment period. Parallel axis plots of time intervals indicated that the intercept-slope model for the three response variables would suffice. Contrasts were then constructed to compare the intercepts and slopes of the calcitriol and dihydrotachysterol groups. An additional longitudinal data analysis, in which the model consisted of an intercept for the control period and a slope over cumulative dose for the treatment period, was applied.

The occurrence of hypercalcemia was recorded for each patient, in addition to dates for starting and stopping treatment. Thus the time to development of hypercalcemia was examined by stratified proportional hazard regression analysis,[21] an appropriate analytic method because (1) it modeled the time from the start of the medication regimen to the occurrence of hypercalcemia as a function of treatment group, (2) it allowed for right-censoring (i.e., if hypercalcemia did not develop, the duration of treatment was important information and was used in the model), and (3) it allowed for multiple episodes of hypercalcemia per patient.

RESULTS

The number of patients per clinical center entering the control period varied from 2 to 15; three centers had more than 10 patients. The number of patients randomly assigned to either of the two treatment arms and who completed the study varied from 1 patient to 10 patients per center; two centers had 10 patients each.

Comparability of the groups. A total of 143 children fulfilled the entry criteria and entered the control period, and after documentation of elevated serum concentrations of parathyroid hormone, 94 were randomly assigned to the two treatment arms. A period of at least 12 months of treatment

Table I. Demographic and laboratory characteristics of 143 study patients at entry to the control period and 82 patients who completed the study at the beginning of the treatment periods

Characteristics	Control (n = 143)	Calcitriol (n = 40)	Dihydrotachysterol (n = 42)
Age (yr)	5 ± 3	6 ± 3	5 ± 3
Height (cm)	104 ± 20	108 ± 21	105 ± 18
Weight (kg)	18 ± 9	29 ± 9	18 ± 8
Sex			
Male	94	29	26
Female	49	11	16
Race			
Black	29	4	8
White	102	33	31
Other	12	3	3
Diagnosis			
Obstructive uropathies	101 (71%)	32 (80%)	29 (69%)
Renal dysplasia	28 (20%)	7 (18%)	8 (19%)
Glomerular diseases	12 (8%)	1 (2%)	5 (12%)
No diagnosis	2 (1%)	0	0
TOTAL	143 (100%)	40 (100%)	42 (100%)
Serum chemistry			
Urea nitrogen			
mmol/L	12 ± 6	13 ± 6	12 ± 5
(mg/dl)	(34 ± 16)	(36 ± 17)	(34 ± 13)
Creatinine			
μmol/L	133 ± 62	124 ± 71	133 ± 53
(mg/dl)	(2 ± 1)	(1 ± 1)	(2 ± 1)
Calcium			
mmol/L	3 ± 0	3 ± 0	3 ± 0
(mg/dl)	(10 ± 1)	(10 ± 1)	(10 ± 1)
Phosphate			
mmol/L	2 ± 0	2 ± 0	2 ± 0
(mg/dl)	(5 ± 1)	(5 ± 1)	(5 ± 1)
Parathyroid hormone, pg/ml	1321 ± 1834	1521 ± 2249	1088 ± 907
Alkaline phosphatase, IU/L	272 ± 123	267 ± 113	280 ± 127
Osteocalcin, ng/ml	56 ± 37	57 ± 31	62 ± 38
Sodium, mmol/L	140 ± 3	140 ± 2	140 ± 3
Potassium, mmol/L	5 ± 1	4 ± 1	5 ± 1
Chloride, mmol/L	107 ± 4	106 ± 4	107 ± 3
Carbon dioxide content, mmol/L	21 ± 4	22 ± 4	21 ± 4
Hemoglobin			
gm/L	117 ± 24	122 ± 18	121 ± 16
(gm/dl)	(12 ± 2)	(12 ± 2)	(12 ± 2)
Hematocrit	0.35 ± 0.6	0.36 ± 0.5	0.36 ± 0.5
RDA			
%RDA for calories	79 ± 22	81 ± 5	80 ± 5
%RDA for protein	158 ± 58	165 ± 14	153 ± 15

All values expressed as mean ± SD.
RDA, Recommended dietary allowance.

was completed by 82 patients, for a total follow-up of 21.0 ± 12.4 and 22.1 ± 14.8 months (mean ± SD) of observations per patient for calcitriol and dihydrotachysterol, respectively. The average dosage of calcitriol was 17.1 ± 5.0 ng/kg per day (mean ± SD) versus that of dihydrotachysterol of 13.8 ± 3.9 μg/kg per day. Forty-seven patients received the same dosage throughout the study; the dose was increased in the course of the study but the dosage on a kilogram-per-body-weight basis remained the same.

