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Chronic hypoparathyroidism
cystinosis
1,25-dihydroxyvitamin D_3
Hereditary hypophosphatemia
1α-hydroxyvitamin D_3
nutritional rickets
pseudodeficiency rickets

1,25-Dihydroxyvitamin D_3 and 1,α-Hydroxyvitamin D_3 in Children: Biologic and Therapeutic Effects in Nutritional Rickets and Different Types of Vitamin D Resistance

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Extract

This investigation confirms the high level of biologic activity and the similarity of the effects of small doses of 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2$-D_3) and of its analog 1α-hydroxyvitamin D_3 (1α-OH-D_3) on children with nutritional rickets, "pseudodeficiency" rickets (PDR), hereditary hypophosphatemia, chronic idiopathic hypoparathyroidism, and chronic renal failure. It also shows that cystinotic patients may develop, at the end stage of the disease, a certain degree of resistance to 1,25-$(OH)_2$-D_3. The comparison of the therapeutic effects of long term oral administration of 1,25-$(OH)_2$-D_3 or 1α-OH-D_3 to two D-deficient children and two sibs with PDR demonstrates differences in sensitivity. In the patients with nutritional rickets, 0.5 μg/24 hr of either drug corrects the biochemical abnormalities, initiates healing of skeletal lesions in 28 days, and cures the metaphyseal lesions in 60 days of therapy. In contrast, it appears that doses of either drug that are curative in D deficiency rickets are only partly active in PDR. These observations indicate that the hypothesis of a deficit in 25-hydroxycholecalciferol 1α-hydroxylase in patients with PDR must await for confirmation more direct evidences, and that such a deficit, even if proven, may not account for all of the biochemical and skeletal alterations seen in patients with this inherited disorder.

Speculation

The similarity of action of 1,25-$(OH)_2$-D_3 and 1α-OH-D_3 observed in the present study presents additional evidence that 1α-OH-D_3 can be considered a valuable substitute for the hormonal form of cholecalciferol, especially for the management of children with chronic renal failure, hypoparathyroidism, or pseudodeficiency rickets. In this latter disease, the active therapeutic doses of either drug appear to be greater than the amount required for the treatment of simple nutritional rickets. This observation indicates that investigations on the pathogenesis of pseudodeficiency rickets must be continued in order to confirm or invalidate the hypothesis suggested by us and others that this inherited disorder might be related to a deficit in 25-hydroxycholecalciferol 1α-hydroxylase.

During the past few years the metabolism of vitamin D has undergone extensive investigations. Results obtained so far have led to the isolation and identification of several active metabolites. Their sites of synthesis and the role of several ionic and/or hormonal factors for the activation or the inhibition of these syntheses have been analyzed (3, 21, 23, 26, 31). The transport, storage, inactivation of these metabolites, and mechanism of their intracellular transport and action are currently under study in several laboratories. Even though incomplete, these new concepts of vitamin D metabolism are of great theoretical value. Furthermore, they help to clarify our understanding of vitamin D resistance observed in such diseases as chronic renal failure, hepatocellular failure, hypoparathyroidism, or during anticonvulsant therapy. Moreover they indicate that the use of these metabolites, especially that of the hormonal form 1,25-$(OH)_2$-D_3 instead of cholecalciferol itself, might provide a more specific treatment for some pathologic states. The chemical synthesis of 1,25-$(OH)_2$-D_3 is difficult and sufficient quantities for long term clinical trials are not easily available. Recently an analog of this active vitamin D derivative has been discovered: 1α-OH-D_3 (22). Preparation of this compound is less difficult and less expensive (6, 18, 22). The present investigation was undertaken in order to analyze the comparative biologic effects of 1,25-$(OH)_2$-D_3 and 1α-OH-D_3 in children with different types of D resistance, and to determine whether 1α-OH-D_3 could be a valuable substitute for 1,25-$(OH)_2$-D_3 in pediatric pharmacology.

Preliminary results obtained during this investigation established that children with PDR were sensitive to quite small doses of 1,25-$(OH)_2$-D_3. These observations led us to suggest that this inherited disorder might be caused by a deficit in 25-hydroxycholecalciferol 1α-hydroxylase (4); a hypothesis also suggested by Fraser *et al.* (14), and more recently by Prader (29), Fanconi (13), and Scriver *et al.* (32). According to this hypothesis the biochemical and skeletal lesions in PDR, just as they are in simple D deficiency rickets, may be related to a deficit in 1,25-$(OH)_2$-D_3. Hence, one would expect children with PDR and patients with D deficiency rickets to respond similarly to 1,25-$(OH)_2$-D_3 or 1α-OH-D_3 therapy. In an attempt to test the validity of this assumption our study was completed by a comparison of the therapeutic effects of small daily oral doses of 1,25-$(OH)_2$-D_3 or

1α-OH-D_3 in two children with nutritional rickets and two sibs with pseudodeficiency rickets.

SUBJECTS AND METHODS

SHORT TERM PROTOCOL

Investigations were carried out in 19 subjects (34) including 1 normal control aged 14 years 6 months, 4 children with D deficiency rickets, 4 patients with pseudodeficiency D-resistant rickets (PDR) as described by Prader, Illig, and Heierli (30), 2 with hereditary hypophosphatemic D-resistant rickets (VDRR), 1 adolescent with late acquired D-resistant rickets as described by McCance (25), and who had been in spontaneous recovery for 18 months, 1 patient with chronic idiopathic hypoparathyroidism, 4 children with terminal stage chronic renal failure, and 2 children with cystinosis. In these different diagnostic groups the effects of short term administration of 1,25-$(OH)_2$-D_3 were studied with some patients whereas 1α-OH-D_3 was given to the others. The two children with cystinosis had severe impairment of their glomerular functions, *i.e.*, creatinine clearances, were, respectively, 6 and 30 ml/min/1.73 m^2; both received 1,25-$(OH)_2$-D_3. The effects of 1,25-$(OH)_2$-D_3 and of 1α-OH-D_3 were analyzed in the same patient with chronic idiopathic hypoparathyroidism. All children with VDRR or with PDR, the adolescent with late acquired D-resistant rickets, and the patient with chronic idiopathic hypoparathyroidism had been previously treated with vitamin D or 25-OH-D_3. Therapy had been stopped for 2 months to 16 months when the present study was started. None of the other subjects had received any vitamin D.

