1,25-Dihydroxycholecalciferol in renal osteodystrophy

Epiphysiolysis—anticonvulsant therapy

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SUMMARY Three children with azotaemic renal osteodystrophy were treated with 1,25-dihydroxycholecalciferol ($1,25(\text{OH})_2\text{D}_3$). All showed clinical, biochemical, and radiological improvement within 6 months of starting treatment. There were no complications. The dose of $1,25(\text{OH})_2\text{D}_3$ required was $0.5 \mu\text{g}$ per day for 2 children aged 22 and 30 months, and $2 \mu\text{g}$ per day for a 15-year-old boy. 2 of the patients were receiving phenobarbitone and phenytoin and in one of them prior treatment with dihydrotachysterol 0.5 mg daily and $6 \mu\text{g}$ 1α -hydroxycholecalciferol ($1\alpha\text{OHD}_3$) daily had failed to induce improvement. In one patient, in whom serial iliac bone samples were available, $2 \mu\text{g}$ $1,25(\text{OH})_2\text{D}_3$ resulted in histological improvement in previously severe osteomalacia. $1,25(\text{OH})_2\text{D}_3$ appears to be an effective and safe drug in the treatment of uraemic osteodystrophy.

Chronic renal failure in childhood may be accompanied by severe musculoskeletal complications such as growth retardation, slipped epiphyses with metaphyseal fractures, and uraemic rickets (Haust *et al.*, 1964; Kirkwood *et al.*, 1972; Krempien *et al.*, 1974; Mehls *et al.*, 1975). These complications often affect the quality of life which can now be maintained and prolonged by regular dialysis and renal transplantation (Schärer *et al.*, 1975).

The recent elucidation of the vitamin D metabolic pathways (DeLuca, 1976) has permitted the synthesis of active vitamin D metabolites such as $1,25$ -dihydroxycholecalciferol ($1,25(\text{OH})_2\text{D}_3$) and 1α -hydroxycholecalciferol ($1\alpha\text{OHD}_3$), and allowed a more physiological approach to the treatment of uraemic osteodystrophy. A few long-term studies with $1,25(\text{OH})_2\text{D}_3$ have already been carried out in adults (Brickman *et al.*, 1974; Henderson *et al.*, 1974; Silverberg *et al.*, 1975; Pierides *et al.*, 1975), but there are no reported studies in children and no dose recommendations are available.

This paper describes our experience with long-term $1,25(\text{OH})_2\text{D}_3$ in 2 children aged 22 and 30 months, and in a 15-year-old boy. In 2 of the 3 cases uraemic osteodystrophy was complicated

further by long-term treatment with phenobarbitone and phenytoin.

Case reports

Case 1. Presented at birth (11 May 1973) with dislocation of both hips, hypospadias, and posterior urethral valves with hydroureters and hydronephrosis (plasma creatinine $212 \mu\text{mol/l}$ (2.4 mg/100 ml), bicarbonate 9.5 mmol/l (9.5 mEq/l)). After cauterization of the urethral valves he grew satisfactorily during the first 6 months (Fig. 1). In June 1974, aluminium hydroxide 5 ml and then 10 ml daily (equivalent to 200 and $400 \text{ mg Al}_2\text{O}_3$) was given. By February 1975 his height and weight were below normal (Fig. 1), he was weak and unable to stand; the wrists and ankles were enlarged; and there was a rickety rosary. X-rays showed fragmentation and expansion of poorly mineralized metaphyses with loss of definition of bone cortices and no zone of provisional calcification (Fig. 2a). Serum Ca was 2.24 mmol/l (9.0 mg/100 ml), P 2.1 mmol/l (6.5 mg/100 ml), alkaline phosphatase 190 units/l (normal range for adults 20 – 90 units/l), and parathyroid hormone (PTH) 8.0 units/l (normal up to 1.6 units/l).

He was given $1,25(\text{OH})_2\text{D}_3$, $0.1 \mu\text{g}$ per day, and the dose was gradually raised to $0.5 \mu\text{g}$ per day. Clinical improvement and radiological healing began $3\frac{1}{2}$ months after treatment with $1,25(\text{OH})_2\text{D}_3$.

