Treatment of hypophosphataemic vitamin D-resistant rickets with massive doses of 1 α -hydroxy-vitamin D₃ during childhood

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SUMMARY Plasma levels of 1,25 dihydroxy-vitamin D (1,25-(OH)₂-D) were low in 3 children with hypophosphataemic vitamin D-resistant rickets (HVDRR) during childhood, but increased after very large doses (0.5 to 2 μ g/kg per day) of 1 α -hydroxy-vitamin D (1 α -OH-D₃). This treatment has two advantages. Firstly, hypercalcaemia is easily controlled by reducing the dose of 1 α -OH-D₃ because of its short half-life. Secondly, the administration of 1 α -OH-D₃ to patients with HVDRR can enhance the tubular reabsorption of phosphate, and this seems desirable in treating HVDRR.

Hypophosphataemic vitamin D-resistant rickets (HVDRR) is associated with hypophosphataemia with decreased tubular reabsorption of phosphate (P), normal plasma calcium (Ca), 25 hydroxy-vitamin D (25-OH-D), and 1,25 dihydroxy-vitamin D (1,25-(OH)₂-D) concentrations.¹ HVDRR is commonly treated with large oral phosphorus supplements and pharmacological doses of vitamin D, but treatment remains unsatisfactory. A recent paper showed that 1 α -hydroxy-vitamin D (1 α -OH-D₂) was effective in patients with HVDRR.² The present study was designed to assess the plasma 1,25-(OH)₂-D concentrations before and after the treatment with 1 α -OH-D₃ and the clinical responses to treatment with 1 α -OH-D₃ in patients with HVDRR.

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Materials and methods

Three patients who had shown the characteristic clinical and biochemical features of HVDRR were studied. Their ages, physical findings, and clinical features are listed in Table 1. Each patient was a sporadic case. The plasma levels of 1,25-(OH)₂-D were measured by the competitive protein-binding assay which has been reported.³⁻⁴ 10 normal children (4 boys and 6 girls), aged between 2 and 15 years, were studied as controls. All plasma samples were obtained early in the morning after overnight fasting during the autumn. Tubular reabsorption of phosphate was estimated by the 24-hour clearance rate and the renal threshold phosphate concentration (TmP/GFR) was measured according to the method of Bijvoet.⁵

Results

Plasma 1,25-(OH)₂-D concentration. The mean plasma level of 1,25-(OH)₂-D in controls was 72 $\pm$ 17.9 (means $\pm$ SD) pg/ml. In Case 1 this increased from 11.2 to 96.0 pg/ml 3 months after

Table 1 Clinical details of patients with HVDRR

Case	Sex	Age (years)	Height (cm)	Weight (kg)	Radiographical diagnosis
1	Male	1	81.5	11	Moderate bowing of extremities: severe epiphyseal disease
2	Male	13	135.4	30	Severe bowing of extremities: moderate epiphyseal disease
3	Female	1	79.9	10.4	Moderate bowing of extremities: severe epiphyseal disease

daily administration of 24 μg of $1\alpha\text{-OH-D}_3$. In Case 2 it increased from 16.8 to 60.0 pg/ml 2 months after daily administration of 16 μg of $1\alpha\text{-OH-D}_3$. In Case 3 it increased from 22.5 to 80.4 pg/ml 2 months after daily administration of 5 μg of $1\alpha\text{-OH-D}_3$.

Untreated. Each patient had hypophosphataemia, decreased tubular reabsorption of phosphate, and TmP/GFR as shown in Table 2. Their plasma levels of 25-OH-D and serum Ca were normal. Their plasma levels of parathyroid hormone (PTH) were below 250 pg/ml, but still considered normal. The levels of plasma alkaline phosphatase were raised to 79.8 KA units (normal, 3–20 KA units) in Case 1,

700 mU/ml (normal, 25–85 mU/ml) in Case 2, and 64 KA units in Case 3.

Treated.

Case 1

Oral administration of $1\alpha\text{-OH-D}_3$ began in September 1976 and doses were gradually increased from 2 to 24 μg (2.0 $\mu\text{g/kg}$), as shown in Fig. 1. Radiological examination in December showed a moderate improvement in bone. There was a rise in serum P and an increase in TmP/GFR (Table 2). Meanwhile, alkaline phosphatase levels had decreased to 48 KA units. In July 1977 slight hypercalcaemia developed but this was easily controlled

Fig. 1 Metabolic observations in Case 1 during the administration of $1\alpha\text{-OH-D}_3$.

Conversion: traditional units to SI—Ca: 1 mg/100ml $\approx$ 0.25 mmol/l, P: 1 mg/100 ml $\approx$ 0.32 mmol/l.

Fig. 2 Metabolic observations in Case 2 during the administration of 1α -OH- D_3 .

by reducing the daily dose of 1α -OH- D_3 to $12\text{ }\mu\text{g}$ ($1.0\text{ }\mu\text{g/kg}$) (Fig. 1).

Case 2

Oral administration of 1α -OH- D_3 began in August 1976 and doses were gradually increased from 4 to $16\text{ }\mu\text{g}$ ($0.5\text{ }\mu\text{g/kg}$), as shown in Fig. 2. Radiological examination in August showed a complete healing of bone. There was neither a rise in serum P nor an increase in TmP/GFR (Table 2). Alkaline phosphatase levels decreased to 322 mU/ml .