The 1,25-$(OH)_2$-D_3 used was biosynthetically prepared in the Laboratoire des Tissus Calcifiés, Paris, from synthetic 25-OH-D_3 (Laboratoire Roussel, Paris, France) and D-deficient chick kidney homogenate according to the technique described by Omdahl, *et al.* (27). 1α-OH-D_3 was synthetized in the department of Biochemistry, University of Wisconsin, Madison, Wisconsin, by M. F. Holick and H. F. DeLuca. The drugs were administered orally as propylene glycol solutions. Before their utilization all batches of 1,25-$(OH)_2$-D_3 and of 1α-OH-D_3 were tested for their biologic activity. Doses used were 2 μg/24 hr for 5 days for 1,25-$(OH)_2$-D_3 and 1 μg/24 hr for 5 days for 1 α-OH-D_3 in all cases studied, except for the patient with chronic idiopathic hypoparathyroidism who was given 2 μg/24 hr for 5 days of 1α-OH-D_3 then, after an interval of 7 days, 2 μg/24 hr for 5 days of 1,25-$(OH)_2$-D_3.

LONG TERM PROTOCOL

The therapeutic effects of 1,25-$(OH)_2$-D_3 were investigated with two sibs with PDR and a child with D deficiency rickets. 1,25-$(OH)_2$-D_3 was administered orally at a dose of 1 μg/24 hr for 28 days to the patients with PDR and at a dose of 0.5 μg/24 hr for 2 months to the patient with nutritional rickets. The actions of long term administration of 1α-OH-D_3 were studied in two patients. A child with D deficiency rickets was given 0.5 μg/24 hr for 25 days. For one of the sibs with PDR the effects of 1α-OH-D_3 therapy were evaluated at two dose levels, *i.e.*, 0.5 μg/24 hr for 25 days then 1 μg/24 hr for 20 days. For this patient balance studies of stable calcium and phosphorus were performed during 14 5-day periods. Carmine was used as a fecal marker. The patients with D-deficiency rickets and the children with PDR had radiologic examinations of the wrist and knee bones at the initiation and at the end of 1,25-$(OH)_2$-D_3 and/or 1α-OH-D_3 therapy.

During the short term and the long term studies the following biochemical data were collected: serum calcium, phosphorus, creatinine, citrate, alkaline phosphatase; urine calcium, phosphorus creatinine, and cyclic AMP; endogenous creatinine clearance, tubular reabsorption of phosphorus (TRP), and phosphorus maximum tubular reabsorption rate per 100 ml glomerular filtration rate (Tm/GFR) calculated according to the nomogram of Bijvoet *et al.* (7). The laboratory techniques used were the following: phosphorus, Fiske and SubbaRow (AutoAnalyzer); creatinine (AutoAnalyzer); calcium, automated complexometric titration (Marius calcium titrator, Amsterdam, Netherlands); alkaline phosphatase, Bodansky method; citrate, an enzymatic technique (33); urinary cyclic AMP, a modification of the Gilman method (16).

RESULTS

BIOLOGIC EFFECTS OF SHORT TERM ADMINISTRATION OF 1,25-$(OH)_2$-D_3 OR 1α-(OH)-D_3

1,25-$(OH)_2$-D_3 had no effect on any of the biochemical parameters studied in the two children with cystinosis. For all other patients oral administration of 2 μg/24 hr for 5 days of the active metabolite of vitamin D promoted a clear-cut rise in serum calcium concentrations (Fig. 1). An increase in serum phosphorus concentrations was observed in the child with D deficiency rickets, three patients with pseudodeficiency rickets, and the child with VDRR (Fig. 2). In this last patient a transient rise in TRP, *i.e.*,

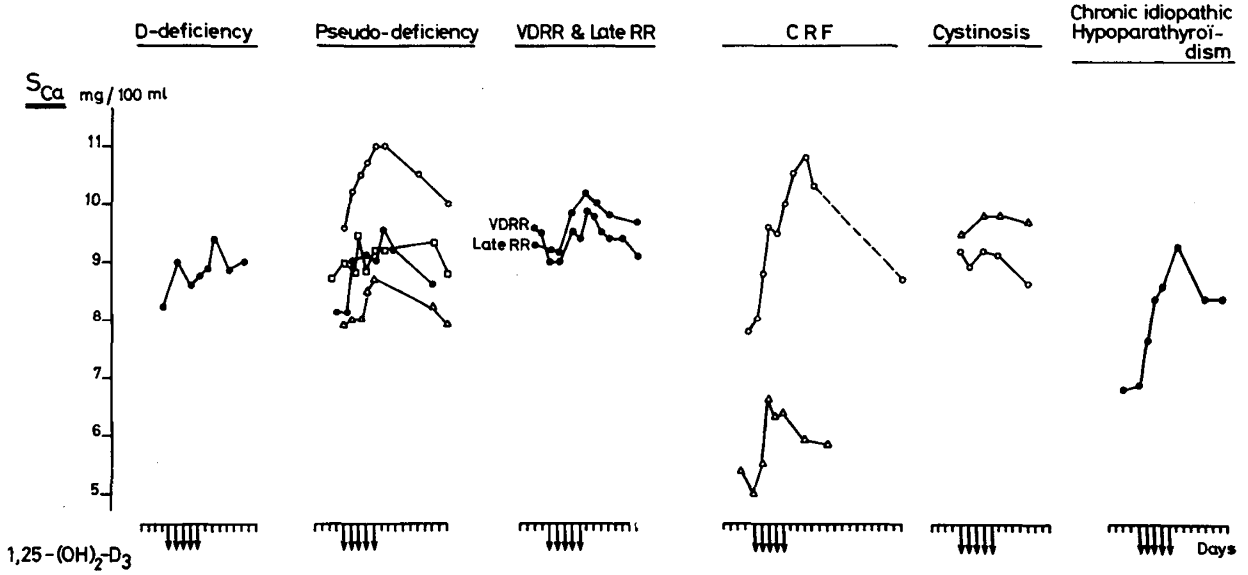

Fig. 1. Serum calcium concentrations (S_{Ca}) during short term protocol with 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2$-D_3). The arrows on the horizontal axis represent days of oral 1,25-$(OH)_2$-D_3 administration. *VDRR:* hereditary hypophosphatemic rickets; *Late RR:* late acquired D-resistant rickets; *CRF:* chronic renal failure.

