RENAL BONE DISORDERS IN CHILDREN: THERAPY WITH VITAMIN D₃ OR 1,25-DIHYDROXYCHOLECALCIFEROL

M Bulla, G Delling, G Offermann, R Ziegler, G Benz, H Lühmann, A Sanchez de Reutter, M Severin
Univ. Kliniken, Köln-Hamburg-Berlin-Ulm, FRG

Summary

Twelve children with chronic renal failure (CRF) and sixteen children receiving regular dialysis therapy (RDT) were treated with between 10,000 and 50,000 IU of vitamin D daily. This was associated with an increase in serum calcium levels and reduction in PTH levels. In the children with CRF, secondary hyperparathyroidism was improved with treatment but its development was not completely prevented nor was healing complete. In the patients receiving RDT, treatment with vitamin D improved the changes associated with secondary hyperparathyroidism in 50% of cases but these features sometimes reappeared despite continuing treatment. Hypercalcaemia or metastatic calcification was not seen.

Subsequently, 1,25(OH)₂D₃ was administered to 14 children receiving RDT. This was associated with the return of serum calcium levels to normal, inhibition of PTH synthesis and an improvement in intestinal calcium absorption. Fibro-osteoclasia was cured and there was improvement in actual bone resorption. There was also improvement in osteoidosis in those children who showed disturbances of mineralisation. Calcification in the limbus area of the eyes may occur and hypercalcaemia was seen commonly. Treatment with 1,25(OH)₂D₃ should only be offered to children with severe renal bone disease. Neither vitamin D₃ nor 1,25(OH)₂D₃ can guarantee complete recovery of osteodystrophy and of growth arrest in uraemic children.

Introduction

Renal osteodystrophy and growth arrest are some of the greatest problems in renal insufficiency in children [1–4]. The treatment with vitamin D₃ (vit.D) or 1,25(OH)₂D₃ in children with renal bone disorders is said to improve fibro-osteoclasia as well as the disturbances of mineralisation and to stimulate growth. Therefore we investigated the results of treatment in children with chronic renal failure (CRF) or on regular dialysis treatment (RDT).
Patients and Methods

The children were aged 7 to 14 years. All the children had a body height below the 3rd percentile, the bodyweight ranged between 19 and 43kg, the endogenous creatinine clearance (corrected to 1.73m² body surface) between 10 to 30ml/min in children with CRF and 0 to 5ml/min in dialysed children. Dialysis treatment was performed 5 hours 3 times a week using capillary dialysers. Dialysis fluid calcium concentration was 3.5 to 4.0mEq/L. The serum phosphate level was stabilised to 5.5 or 6.5mg/dl by individual doses of aluminium hydroxide (Al OH₃). Metabolic acidosis was corrected orally in case of decompensation.

Twelve children with CRF and sixteen children on RDT were treated with 10,000 IU vit.D/day up to 50,000 IU/day in relation to the severity of renal bone disorder (RBD). Additional calcium supplementation of 1.0g per day was given orally. Vertical iliac crest bone biopsies were performed in each child after 12 or 24 months of therapy.

After the treatment with vit.D we selected 14 dialysed children for treatment with 1,25(OH)₂D₃. The initial dose was 0.25μg/day. Between the 6th and 12th week the doses were raised to 0.5μg/day, in some cases even up to 1.0 or 1.5μg/day. Calcium (1.0g) was added orally. Later on, in relation to the serum calcium and alkaline phosphatase levels the dose was reduced individually. Iliac crest bone biopsies were done before and 12 months after treatment.

Results

Vit.D in combination with calcium supplementation nearly normalised the serum concentration of total calcium and alkaline phosphatase within 12 months in children with CRF and within 8 months in children on RDT. Ionised calcium rose up to lower normal level. 25(OH)D₃ (measured by competitive protein binding assay, [5–7] rose up to a mean of 200ng/ml in CRF and 450ng/ml in dialysed children. iPTH (obtained by the method of Arnaud [8]) was reduced to a mean of 160pg/ml in CRF and nearly normalised in RDT. Serum phosphate levels could be controlled well by Al OH₃. Radiographic signs of secondary hyperparathyroidism improved (38%) or disappeared totally (22%), but demineralisation and retarded bone age remained unchanged. Sixteen to 24 months later, on vit.D therapy, reappearance of secondary hyperparathyroidism occurred in 23% of children with CRF and on RDT. Bone pain and muscle weakness disappeared but relapses were seen often. In both treatment groups there was no growth gain but hypercalcaemia or episodes of extraosseous calcifications were not seen.

In analysing bone biopsies (for method see [9,10]) in cases with CRF, in contrast with the good clinical results, we found only 2 cases with pure osteoidosis (=type II of RBD [see 11]) and 9 cases with impaired mineralisation and fibro-osteoclasia as a sign of secondary hyperparathyroidism (=type III of RBD). Vit.D in combination with RDT showed better results: only 6 cases of type III and 10 cases of type II of RBD.

The volume density of trabecular bone as well as the mean trabecular diameter, the total surface of the spongy bone, the volume density of the spongy bone
and the total surface of osteoid seams were increased more pronouncedly in cases with CRF than in cases on RDT. The osteoblast population showed a small reduction. The number of osteoclasts differed: there was a high incidence and an increased surface density in relation to bone interface in cases with secondary hyperparathyroidism, whereas cases with pure osteodnosis had a reduced incidence combined with a reduction of bone formation.