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Fig. 1 Case 1. Height chart.

when aluminium hydroxide was stopped and the dose of $1,25(\text{OH})_2\text{D}_3$ raised to $0.5 \mu\text{g}$ per day (Fig. 2b). Serial biochemical results and relevant treatment are shown in Fig. 3. The baby became

alert, gained in height and weight, and began to walk. At present, at the age 3.3 years he is still uraemic (plasma creatinine $319 \mu\text{mol/l}$; $3.6 \text{ mg}/100 \text{ ml}$) but remarkably well and has normal radiological skeletal appearances. Histological bone studies were not made.

Case 2. Presented soon after birth (born 24 Dec 1960) with the nephrotic syndrome due to focal glomerulosclerosis. At 10 years of age hypertension and pro-

Fig. 3 Case 1. Effect of treatment with $1,25(\text{OH})_2\text{D}_3$ on biochemical findings.

Fig. 2 a, b. Case 1. Radiological regression of right wrist abnormalities during treatment with $1,25(\text{OH})_2\text{D}_3$.

gressive renal failure developed. At 11½ years he had a generalized convulsion and treatment with phenytoin was begun. Serum Ca was low, 1.4 mmol/l (5.6 mg/100 ml), alkaline phosphatase 486 units/l, and plasma creatinine 730 µmol/l (8.3 mg/100 ml). Because of the hypocalcaemia, vitamin D₂ 10 000 units daily was given and the dose was raised to 50 000 units daily a month later. A transiliac bone biopsy

in October 1972, one month after starting regular haemodialysis, showed mild osteitis fibrosa and moderate osteomalacia (Table). In January 1974 he received a living-donor kidney transplant from his mother, but because of a recurrence of fits the anti-convulsant therapy was continued. Serum alkaline phosphatase rose progressively and he became hypocalcaemic (Fig. 4). In June 1975 he complained

Table Summary of quantitative histology in serial iliac bone samples in Case 2.

Date (age, yr)	No. of osteoclasts per mm ²	Osteitis fibrosa grade (0-5)*	Percent measured area occupied by			Percentage mineralization of cancellous bone	Maximum no. of osteoid lamellae	Osteomalacia
			Total bone	Mineralized bone	Osteoid			
Oct 1972 (11.8)	0.48	1.5	27.8	23.1	4.69	83.1	5	Moderate
June 1975 (14.5) (pre 1,25 (OH) ₂ D ₃)	1.69	2.5	38.4	21.3	17.04	55.6	9	Severe
March 1976 (15.3) (post 1,25 (OH) ₂ D ₃)	0.69	2	18.7	17.7	0.93	95.0	4	Almost resolved†
May 1976 (15.5) (post-mortem)	0.47	1.5	31.8	28.7	3.12	90.2	4	Beginning to relapse
Control data‡ (mean ± SD)	0.08 ± 0.06	0	22.7 ± 3.1	22.6 ± 3.0	0.13 ± 0.10	99.5 ± 0.4	4	Nil

* See Ellis and Peart (1973).

† In addition to data summarized, in comparison with the previous biopsy the proportion of bone surface covered by osteoid had fallen from 92.1% to 40.9% but the proportion of surface osteoid bearing a calcification front had risen only from 41.6% to 47.1%.

‡ Ellis & Peart (1972).

1, 25(OH)₂D₃ = 1,25 dihydroxycholecalciferol.

Fig. 4 Case 2. Post-transplant biochemical results and effect of treatment with 1αOHD₃ and 1,25(OH)₂D₃.

of musculoskeletal pains and x-rays of the wrists showed rachitic changes. A transiliac bone biopsy now showed moderately severe osteitis fibrosa and very much worse osteomalacia, with marked hyperosteoidosis (Fig. 5a). Woven and lamellar osteoid was present, but most of the surface osteoid was lamellar in type and there was some patchy mineralization of osteoid so that lamellae passed

Fig. 5 Case 2. (a) June 1975 (age 14.5 years) iliac bone biopsy; osteitis fibrosa and severe osteomalacia. (b) March 1976 (age 15.3 years) biopsy; improvement of osteomalacia after $1,25(\text{OH})_2\text{D}_3$. Undecalcified sections. Goldner's stain (mineralized bone stains green (light) and osteoid red (dark)). $\times 35$.

uninterrupted through mineralized bone and osteoid.