61% during therapy vs 36% during the control period, occurred. Serum phosphorus decreased slightly then increased sharply in the two children with severe chronic renal failure. In contrast, in the adolescent with chronic idiopathic hypoparathyroidism 1,25-$(OH)_2$-D_3 administration promoted a fall in serum phosphorus concentration; this effect persisted 1 week after cessation of therapy. No changes of endogenous creatinine clearance were observed during this investigation. The effects of 1,25-$(OH)_2$-D_3 on serum citrate, as on the other parameters studied, were variable from case to case.

BIOLOGIC EFFECTS OF SHORT TERM ADMINISTRATION OF 1α-OH-D_3

Figure 3 illustrates the variations in serum calcium concentrations. A rise was observed in all subjects studied, either during 1α-OH-D_3 administration or during the post-treatment period. The maximal variation from baseline level (+1.4 mg/100 ml) was found in a D-deficient, severely hypocalcemic child who had been given iv calcium gluconate infusion 12 hr before 1α-OH-D_3 therapy. Serum phosphorus concentration (Fig. 4) decreased in the patient with chronic idiopathic hypoparathyroidism; in all other subjects, except one child with chronic renal failure receiving anticonvulsant therapy, serum phosphorus concentration rose. An augmentation in serum citrate concentration was found in seven of eight subjects studied. A transient rise in TRP occurred during therapy in the child with VDRR. 1α-OH-D_3 did not modify endogenous creatine clearance and urinary excretion of calcium; the effects on serum alkaline phosphatase and urinary excretion of cyclic AMP were variable.

THERAPEUTIC EFFECTS OF LONG TERM ORAL ADMINISTRATION OF BIOSYNTHETIC 1,25-$(OH)_2$-D_3

This study was carried out with two sibs with pseudodeficiency rickets and one child with D deficiency rickets. The patients with

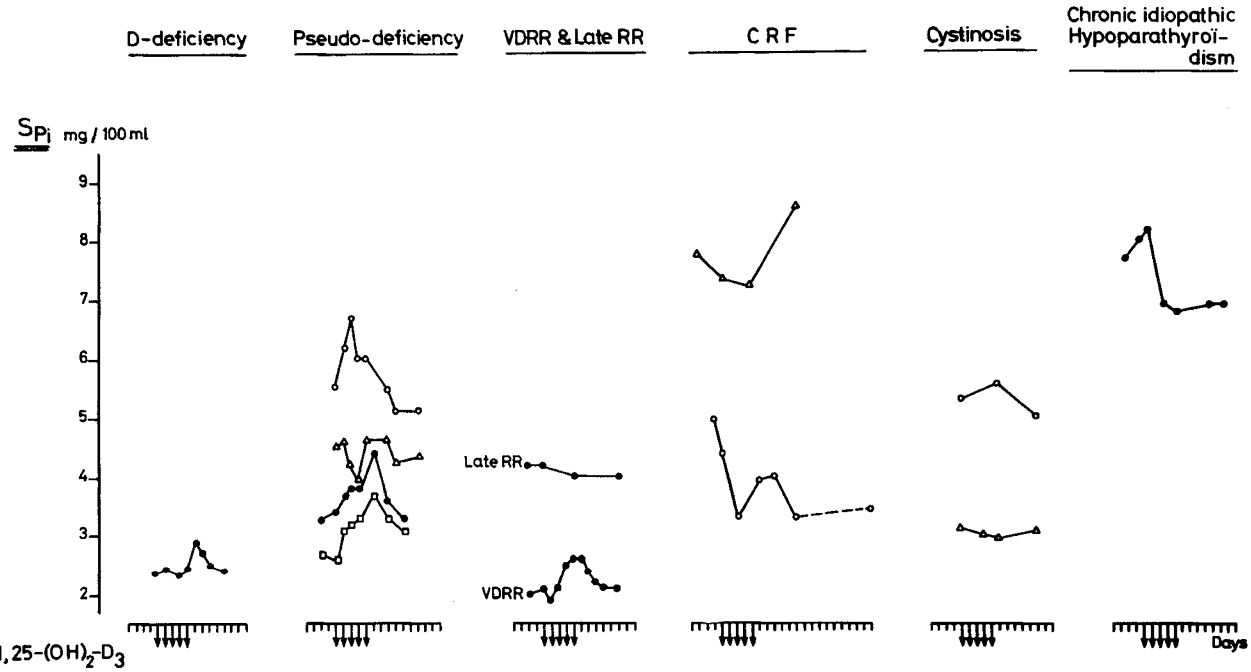

Fig. 2. Serum phosphorus concentrations (S_{Pi}) during short term protocol with 1,25-dihydroxyvitamin D_3 ($1,25$-$(OH)_2$-D_3). Illustrations and abbreviations are the same as in Figure 1.

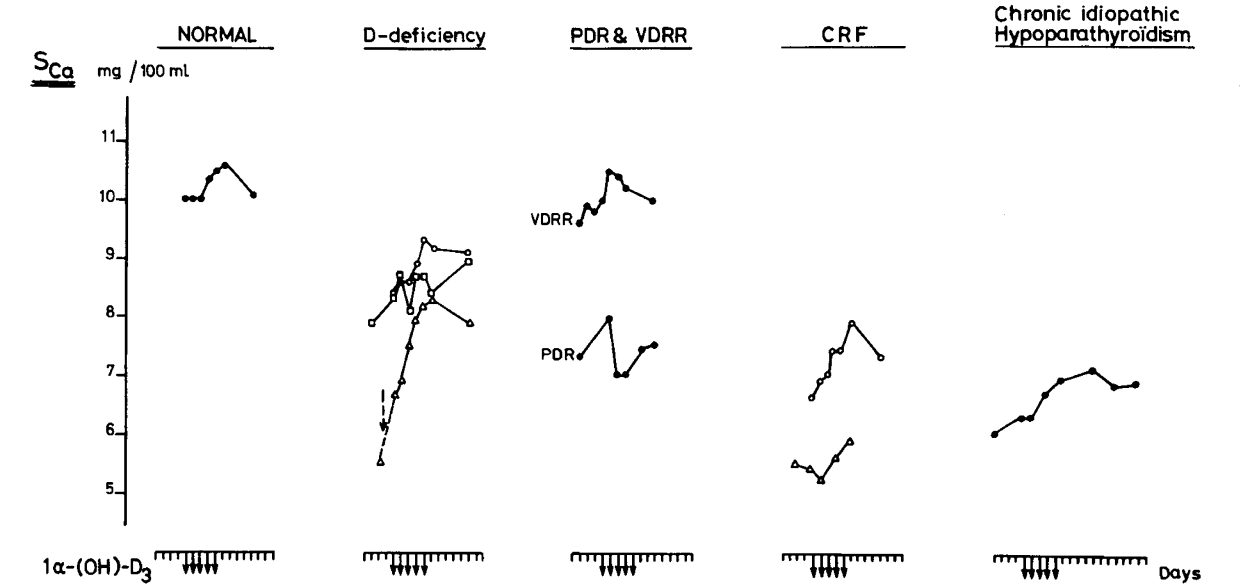

Fig. 3. Serum calcium concentrations during short term protocol with 1α-hydroxyvitamin D_3(1α-(OH)-D_3): 1 μg/24 hr for 5 days. The dotted arrow indicates a 12-hr calcium gluconate infusion given to a severely hypocalcemic D-deficient child.