The two groups were closely matched at entry into the control period and during the treatment period; the physical characteristics of age, sex, race, and primary renal diseases were similar, as were the values for serum urea nitrogen, creatinine, hemoglobin, and hematocrit, and the per-

Table II. Reasons for patient withdrawal from study

Dropout during control period (n = 49)	
GFR ≥60 ml/min/1.73 m²	15
PTH <180 pg/dl	1
Bone age >9 years	6
Medical noncompliance	7
Fewer than two food records returned	5
Moved/no return	11
Dialysis/transplantation	4
Dropout during treatment period (n = 12)	
Parent's decision	4
Physician decision	3
Medical noncompliance	2
Moved/no return	2
Dialysis/transplantation	1

centage of the recommended dietary allowances of caloric and protein intakes (Table I). The serum electrolyte values, including acid-base balance, were stable.

The nutritional variables of standardized caloric intake (80.9% ± 4.9% and 80.3% ± 5.3% of the recommended dietary allowances) and standardized protein intake (164.5% ± 13.9% and 153.2% ± 15.0% of the recommended dietary allowances) for calcitriol- and dihydrotachysterol-treated groups, respectively, were not confounding variables for the growth responses. Longitudinal data analysis revealed that these nutritional variables did not significantly differ ($p = 0.9359$ and $p = 0.5920$, respectively) between the two groups during treatment.

Dropouts. The major reasons for the 49 patient dropouts during the control period were as follows: 30.6% had a calculated GFR[16] that continued to be higher than 60 ml/min per 1.73 m², and 22.4% relocated to an area more than 100 miles from any of the participating centers. Of the 94 patients randomly assigned to one of the two treatment arms, 12 patients dropped out (Table II).

Compliance. All patients who missed two or more doses in 28 days were counseled and closely monitored. Six patients exceeded this 7% noncompliance rate. Four of these patients withdrew from the study; two improved their compliance and remained in the study group.

Linear growth data. The mean z score for height for all 143 patients at entry into the control period was −1.6 ± 0.2. The control height z scores for patients at the end of the control period who were randomly assigned to receive calcitriol treatment had a value of −1.62 ± 0.22 (mean ± SEM), whereas control values for patients who received dihydrotachysterol treatment were −1.66 ± 0.22 (Table III).

Neither treatment had an effect on linear height z scores (Table III). Although the treatment period slopes were positive, they were not significantly different from zero ($p > 0.10$). Similar results were observed for the weight z scores. When cumulative dose was substituted for time in the study, the results were similar for height and weight z scores.

Renal function. There was a significant decrease in GFR during the treatment periods for both the calcitriol-treated group ($p = 0.0050$) and the dihydrotachysterol-treated group ($p = 0.0045$) (Table III). However, in comparison with the respective slopes during the control period, there were no significant differences. When GFR was analyzed in relation to cumulative dose (Figure), there was a significant decrease during the treatment periods (Table IV) for both calcitriol ($p < 0.0001$) and dihydrotachysterol ($p = 0.0022$). The calcitriol group had a significantly steeper rate of decline in GFR than the dihydrotachysterol group ($p = 0.0026$).

Hypercalcemia. The time to development of hypercalcemia in patients during calcitriol treatment was 11.3 ± 9.3 months (mean ± SD), and for patients who received dihydrotachysterol treatment, the interval was 12.2 ± 12.1 months. A total of 47 episodes of hypercalcemia were encountered in patients during calcitriol treatment, and 41 episodes occurred during dihydrotachysterol treatment, but there was no significant difference between the two groups with regard to the severity of hypercalcemia. There was no significant difference in the frequency of hypercalcemia in the two treatment arms. The time from onset of hypercalcemia to resumption of treatment was 71 ± 104 days for calcitriol and 60 ± 65 days for dihydrotachysterol ($p = 0.92$, nonparametric log rank test). No significant effects of serum calcium on GFR were discovered ($p > 0.01$).

DISCUSSION

Our study is the first randomized, double-blind clinical trial in children with early chronic renal insufficiency to test the effect of calcitriol versus dihydrotachysterol on height z scores,[17] calculated GFRs,[14, 16] and hypercalcemia. The stringent entry criteria and the relatively stable renal function during the control period successfully precluded dialysis or transplantation as major reasons for patient dropouts.