For the next $3\frac{1}{2}$ months he received 2 and then $6\text{ }\mu\text{g}$ $1\alpha\text{OHD}_3$ daily, but there was no clinical or biochemical improvement (Fig. 4). $1,25(\text{OH})_2\text{D}_3$, $2\text{ }\mu\text{g}$ per day was then introduced; there was rapid clinical, biochemical, and radiological improvement. Serum Ca rose and alkaline phosphatase fell to normal. Improvement occurred despite a gradual decline of renal function due to chronic rejection and peritoneal dialysis was required in March 1976. A further transiliac bone biopsy showed resolution of the osteomalacia (Fig. 5b, Table) but persistence of less severe osteitis fibrosa consistent with the chronic renal failure. Histological mineralization of bone had not returned entirely to normal. Occasional elongated crescentic zones of osteoid persisted deep in the now otherwise mineralized bone. The amount of total bone had decreased and trabeculae were irregular in outline as a result of previous and active resorption. $1,25(\text{OH})_2\text{D}_3$ was stopped.

Three months later in May 1976 he died and the iliac bone showed less severe osteitis fibrosa, but there was now early deterioration in mineralization with an increase in osteoid (Table). The cancellous bone pattern was still very abnormal with irregular cement lines and patchy thinning of trabeculae as a result of old and active resorption. Most of the new bone being formed was lamellar in type, but there was some active woven bone at the surface and a considerable amount of old residual woven bone was present deeper in the trabeculae. Permission was not obtained for a full necropsy and the parathyroid glands could not be examined.

Case 3. Presented with generalized convulsions 12 days after birth (born 16 May 1973). The bladder was distended and there was bilateral ureteric reflex with hydronephrosis due to posterior urethral valves (plasma urea 50 mmol/l ; 301 mg/100 ml). These valves were treated by diathermy on day 16 of life. In November 1973 bilateral ureteric reimplantation and a wedge resection of the bladder neck were undertaken. He recovered with a plasma creatinine of about $175\text{ }\mu\text{mol/l}$ (2.0 mg/100 ml), but continued to have regular convulsions between September 1974 and October 1975, despite continuous treatment with phenytoin and intermittent courses of phenobarbitone. During this period he also had hypocalcaemia, and vitamin D_2 500 units daily was prescribed.

By November 1975 he had deteriorated and could only crawl on the floor with difficulty. Radiology showed disorganization and fractures of the metaphyseal areas of long bones, most prominent at the proximal ends of the humeri and lower ends of both femora (Figs. 6a, 7a). A wedge iliac crest bone

Fig. 6 Case 3. X-rays of right shoulder showing metaphyseal fracture and slipped epiphysis of humerus (a) on 28 Nov 1975 before and (b) on 15 Apr 1976 after treatment with $1,25(\text{OH})_2\text{D}_3$.

biopsy showed reduced endochondral ossification with few cartilage and bony trabeculae. The amount of cancellous bone was reduced and since resorption of the outer aspect of the cortical bone associated with normal remodelling continued, the cortical bone at the 'metaphysis' was markedly thinned. There was moderately severe osteitis fibrosa (grade 2.5), but mineralization of bone and cartilage was normal. (Quantitative histology: total bone 10.0%; mineralized bone 9.6%; osteoid 0.4%; cancellous bone 96.0% mineralized; osteoid seams 1–2 lamellae thick).

Treatment with $1,25(\text{OH})_2\text{D}_3$, 0.5 μg per day was started. Within weeks the baby became alert and began to walk. Repeat x-rays 3 and 5 months later (Figs. 6b, 7b) showed complete healing and remodelling of all metaphyseal fractures. In March 1976 after further convulsions associated with a parainfluenza A type pyrexial illness, sodium valproate 100 mg twice daily was substituted for phenytoin. The boy, now nearly 4, is remarkably well, able to walk, and no fits have occurred since March 1976. Treatment with $1,25(\text{OH})_2\text{D}_3$, 0.25 μg daily has been continued. A post-treatment bone biopsy was not obtained.

Discussion

Our 3 patients illustrate some of the skeletal complications and therapeutic problems that can arise in children with azotaemic renal osteodystrophy.