PDR were aged, respectively, 5 years and 7 years when the present investigation was started. They had both been under the medical survey of one of us (S.B.) for the past 5 years. During this period of time their requirements for 25-OH-D_3 had been found to be between 250 and 300 μg/24 hr in order to obtain and maintain a normal growth, normalization of biochemical parameters, and complete healing of skeletal ricketic lesions. For these patients 25-OH-D_3 therapy had been stopped for 2 months when the biologic and therapeutic effects of 1,25-$(OH)_2$-D_3 were studied. Forty-five days after the end of the short term protocol they were given 1 μg/24 hr of 1,25-$(OH)_2$-D_3 for 28 days (Fig. 5). When this treatment was started both children were in evident relapse as substantiated by low serum calcium and phosphorus concentrations (8.3 and 8.1 mg/100 ml for calcium and 2.9 and 3.3 mg/100 ml for phosphorus) and typical metaphyseal ricketic x-ray lesions. Treatment with 1,25-$(OH)_2$-D_3 promoted normalization of serum calcium and phosphorus concentrations. Serum calcium increased, respectively, to 9.8 and 9.9 mg/100 ml; serum phosphorus rose progressively and was found at 4.1 and 6.2 mg/100 ml (Fig. 5). Serum citrate remained in the normal range. Radiograms taken at the end of 1,25-$(OH)_2$-D_3 therapy visualized the appearance of metaphyseal calcification lines. Thus a dose of 1,25-$(OH)_2$-D_3 250–300 times less than that necessary with 25-OH-D_3 appeared to be quite active in these children with pseudodeficiency rickets.

The child with nutritional rickets was aged 26 months. She had not been given the usual prophylactic doses of vitamin D. When admitted to the hospital she had florid rickets with gross skeletal

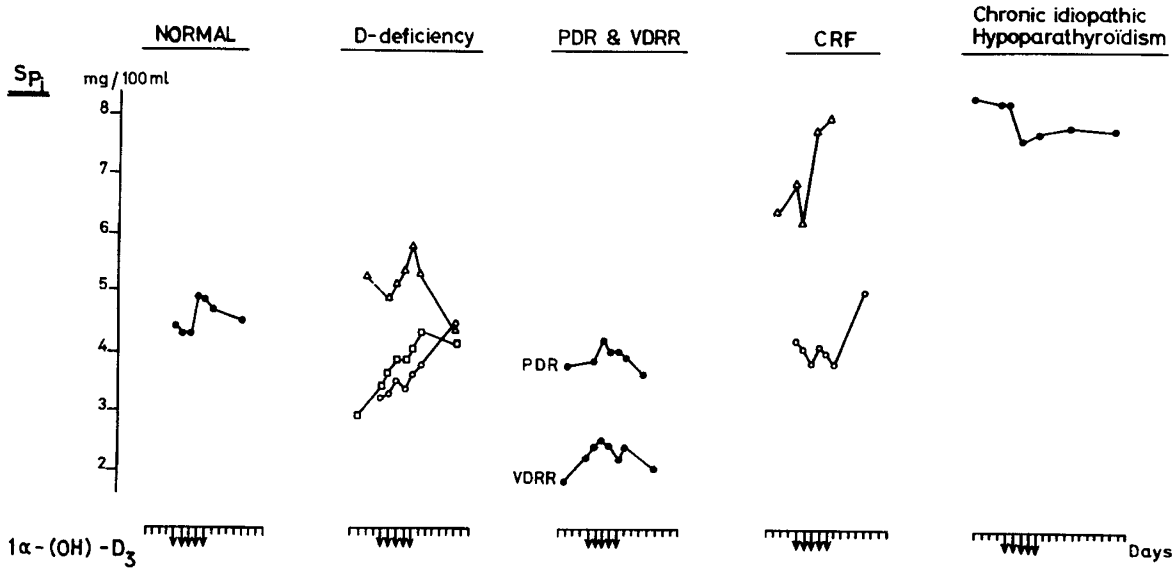

Fig. 4. Serum phosphorus concentrations during short term protocol with 1α-hydroxyvitamin D_3(*1α-(OH)-D_3*). Illustration and abbreviations are as in Figure 3.