On treatment with 1,25(OH)$_2$D$_3$ the serum concentration of total calcium, ionised calcium and alkaline phosphatase could be normalised within 4 to 5 months except in 2 children who never responded and 3 children who responded late. In 4 cases alkaline phosphatase fell to subnormal values. Serum phosphate was difficult to control. iPTH, nearly normalised by vit.D in most cases before, stayed unchanged (for method see [12,13]), 1,25(OH)$_2$D$_3$ levels, obtained by the method of Eisman [14] rose up to a maximum of 374pmol/L. After normalisation of the alkaline phosphatase, 6 episodes of severe hypercalcaemia occurred in 5 children. Radiographic examinations showed rapid improvement of signs of secondary hyperparathyroidism, good improvement of other bone abnormalities in 28%, no change in 44%, new appearance of acroosteolysis and subperiosteal resorption zones in 29% of children.

There was no improvement in bone retardation or growth arrest. Bone pains and muscle weakness disappeared 2 months after the start of 1,25(OH)$_2$D$_3$ and reappeared only in the non-responders. Regular ophthalmological examination showed increasing calcification in the limbus area 3 to 9 months after start of therapy in cases both with and without hypercalcaemia.

Comparing the histological results of pretreatment findings with 7 cases of type III and 7 cases of type II and of post treatment results with 5 cases of type II and 9 cases of type III RBD, there were no remarkable changes in the bone structure. But the remodelling surface showed marked change. The volume density of osteoid had been reduced from the high pre-existing values before therapy. The surface density of osteoid seams was significantly reduced in pure osteodnosis, but the values were still elevated. The osteoblasts were considerably reduced, in a few cases the reduction reached the lower part of the normal range or even zero. The parameters of bone resorption had been reduced in cases with fibro-osteolasia, in 2 cases with osteodnosis they increased. In 2 cases the endosteal fibrosis had been reduced.

Discussion

Uraemic osteodystrophy in children can be divided into 2 different skeletal lesions: 1) lesions in the growing zone with disturbed, reduced proliferation of chondrocytes. The primary marrow space is fibrosed and shows a high numerical density of osteoclasts as a consequence of secondary hyperparathyroidism; 2) the morphological changes of the endosteal surface of trabecular bone are identical to the lesions in adults: endosteal fibrosis, resorption by an increased number of osteoclasts and increased osteoid seams due to disturbed mineralisation [4]. Our morphological and clinical investigations show that neither vit.D nor 1,25(OH)$_2$D$_3$ can cure the lesions in the growing zones. Therefore no improvement in body height can be expected. But vit.D and 1,25(OH)$_2$D$_3$ can improve the changes in endosteal surfaces associated with secondary hyperparathyroidism. 1,25(OH)$_2$D$_3$ slightly improves osteodnosis in uraemic children.
References


Open Discussion

KERR (Chairman) Before we open the discussion; on your slides you said the phosphate was controlled at 5.5 to 6.5mEq/l. I presume that should be milligrams percent, should it?

BULLA Oh, yes that is a mistake.

KERR And the patients who relapsed? They relapsed in spite of phosphate being controlled at that level

BULLA We had no difficulty in controlling the phosphate level, and they relapsed even when the phosphate was at this level. For 1,25 DHCC we had big problems. The phosphate levels fell in the first weeks of treatment and then they rose up and they came to dangerous values. I think we even had limbic calcification in those cases with no hypercalcaemia, because of the product of calcium and phosphate.

MALLUCHE (Los Angeles) This is an elaborate study which regrettably is hamperecked by problems inherent with histological studies. The variance within the skeleton should be considered whenever long term effects of treatment are evaluated.
This can be achieved by taking two bone biopsy specimens some 3cm apart before therapy. The changes in the bone biopsy found after therapy should be considered to be due to therapy only when they are significantly (analysis of variance) greater than the variance between the two samples obtained before therapy.

BULLA Yes I agree with you, but I have to say these are children and we do not do bone biopsies too often.

MALLUCHE You don't have to do more than one biopsy, just take two samples at the time of the first biopsy.

KERR This is a problem particularly in estimating bone mass and not for all the other parameters we have discussed.

SCHARER (Heidelberg) It is essential if one deals with paediatric patients that dosages are related to body surface area or to kilograms and as I see from your presentation they were given as absolute dosages.

BULLA I can give you this correctly to the kilogram for the children. We had given for start 0.006 to 0.012 microgram/kg/day and then we elevated this up to 0.012 to 0.125mg/kg/day, and there were some children that needed more and then we elevated this, for these ones, to 0.025 to 0.05mg/kg/day. And after the response to this treatment, we go down in most cases to the initial doses. That means 0.006 to 0.01mg/kg/day.

SCHARER You say that growth arrest was not changed in your patients. Does that mean that your patients all have a complete growth arrest before and during treatment?

BULLA Some had complete growth arrest and stayed in the same stage of growth arrest. Some had a little growth, that means before treatment a mean of 1 to 3cm per year and after treatment it was the same; we had only 1.5 to 3cm per year. That is no gain, no better results than I had before. It was really a pity, but it is so.