Nature of azotaemic renal osteodystrophy in children. In adults measurements of serum PTH indicate that

in uraemia secondary hyperparathyroidism occurs early (Reiss *et al.*, 1969; O'Riordan *et al.*, 1970). Histological studies both in acute renal failure (Zech *et al.*, 1973) and chronic renal failure (Ellis and Peart, 1973; Malluche *et al.*, 1976) also confirm that osteitis fibrosa is the earliest and predominant histopathological lesion. Osteomalacia with a mineralization deficit may be superimposed on osteitis fibrosa at any level of renal failure and though deficiency of $1,25(\text{OH})_2\text{D}_3$ is a very important contributing factor, other still poorly-understood mechanisms must operate together and contribute to the development of osteomalacia in these patients (Malluche *et al.*, 1976).

In children the situation has become unnecessarily complicated historically by the development of two antagonistic schools of thought, one favouring osteitis fibrosa, the other osteomalacia, as the significant underlying bone disorder, though in all large histopathological series of 'renal rickets' there are examples of both pure osteitis fibrosa and mixtures of osteitis fibrosa with osteomalacia (Gilmour, 1947; Follis, 1950; Hamperl and Wallis, 1933). Thus, Stanbury and his colleagues (Stanbury, 1957; Stanbury and Lumb, 1962; Stanbury *et al.*, 1969), arguing against Albright and Reifenstein's (1948) idea that renal rickets is not rickets at all but osteitis fibrosa, and perhaps impressed by the response to large doses of vitamin D, reached the other view, that renal rickets may be indistinguishable from dietary vitamin D deficiency rickets. Clearly the truth lies between these two extremes. Experience in our centre indicates that in uraemic children with radiological 'rickets', osteitis fibrosa is a universal finding

Fig. 7 Case 3. X-rays of right knee showing metaphyseal fracture and epiphyseal displacement of femur (a) before and (b) after treatment with $1,25(\text{OH})_2\text{D}_3$.

but that in some of them there is additional osteomalacia, as defined by the presence of excess osteoid, wide osteoid seams with more than 4 birefringent lamellae, and a reduced calcification front (e.g. Case 2).

These children with radiological rickets should be clearly distinguished from children with slipped epiphyses and metaphyseal fractures who have histologically severe osteitis fibrosa and no osteomalacia (e.g. Case 3) (Mehls *et al.*, 1975; Stanbury, 1957). Interestingly, however, both these lesions respond to treatment with active vitamin D metabolites, in our patients $1,25(\text{OH})_2\text{D}_3$, indicating that both osteitis fibrosa and osteomalacia in these children are the result of $1,25(\text{OH})_2\text{D}_3$ deficiency. Recognition

of the relationship between osteitis fibrosa and $1,25(\text{OH})_2\text{D}_3$ deficiency has important therapeutic implications, for treating these children with aluminium hydroxide alone in the belief that their osteitis fibrosa is the result of uraemic phosphate retention (Slatopolsky *et al.*, 1971) can result in marked worsening of their osteodystrophy (Dent *et al.*, 1961). Vitamin D should be the mainstay of treatment in uraemic children with either renal rickets or slipped epiphyses.

Effect of anticonvulsant drugs on renal osteodystrophy. The adverse effect of hepatic microsomal enzyme inducing drugs such as phenobarbitone and phenytoin on the calcium and vitamin D metabolism of

nonuraemic children is now well described (Richens and Rowe, 1970; Silver *et al.*, 1974; Hahn *et al.*, 1975). It appears that in uraemic patients anticonvulsant drugs have an even greater detrimental effect on vitamin D metabolism (Pierides *et al.*, 1976a, b). 2 of our 3 cases highlight these iatrogenic complications, which may in fact be commoner in children who have increased tendency towards convulsions and need treatment with anticonvulsants. Not only do such anticonvulsant drugs increase the incidence of severe uraemic osteodystrophy, but they also influence the response to treatment with vitamin D. In agreement with previous observations (Chan *et al.*, 1975; Pierides *et al.*, 1976b), 2 μg and then 6 μg of daily oral $1\alpha\text{OHD}_3$ given to Case 2 (Fig. 4) failed to induce either a clinical or biochemical improvement, whereas $1,25(\text{OH})_2\text{D}_3$ was dramatically effective. The failure of $1\alpha\text{OHD}_3$ is presumed to be the result of interference with its required hepatic 25-hydroxylation before its metabolic effects are mediated. In Case 3, it is probable that the unusually severe degrees of metaphyseal destruction and fracturing was the result of the unfortunate combination of uraemia with anticonvulsant therapy, thus depleting $1,25(\text{OH})_2\text{D}_3$ stores even more.