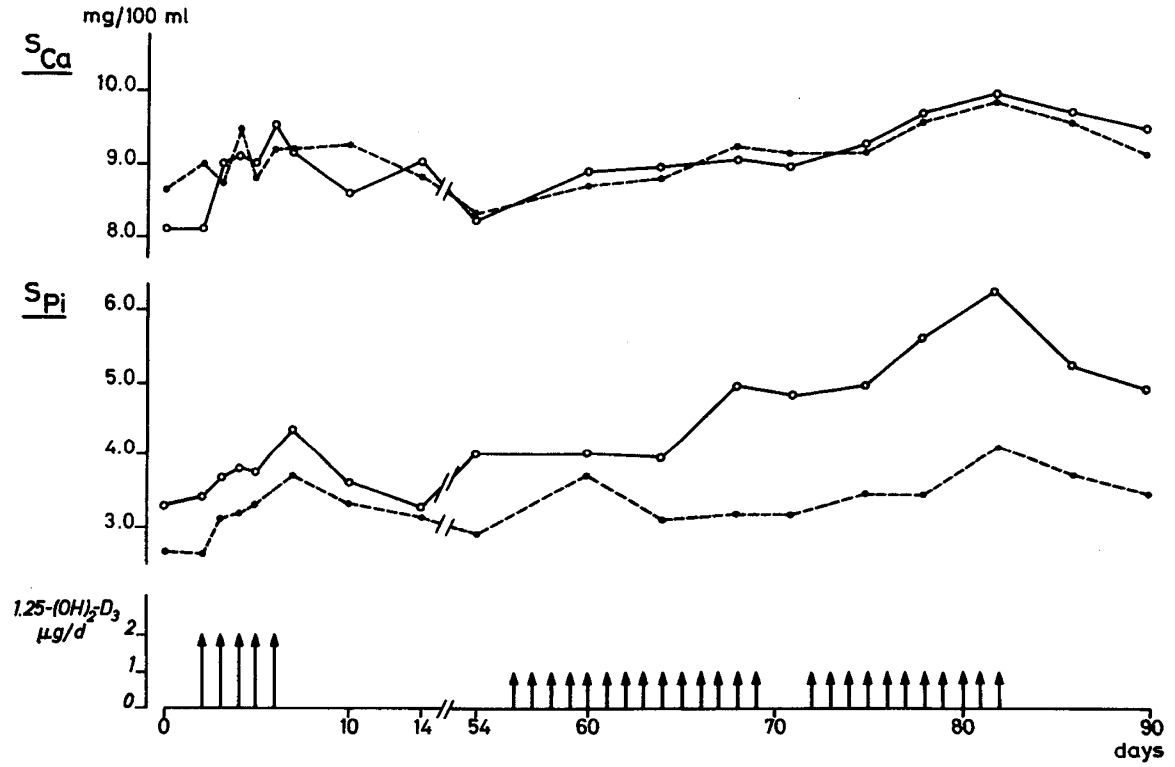

Fig. 5. Effects of short term and long term oral administration of biosynthetic 1,25-dihydroxyvitamin D_3 (*1,25-$(OH)_2$-D_3*) on two sibs with pseudodeficiency rickets. *SCa:* serum calcium concentration: S_{Pi}: serum phosphorus concentration. *Arrows:* days and doses of 1,25-$(OH)_2$-D_3 therapy.

lesions. She was treated during 2 months with a daily oral dose of 0.5 μg biosynthetic 1,25-$(OH)_2$-D_3. She received during this period a total dose of 30 μg. A rapid normalization of her serum calcium phosphorus alkaline phosphatase and of her P Tm/GFR was obtained (Fig. 6). This treatment promoted a complete healing of her x-ray metaphyseal lesions. No biochemical or radiologic evidence of a relapse was observed 2 months after cessation of 1,25-$(OH)_2$-D_3 administration.

THERAPEUTIC EFFECTS OF LONG TERM ORAL ADMINISTRATION OF 1α-OH-D_3

The effects of long term administration of 1α-OH-D_3 were investigated with two patients: a 16-month-old child with D deficiency rickets and one patient with pseudodeficiency rickets who had been treated previously with 1,25-$(OH)_2$-D_3. For the child with D deficiency, treatment was restarted with 1α-OH-D_3 5 days after the end of the short term protocol. At that time, the laboratory data for this patient were as follows: serum calcium 9.1 mg/100 ml; serum phosphorus 4.1 mg/100 ml; serum alkaline phosphatase 29 Bodansky units (Bod. u) (Fig. 7). Serum citrate was normal at 2.3 mg/100 ml. Urinary cyclic AMP to creatinine ratio was elevated to 25; phosphorus Tm/GFR was 3.44. On treatment with 0.5 μg/24 hr for 28 days serum calcium and citrate remained in the normal range, serum phosphorus concentration increased progressively and reached 6.1 mg/100 on the 28th day, and serum alkaline phosphatase activity became normal. Tm/GFR reached 5.19, whereas urinary cyclic AMP to creatinine ratio fell to 7.2 on the 21st day. Comparison of radiograms obtained at the start and at the end of 1α-OH-D_3 therapy demonstrated initiation of healing of the bone lesions. One week after cessation of treatment serum calcium had decreased from 9.7 to

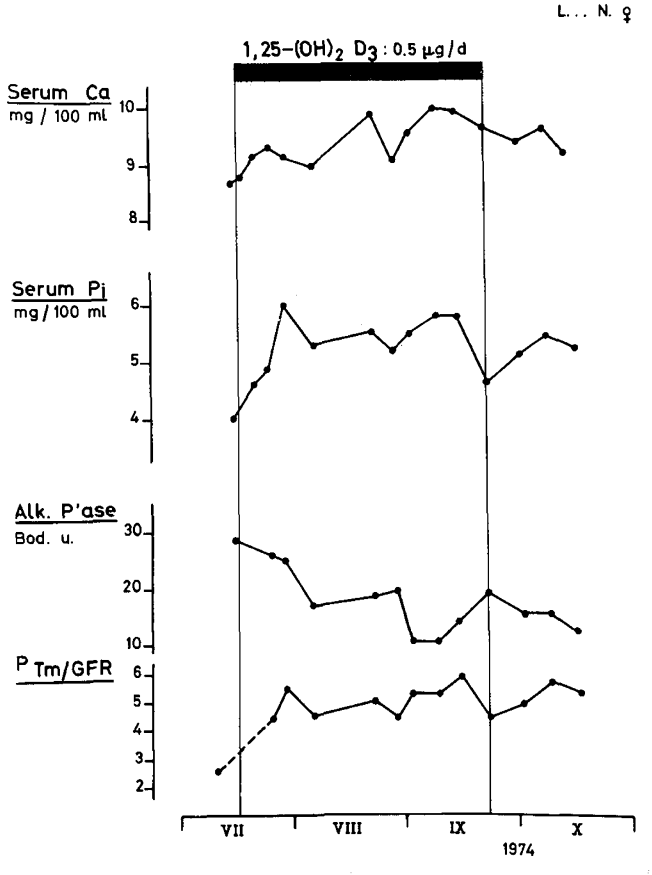

Fig. 6. Long term therapy with 1,25-dihydroxyvitamin D_3 (*1,25-(OH)$_2$-D_3*) in a 26-month old child with D-deficient rickets. *Tm/GFR:* maximum tubular reabsorption rate per 100 ml glomerular filtration rate, calculated according to the nomogram of Bijvoet *et al.* (7).