These children with early chronic renal insufficiency already had growth retardation. There were no significant changes in z scores for height during treatment with either calcitriol or dihydrotachysterol. The previous reports[11, 12] of accelerated linear growth after calcitriol therapy were made on the basis on a few heterogeneous patients (including some treated with dialysis or after transplantation). None of the previously published series[11, 12] included more than 11 children, and all studies were uncontrolled and nonblinded and were based on short-term growth velocity data. Our controlled and double-blind study shows that, although there were some cases of growth responses to administration

Table III. Parameter estimates and standard errors for both treatment groups and their comparisons*

Group	Parameter	Estimate	SE	p
Height z score				
Calcitriol	Control slope	−0.0039	0.2446	0.9872
	Treatment slope	0.1775	0.1069	0.1012
	Treatment minus control	−0.1814	0.3023	0.5503
DHT	Control slope	0.2971	0.2390	0.2176
	Treatment slope	0.1322	0.1034	0.2052
	Treatment minus control	0.1649	0.2947	0.5774
Calcitriol minus DHT	Control slope	−0.3010	0.3420	0.3815
	Treatment slope	0.0453	0.1487	0.7618
	Treatment minus control	−0.3463	0.4222	0.4147
Weight z score				
Calcitriol	Control slope	0.0984	0.1389	0.4782
	Treatment slope	0.0722	0.0440	0.1050
	Treatment minus control	0.0262	0.1536	0.8650
DHT	Control slope	0.2946	0.1352	0.0324
	Treatment slope	0.0341	0.0428	0.4287
	Treatment minus control	0.2605	0.1500	0.0864
Calcitriol minus DHT	Control slope	−0.1962	0.1938	0.3130
	Treatment slope	0.0381	0.0614	0.5360
	Treatment minus control	−0.2343	0.2142	0.2775
GFR				
Calcitriol	Control slope	0.5547	1.7089	0.7464
	Treatment slope	−2.9716	1.0274	0.0050
	Treatment minus control	3.5263	2.2115	0.1150
DHT	Control slope	−3.1791	1.8346	0.0872
	Treatment slope	−2.8748	0.9808	0.0045
	Treatment minus control	−0.3043	2.2937	0.8947
Calcitriol minus DHT	Control slope	3.7338	2.5072	0.1406
	Treatment slope	−0.0968	1.4204	0.9461
	Treatment minus control	3.8306	3.1851	0.2328

DHT, Dihydrotachysterol.
*On the basis of longitudinal data analyses with time (years).[20]

Table IV. Parameter estimates and standard errors for both treatment groups and their comparisons*

Group	Parameter	Estimate	SE	p
GFR				
Calcitriol	Treatment	−0.0008	0.0001	<0.0001
DHT	Treatment	−0.0003	0.0001	0.0022
Calcitriol minus DHT	Treatment	−0.0005	0.0002	0.0026

DHT, Dihydrotachysterol.
*On the basis of longitudinal data analysis with cumulative dose.[20]

of calcitriol, the spread of response was so large that the mean values for growth in the calcitriol-treated group were not different from those of the dihydrotachysterol-treated group. Because a majority of children with early chronic renal insufficiency have growth retardation, perhaps earlier treatment with either calcitriol or dihydrotachysterol should be instituted.[22, 23] However, the vitamin D metabolites must be used with caution, including careful follow-up and monitoring of renal function and serum calcium concentration.

The possibility of accelerated deterioration of renal function as a result of calcitriol nephrotoxicity, with or without hypercalcemia, in chronic renal failure was suggested by Christiansen et al.[9] Although the first prospective, double-blind trial of calcitriol versus placebo in 13 adult patients showed no deterioration of renal function,[24] there was still widespread concern about calcitriol administration to patients with mild to moderate renal impairment.[25] Our data show that both calcitriol- and dihydrotachysterol-treated groups had significant declines in GFR during the treatment phase.

The rate of deterioration of renal function may be related to the natural decline of GFR because of the primary renal