Case 3

Oral daily administration of $5\text{ }\mu\text{g}$ ($0.5\text{ }\mu\text{g/kg}$) began in January 1978, as shown in Fig. 3. Radiological examination on June 1978 showed complete healing of bone. There were pronounced increases in serum P and TmP/GFR (Table 2). Alkaline phosphatase levels decreased to 36 KA units

Discussion

The plasma 25-OH-D levels in 2 of these patients were rather high before treatment, but none of them had had previous treatment with vitamin D. It is suggested that the relatively high levels of 25-OH-D were due to a diet, rich in vitamin D. The plasma level of $1,25\text{-(OH)}_2\text{-D}$ was significantly higher in normal children than in adults,⁶ but was low in the 3 children. Their plasma levels remained relatively low even after administration of massive doses of 1α -OH- D_3 . Our results in children conflict with those for adults.¹ However, these findings do not suggest an impaired conversion of 25-OH-D to $1,25\text{-(OH)}_2\text{-D}$ in patients with HVDRR, because massive doses of 1α -OH- D_3 were required to induce a therapeutic response in patients with HVDRR.

Peacock *et al.*⁷ also suggested that the plasma concentrations of $1,25\text{-(OH)}_2\text{-D}$ during treatment of

Table 2 Summary of the response to treatment with 1α -OH- D_3 (means $\pm$ SD)

	Serum values					24-h urine calcium and phosphate excretion			
	PTH (pg/ml)	25-OH-D (ng/ml)	1,25-(OH) ₂ -D (pg/ml)	Calcium (mg/100ml)	Phosphate (mg/100ml)	Calcium (mg/day)	Phosphate (mg/day)	TRP (%)	TmP/GFR (mg/100ml)
Case 1 (boy, 1 year)									
Before treatment	<250	50.0	11.2	9.8 ± 0.5 (n=7)	2.1 ± 0.3 (n=7)	31.5 ± 13.4 (n=15)	155 ± 60.4 (n=15)	69.0 ± 7.1 (n=15)	1.5 ± 0.1 (n=4)
3 months after (24 µg/day)	<250	22.2	96.0	9.3 ± 0.3 (n=7)	3.0 ± 0.2 (n=7)	41.4 ± 15.9 (n=15)	146.4 ± 87.8 (n=15)	83.8 ± 7.5 (n=15)	2.5 ± 0.2 (n=4)
Case 2 (boy, 13 years)									
Before treatment	<250	42.0	16.8	10.0 ± 0.2 (n=6)	2.4 ± 0.3 (n=6)	40.0 ± 2.8 (n=6)	410 ± 177 (n=6)	80.0 ± 1.7 (n=4)	1.9 ± 0.2 (n=4)
2 months after (16 µg/day)	<250	9.2	60.0	9.5 ± 0.2 (n=5)	2.5 ± 0.1 (n=5)	58.3 ± 3.3 (n=4)	560 ± 273 (n=4)	84.0 ± 5.8 (n=4)	2.0 ± 0.3 (n=4)
Case 3 (girl, 1 year)									
Before treatment	<250	19.4	22.5	10.2 ± 0.4 (n=5)	2.3 ± 0.4 (n=5)	40.0 ± 12.5 (n=6)	210.2 ± 62.6 (n=6)	58.8 ± 14.3 (n=6)	1.4 ± 0.6 (n=4)
5 months after (5 µg/day)	<250	17.2	80.4	10.8 ± 0.4 (n=5)	2.8 ± 0.3 (n=5)	48.2 ± 21.9 (n=6)	138.5 ± 55.2 (n=6)	80.4 ± 5.8 (n=5)	2.3 ± 0.3 (n=4)
Normal range	<550	19.5 ± 3.7*	72 ± 17.9						4.97 ± 0.61†

*Means $\pm$ SE 12 , †see reference 13.PTH, parathyroid hormone; 25-OH-D, 25 hydroxy-vitamin D; 1,25-(OH) $_2$ -D, 1,25 dihydroxy-vitamin D; TRP, tubular reabsorption of phosphate; TmP/GFR, renal threshold phosphate concentration. Fig. 3 Metabolic observations in Case 3 during the administration of 1α -OH- D_3 .

patients with HVDRR were much lower than those achieved by patients with renal failure on 1–2 μ g of 1α -OH- D_3 . The results of the present study suggest that the metabolism of 1,25-(OH) $_2$ -D is accelerated in patients with HVDRR. However, the cause still remains unknown. The relatively low level of 1,25-(OH) $_2$ -D, even after administration of a massive dose of 1α -OH- D_3 , indicates that very large doses are necessary in children with HVDRR. 1α -OH- D_3 has been regarded as a valuable substitute for 1,25-(OH) $_2$ -D.⁸ Our data indicate that the administration of massive doses of 1α -OH- D_3 to patients with HVDRR can enhance the tubular reabsorption of phosphate.⁹ As the plasma PTH concentrations were not raised before treatment in these patients, this action on renal tubular reabsorption of phosphate seemed to be a direct result of 1α -OH- D_3 which was rapidly converted to 1,25-(OH) $_2$ -D before exerting its biological effect on target tissues.¹⁰ The treatment with 1α -OH- D_3 had two good results. Firstly, the pharmacological doses of vitamin D required for bone healing are close to toxic levels and there is always the risk of hypercalcaemia. However, when patients with HVDRR were given 1α -OH- D_3 , hypercalcaemia was easily controlled by reducing the dose of 1α -OH- D_3 because it has a short half-life (3.4 ± 0.4 days).¹¹ Secondly, as we have shown, the administration of 1α -OH- D_3 to patients with HVDRR can enhance the tubular reabsorption of phosphate, and this has a great advantage compared with the vitamin D compound.

Our study suggests that, initially, doses of 0.5–1.0 µg/kg per day of 1α-OH-D₃ are needed to demonstrate radiological and biochemical healing in patients with HVDRR, with subsequent adjustment according to individual requirement.

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