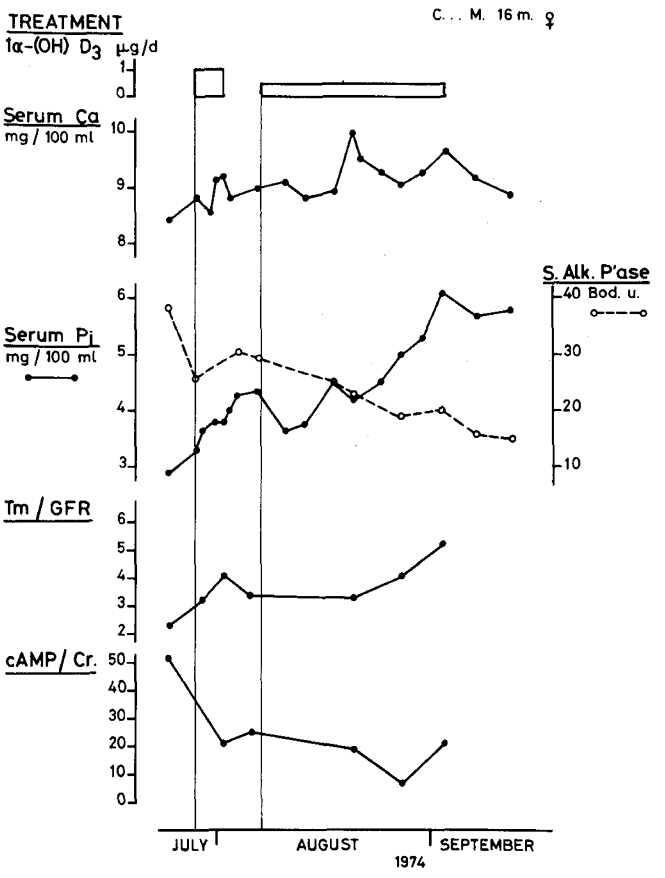

Fig. 7. Effects of short term and long term administration of 1α-hydroxyvitamin D_3 (*1α-(OH)-D_3*) on a D-deficient child aged 16 months. *cAMP/cr:* urinary cyclic AMP (micromoles) to creatinine (grams) ratios. *S. Alk. P'ase:* serum alkaline phosphatase; *Bod. u.:* Bodansky units.

8.9 mg/100 ml; serum phosphorus was still at high normal concentration (5.8 mg/100 ml).

Two months after the end of long term administration of 1,25-$(OH)_2$-D_3 the biologic and therapeutic effects of 1α-OH-D_3 were investigated with the 7 years old sib with pseudodeficiency rickets. At that time as can be seen in Figure 8 this patient was in biochemical relapse; x-ray examination demonstrated the reappearance of skeletal ricketic lesions, and balance studies showed a negative calcium balance with a poorly positive phosphorus balance (Fig. 9). The effects of 1α-OH-D_3 were studied at two dose levels: 0.5 μg/24 hr for 25 days, then 1 μg/24 hr for 20 days.

On long term treatment with 0.5 g/24 hr for 25 days (Fig. 8), serum calcium concentration augmented progressively and reached 7.9 mg/100 ml. Serum phosphorus concentrations, after an initial rise to 4.2 mg/100 ml, fell and remained stabilized around 3.2 mg/100 ml, likewise serum citrate concentration increased from 2.2 mg to 3.0 mg/100 ml on the 5th day, then decreased to 1.4 mg/100 ml. The results obtained in the first period of the balance studies during long term treatment indicated a positive balance for calcium (+114 mg/24 hr) and for phosphorus (+253 mg/24 hr); during the subsequent periods calcium balances were at equilibrium and phosphorus balances were only slightly positive. When the daily oral dose of 1α-OH-D_3 was doubled, the calcium balance of this patient became positive again (+112 mg/24 hr) and remained so throughout the study. A further elevation of serum calcium concentration occurred; serum calcium reached 8.6 mg/100 ml after 3 weeks of therapy. Serum alkaline phosphatase fell from 22.3 to 11.4 Bodansky units. In contrast, no significant changes in serum phosphorus concentration were observed. Net intestinal absorption of phosphorus increased, as shown by a diminution of fecal phosphorus excretion (Fig. 9).

However, this improvement in intestinal absorption was followed, after 10 days of treatment with 1 μg/24 hr 1α-OH-D_3, by an increased urinary output and a decreased tubular reabsorption of phosphorus. As a consequence the phosphorus balances became less and less positive during the last two periods of 1α-OH-D_3 therapy. Five days after 1α-OH-D_3 treatment was stopped, serum calcium concentration fell to 7.5 mg/100 ml, and once again net intestinal calcium absorption decreased, leading to a negative calcium balance. For this patient, the radiologic examinations done at the end of 1α-OH-D_3 therapy at each dose level showed the persistance of ricketic lesions. When these x-rays were compared to the pretreatment radiographs, no healing nor aggravation could be detected.

DISCUSSION

This investigation confirms the high biologic activity of small doses of 1,25-$(OH)_2$-D_3 and of its analog 1α-OH-D_3 in children. The effects observed are: a constant rise in serum calcium concentration in all subjects studied except in cystinotic patients with severe glomerular function impairment; an increase in serum phosphorus and citrate concentration in patients with D deficiency rickets; a lack of normalization of the low serum phosphorus and TRP in hereditary hypophosphatemic D-resistant rickets; a rise in serum calcium with a fall in serum phosphorus in chronic idiopathic hypoparathyroidism. These data are in agreement with the effects reported on children (8, 12–14, 17, 20, 29, 32) and on adults (9–11, 20, 28). Thus the similarity in the actions of 1α-OH-D_3 and of 1,25-$(OH)_2$-D_3 observed in the present study brings about further evidence that 1α-OH-D_3 may be considered a valuable substitute for 1,25-$(OH)_2$-D_3. Our data demonstrate also the high sensitivity of two sibs with PDR to small doses of 1,25-$(OH)_2$-D_3 compared with their resistance to quite large doses of 25-OH-D_3. These results seem in agreement with the hypothesis that pseudodeficiency rickets or vitamin D dependency, might be an inherited disorder of vitamin D metabolism because of a deficit in 25-hydroxycholecalciferol 1α-hydroxylase (4, 13, 14, 29, 32), a hypothesis that has received further support recently with a report of undetectable levels of circulating 1,25-$(OH)_2$-D_3 in the serum of one patient with PDR (19). However, in the comparison of long term administration of 1,25-$(OH)_2$-D_3 or 1α-OH-D_3 to D-deficient children and these two sibs with PDR differences in sensitivity are shown. In the two patients with nutritional rickets 0.5 μg/24 hr of either drug corrects the biochemical abnormalities, initiates healing of skeletal lesions in 28 days, and cures the metaphyseal lesions in 60 days of therapy. In contrast, for the children with PDR the minimal requirement for 1,25-$(OH)_2$-D_3 appears to be 1 μg/24 hr for 28 days and this total dose of 28 μg is not sufficient to achieve healing of bone lesions. Therapy with 1α-OH-D_3 first with 0.5 μg/24 hr for 25 days then with 1 μg/24 hr for 20 days, *i.e.*, a total dose of 32.5 μg, promotes a rise in serum calcium concentration and net intestinal calcium balance, but does not increase serum phosphorus and has no effect on the skeletal alterations. We have shown in a preliminary report of another sibling with PDR that the requirements for 1,25-$(OH)_2$-D_3 or 1α-OH-D_3 of the affected children were also quite high, *i.e.*, 2–4 μg/24 hr and 4–8 μg/24 hr, respectively, for each drug (5). Thus, it appears clearly that does of either 1,25-$(OH)_2$-D_3 or 1α-OH-D_3 that are curative in D deficiency rickets are only partly active in PDR. Several factors such as body mass, severity of secondary hyperparathyroidism, importance of skeletal lesions, or degree of calcium and/or phosphorus depletion may be of importance in this respect. Body mass was obviously different in our two groups of patients: the children with D deficiency rickets were, respectively, 16 and 26 months old, the patients with PDR were 5 and 7 years old. Yet, in the second sibling mentioned above (5), the younger child, aged 8 years, with a body weight of 19 kg did not respond to 2 μg/24 hr of either 1,25-$(OH)_2$-D_3 or 1α-(OH)-D_3, whereas her 12-year-old sister (body weight 29 kg) did respond to these doses. Secondary hyperparathyroidism has been reported in some patients with PDR (2) and in children with D deficiency (1, 15, 24). Measurements