Cases 2 and 3 show clearly the need for careful consideration of all drugs given to uraemic children. In view of their large vitamin D requirements, children are more vulnerable to anticonvulsant drugs than adults and extra care should be taken in the presence of uraemia. It is likely that regular vitamin D supplements, particularly $1,25(\text{OH})_2\text{D}_3$, should be given to any uraemic child started on long-term anticonvulsant drugs. It is of interest that initial studies with sodium valproate suggest this drug may not possess any hepatic microsomal enzyme inducing properties (Jordan *et al.*, 1976). Clearly if these initial observations are confirmed in humans, sodium valproate will prove a very useful anticonvulsant drug.

Aluminium hydroxide-phosphate deficiency. Case 1 is unusual in view of the severe destructive epiphyseal and metaphyseal changes. In retrospect the clinical deterioration started after the introduction of aluminium hydroxide and though no hypophosphataemia was noted it is likely that phosphate deficiency contributed to the development of the marked osteodystrophy. Severe bone changes and osteomalacia are well known to occur in animals on a phosphate-deficient diet (Day and McCollum, 1939) and hypophosphataemia need not always be present in phosphate deficiency (Dent *et al.*, 1961; Clarkson *et al.*, 1972). Dodge and Travis (1965) described 2 children who developed phosphate-deficiency rickets after treatment with aluminium

hydroxide, and Case 3 in the study by Dent *et al.*, (1961) showed marked deterioration of renal rickets after receiving 120 ml aluminium hydroxide suspension daily. It is of interest that improvement in our Case 1 occurred only when aluminium hydroxide was withdrawn.

Treatment with $1,25(\text{OH})_2\text{D}_3$. The results obtained in these 3 children agree with similar data in adults (Brickman *et al.*, 1974; Henderson *et al.*, 1974; Silverberg *et al.*, 1975; Pierides *et al.*, 1975) and indicate that $1,25(\text{OH})_2\text{D}_3$ is a powerful and effective vitamin D metabolite. Experience in adults indicates that 1.0 to 1.5 μg $1,25(\text{OH})_2\text{D}_3$ daily can result in improvement of uraemic osteodystrophy, but in the 2 children aged 22 and 30 months, a much higher weight-related dose, 0.5 μg daily, was required. In view of previous personal experience with uraemic patients on anticonvulsants, 2 μg of $1,25(\text{OH})_2\text{D}_3$ given to Case 2 resulted in a rapid response. No episodes of hypercalcaemia occurred but the dose was carefully reduced as soon as clinical, biochemical, and radiological evidence suggested that healing had occurred.

It should be noted that in Case 2, though there was a dramatic histological improvement of osteomalacia after $1,25(\text{OH})_2\text{D}_3$ with a reduction in the amount of osteoid, reduced width of osteoid seams, and a reduction in the proportion of bone surface comprising osteoid, the calcification front did not return to normal and in many seams was coarsely granular in appearance. We have previously noted that the calcification front does not return entirely to normal in some renal patients treated with $1,25(\text{OH})_2\text{D}_3$ (Pierides *et al.*, 1975) or with $1\alpha\text{OHD}_3$ (Pierides *et al.*, 1976c). Once the bone had mineralized the amount of mineralized bone exposed to resorption increased and presumably this accounts for the irregular thinning of trabeculae and loss of total bone in the post-treatment biopsy when there was still mild active osteitis fibrosa.

It is worth re-emphasizing that $1,25(\text{OH})_2\text{D}_3$ is effective in reducing secondary hyperparathyroidism with improvement of histological osteitis fibrosa as well as osteomalacia. Thus Case 3 with no histological evidence of osteomalacia but only osteitis fibrosa showed an impressive clinical and radiological response after 3 months of $1,25(\text{OH})_2\text{D}_3$. In Case 2 both the osteomalacia and osteitis fibrosa improved (see Table).

An additional advantage is that $1,25(\text{OH})_2\text{D}_3$ has the shortest half-life time of all vitamin D metabolites available. This is of particular advantage when a patient is accidentally overtreated, for hypercalcaemia is usually very short-lived and normal serum calcium is restored within days of

stopping 1,25(OH)₂D₃. It also has a rapid mode of onset and appears to be of unique value in the management of uraemic patients receiving hepatic microsomal enzyme inducing drugs.

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