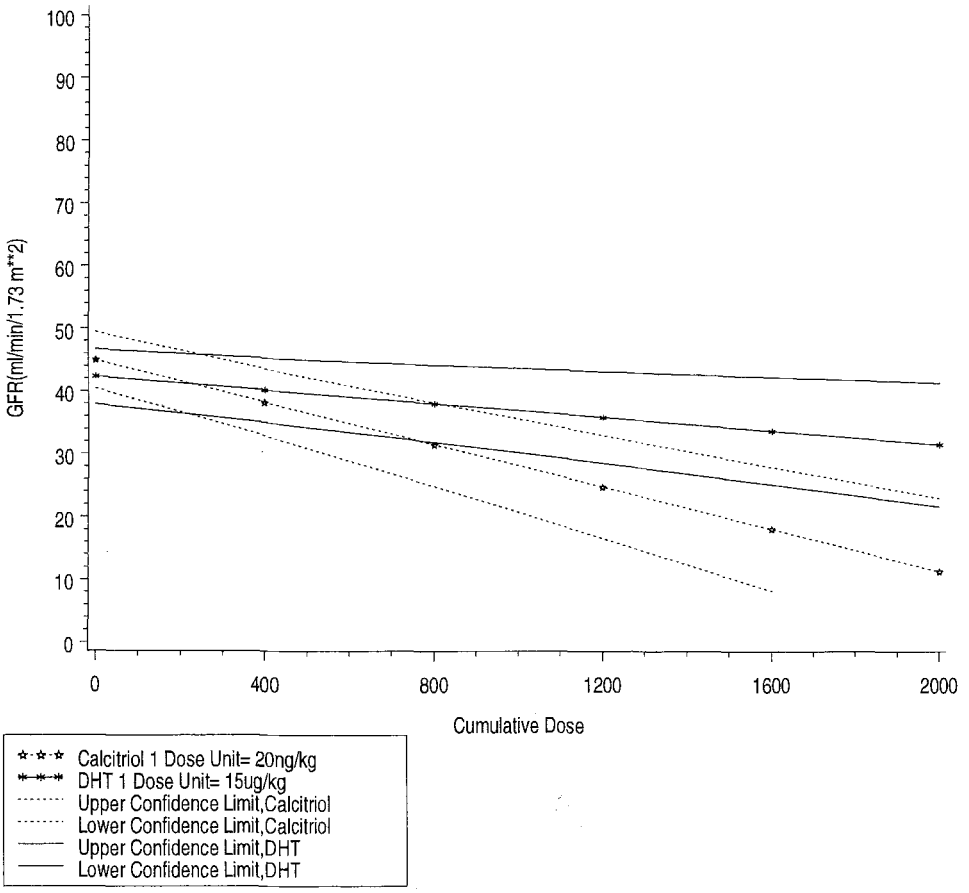

Figure. Fitted regression lines[20] for GFR versus cumulative dose, calcitriol versus dihydrotachysterol *(DHT)*.

disease, independent of the use of the vitamin D metabolites. The inclusion of an untreated group would have settled this concern, but it was untenable to deny treatment to children with elevated serum parathyroid hormone concentrations. We chose dihydrotachysterol as the "control" arm with which to compare calcitriol because the former was the most extensively used form of vitamin D in renal osteodystrophy since its introduction more than 40 years ago. Hypercalcemia is a known complication of treatment with dihydrotachysterol, but accelerated deterioration of renal function has never been raised as a major concern.

When this study was designed, the use of reciprocals of the serum creatinine concentration plotted with time[26, 27] was judged to be the most practical and the least invasive method of estimating renal function in children. Clearance methods requiring urine collections would be compromised because the majority of patients in the study had obstructive uropathy and because the undetermined residual urine volumes would introduce large variables and compromise the interpretation of the data. Subsequent to the initiation of the study, considerable doubts have been raised concerning the use of the reciprocals of the serum creatinine concentration as an index of GFR.[28] However, recent data reported by DeSanto et al.[29] showed that, in children, this continues to be a convenient and reliable single index and serves as a useful indication of renal function. In addition, the calculated GFR[15] has continued to be used in new clinical trials in children with growth failure from renal diseases.[30]

The incidence of hypercalcemia in calcitriol-treated patients with chronic renal failure was one episode every 13 months of treatment[31, 32] in uncontrolled studies. In the first double-blind, prospective trial in adult patients with chronic renal failure, calcitriol administration was associated with one episode of hypercalcemia every 12 months.[24] Our data showed comparable incidence values for both calcitriol and dihydrotachysterol treatment. There was no significant difference between these two medications in terms of frequency or magnitude of hypercalcemia. We conclude that hypercalcemia is an unavoidable complication of the use of

vitamin D metabolites in some patients. Other biochemical data from this clinical trial will be reported subsequently.[33, 34]

In summary, administration of both calcitriol and dihydrotachysterol was associated with a significant decline in renal function. There was no statistical difference in the incidence of hypercalcemia between the two treatment arms. There was no advantage of use of calcitriol over dihydrotachysterol in promoting linear growth. We conclude that dihydrotachysterol, the less expensive medication, can be used with equal efficacy, although careful follow-up is mandatory because of the accelerated rate of renal deterioration encountered with use of either calcitriol or dihydrotachysterol.

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