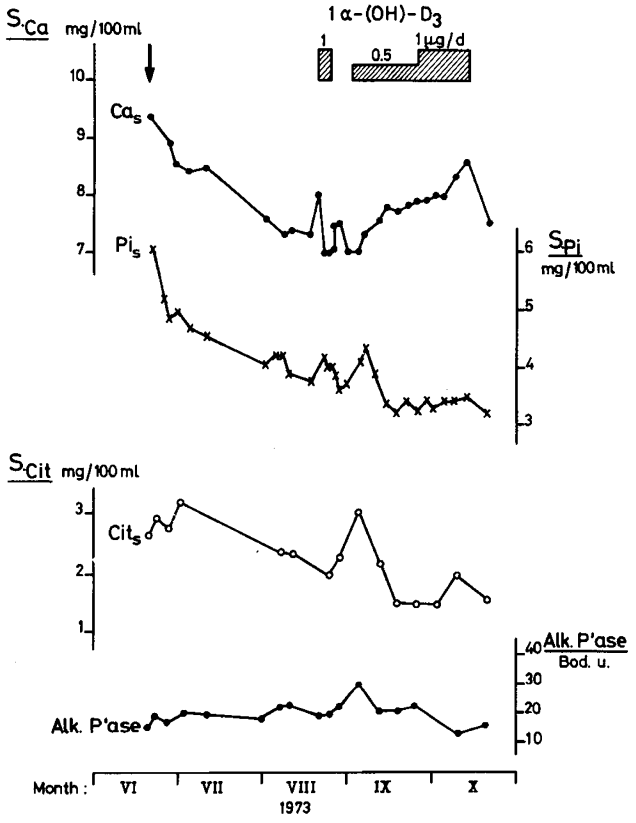

Fig. 8. Long term therapy with 1α-hydroxyvitamin D_3 (*1α-(OH)-D_3*) of one of the sibs with pseudodeficiency rickets (this patient is the one for whom results are illustrated on Fig. 5,——). The arrow indicates the end of 1,25-dihydroxyvitamin D_3 treatment shown in Figure 5. S_{cit}: serum citrate concentrations; S_{Ca} and S_{Pi}: serum Ca and P concentrations, respectively; *Alk. P'ase:* serum alkaline phosphatase; *Bod. u.:* Bodansky units.

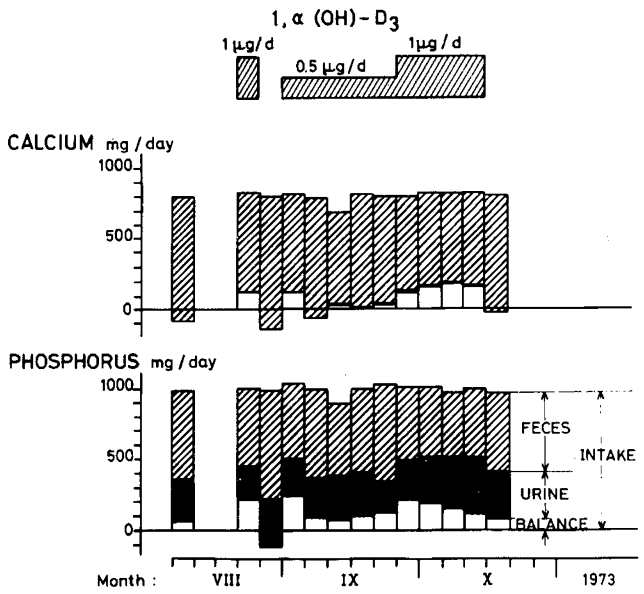

Fig. 9. Stable calcium and phosphorus balance studies of the child with pseudodeficiency rickets (same patient as in Fig. 8), before, during and after 1α-hydroxyvitamin D_3 (*1α-(OH)-D_3*) therapy. Each column represents a 5-day period.

of serum immunoreactive parathyroid hormone were not done in the present investigation. Arnaud *et al.* (1, 2) reported, in their studies in PDR and in D deficiency, a direct correlation between hyperparathyroidism and the clinical severity of these diseases. The same conclusion can be drawn from the analysis of the results published by Fischer *et al.* (15). For our patients the clinical symptoms, including x-ray bone lesions, were, in fact, more severe in the two children with D deficiency rickets. Finally, as for the possible role of a long standing calcium and/or phosphorus depletion in these children with PDR: they had been regularly treated with vitamin D then with 25-OH-D_3 for the past 5 years and their serum calcium and phosphorus concentrations were successfully maintained at normal levels as shown by regular biochemical analyses performed every 2–3 months. Thus, it appears that none of the possible explanations mentioned above help clarify this difference in sensitivity to 1,25-$(OH)_2$-D_3 and 1α-OH-D_3 observed in patients with PDR when compared with children with simple nutritional rickets.

These observations indicate that a deficit in 25-hydroxycholecalciferol 1α-hydroxylase alone may not account for all of the biochemical and skeletal alterations of pseudodefiency rickets. They also suggest that confirmation of this hypothesis for the pathogenesis of this inherited desorder must await more direct evidences.

SUMMARY

The actions of 1,25-$(OH)_2$-D_3 (2 μg/24 hr for 5 days) and of 1α-OH-D_3 (1 μg/24 hr for 5 days) are compared in children. The patients studied include children with D deficiency rickets, hereditary hypophosphatemia, pseudodeficiency rickets, late acquired D-resistant rickets, chronic renal failure, and hypoparathyroidism. The results observed demonstrate the high biologic activity of both drugs, and indicate that 1α-OH-D_3 is a valuable substitute for 1,25-$(OH)_2$-D_3 the hormonal form of cholecalciferol.

The effects of 1,25-$(OH)_2$-D_3 investigated in two children with cystinosis suggest also that cystinotic patients may develop, at the end-stage of the disease, when glomerular function is severely impaired, a certain degree of resistance to the biologic action of 1,25-$(OH)_2$-D_3. The therapeutic action of the two derivatives of vitamin D are analyzed in two children with D deficiency rickets and two sibs with pseudodeficiency. A dose of 1 μg/24 hr for 28 days of 1,25-$(OH)_2$-D_3 in the two patients with pseudodeficiency rickets promotes normalization of chemical abnormalities and initiates healing of skeletal lesions. The fact that such a small dose, considered in the physiologic range, is active in PDR had previously led us and others to suggest that this inherited disorder may be caused by a deficit in 25-hydroxycholecalciferol 1α-hydroxylase. Our present investigation shows clearly that 0.5 μg/24 hr of either 1,25-$(OH)_2$-D_3 or 1α-OH-D_3 is a curative dose in D deficiency rickets but not in PDR. This difference in sensitivity does not seem to be related to differences in body mass, secondary hyperparathyroidism, severity of bone lesions or of calcium, and/or phosphorus depletion. It is concluded that confirmation of this hypothesis for the pathogenesis of PDR must await more direct evidences.

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34. Informed consent was obtained from the parents and when appropriate, from the child.

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Autosomal-recessive vitamin D dependency
calcium
dihydrotachysterol

1α-hydroxyvitamin D_3
vitamin D dependency

Response to Crystalline 1α-Hydroxyvitamin D_3 in Vitamin D Dependency

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Extract

The therapeutic response to chemically synthesized 1α-hydroxycholecalciferol (1α-OH-D_3) was studied in three patients with autosomal recessive vitamin D dependency (ARVDD). The daily maintenance dose for vitamin D_2, to prevent signs of vitamin D deficiency in these patients, was 40–54.5 μg/kg, or about 100 times normal (Table 1). Withdrawal of maintenance therapy with vitamin D_2 resulted in the ultimate reappearance of the vitamin D depletion syndrome in *patients 1* and *2* (Figs. 1 and 2). The third patient presented with the deficiency syndrome despite adequate vitamin D nutrition and was recognized to have ARVDD.

Treatment with 1α-OH-D_3 by mouth in all three patients at dose levels of 1–3 μg/24 hr (80–100 ng/kg) corrected hypocalcemia and suppressed parathyroid hormone-dependent renal loss of amino acids (Figs. 1, 2, and 4). Rickets healed in 7-9 weeks on 1α-OH-D_3 alone (Fig. 3) The therapeutic response was rapid. It was usually seen first in the rise of serum calcium (Figs. 5 and 6). Withdrawal of 1α-OH-D_3 was followed first by a fall of serum phosphorus, then by a fall in serum calcium; the latter occurred within about 2 weeks of withdrawal.

Because the synthesis of 1α-OH-D_3 is simpler than for 1α,25-dihydroxycholecalciferol and because the former is an effective therapeutic analog of vitamin D hormone, we believe these studies in ARVDD reveal 1α-OH-D_3 to be the agent of choice for treatment of this and analogous diseases.

Speculation

Vitamin D dependency or pseudodeficiency rickets is believed to be an inborn error of vitamin D hormone biosynthesis. The putative abnormal enzyme is 25-hydroxycholecalciferol 1-hydroxylase in the recessively inherited trait. Consequently, this experiment of nature offers a special opportunity to examine the requirement in human subjects, for 1α-hydroxyvitamin D_3 metabolites.

Patients with ARVDD (14, 18, 36) develop signs of severe postnatal vitamin D deficiency, despite a nutritional intake of vitamin D_2 or vitamin D_3 (40) that would prevent rickets in normal subjects; hence the term pseudodeficiency preferred by some investigators (34). Persistent hypocalcemia appearing soon after birth is accompanied by an excess of circulating parathyroid hormone (1) which in turn is associated with hyperphosphaturia and hyperaminoaciduria (1, 37). Elevated serum alkaline phosphatase activity, severe rachitic bone lesions, and enamel hypoplasia affecting teeth that form postnatally complete the clinical syndrome (1, 11, 14, 18, 34, 36). Maintenance treatment with vitamin D_2 only at levels about 100 times the normal requirement fully reverses the manifestations of deficiency hence the term vitamin D dependency (18, 36).

The origin of the disturbed physiology in ARVDD lies in a selective disturbance of calcium absorption by intestine (18). A defect either in the biosynthesis of the active hormone form of vitamin D or in the ability of target organ(s) to respond to vitamin D hormone has been proposed (36) to explain the dependency on vitamin D_2, D_3, or 25-OH-D_3 of patients with ARVDD. ARVDD patients respond to microgram doses of chemically synthesized 1α,25-dihydroxycholecalciferol (1α,25-$(OH)_2$-D_3) (12). This finding has been corroborated by several investigators (3). It is surmised that a missing form of vitamin D hormone had been supplied and that ARVDD is likely to be an inborn error of vitamin D hormone biosynthesis, probably at the 1-hydroxylation step (12); this hypothesis is in keeping with the autosomal recessive inheritance of the disease.

Treatment of ARVDD with a "surrogate" vitamin D hormone, such as 1α-hydroxycholecalciferol (1α-OH-D_3) (22, 24), would be advantageous. Crystalline 1α-OH-D_3 is more easily synthesized than 1α,25-$(OH)_2$-D_3, and the former can be effectively administered by mouth. Moreover, ARVDD is an experiment of nature which provides an admirable opportunity to observe the effect of 1α-OH-D_3 in man. The present report reveals the therapeutic value of crystalline 1α-OH-D_3 in ARVDD and its preference over a similar synthetic analog of vitamin D, namely dihydrotachysterol (DHT_2).