

CONTROLLED TRIAL OF CALCITRIOL IN THE PREVENTION OF BONE DISEASE IN HAEMODIALYSED PATIENTS

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Summary

Seventy-six patients receiving regular haemodialysis, without biochemical or radiological evidence of renal osteodystrophy, entered a five-year double-blind placebo-controlled trial of calcitriol (1,25-dihydroxycholecalciferol) in the prevention of bone disease. Significantly more patients on placebo developed bone disease as judged by a sustained elevation of plasma alkaline phosphatase or the development of sub-periosteal erosions on hand radiographs. Serum parathyroid hormone fell significantly in the patients receiving calcitriol and was significantly lower than in patients receiving placebo. It is concluded that calcitriol delays and may prevent the development of metabolic bone disease in patients receiving regular haemodialysis therapy.

Introduction

Patients with established renal osteodystrophy often respond initially to treatment with alfacalcidol (1 α -hydroxycholecalciferol) [1] and calcitriol (1,25-dihydroxycholecalciferol) [2]. However, long term results may be less satisfactory [3-5]. Prophylactic administration of these drugs may be more effective but this has been little studied. In a controlled trial, Memmos et al [6] concluded that calcitriol may be beneficial in haemodialysed patients with normal hand radiographs, but too few patients were studied to show statistically significant differences between placebo and active treatment. We report the results of a five year double-blind placebo-controlled trial of calcitriol in patients without obvious bone disease receiving regular haemodialysis therapy.

Patients and methods

Seventy-six patients aged 17-58 (mean 42) years, who had received regular haemodialysis therapy for 2-77 (mean 20) months, entered the study. Radio-

graphs of hands, chest, pelvis and feet showed no evidence of renal bone disease as assessed independently by two radiologists. In all patients pre-dialysis plasma alkaline phosphatase was less than 100 U/L and plasma calcium, corrected to a plasma albumin of 41 g/L [7] was less than 2.75 mmol/L on four occasions in the two months before entry. Patients who had been treated with vitamin D derivatives within the previous three months, or with regular barbiturate, phenytoin or corticosteroid therapy or who had previously undergone parathyroid surgery were excluded from the trial.

Pre-dialysis plasma calcium, inorganic phosphorus and alkaline phosphatase were measured monthly. Serum parathyroid hormone was measured on three occasions during the two months before entry and thereafter every six months using an immunoradiometric assay [8]. Radiographs were repeated annually.

The patients dialysed for 15–24 hours each week. Dialysate calcium concentration was 1.65 mmol/L, and estimated daily dietary calcium intake was 12–19 mmol. Pre-dialysis plasma inorganic phosphorus was maintained between 1.2 and 1.8 mmol/L with oral aluminium hydroxide.

Allocation to active or placebo treatment was stratified with respect to time on dialysis (double-weighted), age, plasma alkaline phosphatase, the presence or absence of kidneys and which of the two centres was responsible for the particular patient, using the method of minimisation of differences [9].

Initially all patients received one tablet daily containing either 0.25 µg calcitriol or placebo. Plasma calcium was measured weekly and if it did not exceed 2.75 mmol/L the daily dose was increased up to a maximum of four tablets. Subsequently plasma calcium was measured monthly and if it exceeded 2.75 mmol/L the number of tablets was reduced in stepwise fashion. During the first 18 months of the trial many patients developed severe hypercalcaemia (> 3.0 mmol/L) which often persisted for weeks despite a reduction in therapy. The protocol was therefore modified. The maximum dose was reduced to two tablets daily, corresponding to 0.5 µg of the active drug, and if plasma calcium exceeded 2.75 mmol/L treatment was stopped and restarted at a smaller dose when plasma calcium had fallen below 2.75 mmol/L.

Patients were withdrawn from the study if immobilised for one month or more, if major surgery (including renal transplantation) was performed, if hypercalcaemia persisted for more than two months despite stopping treatment, or if unacceptable side-effects occurred. Patients were considered to have developed bone disease if sub-periosteal erosions were observed radiologically in their hands or if plasma alkaline phosphatase rose above 100 U/L for three consecutive months, an initial 'flare' within six months of starting therapy being ignored.

Results

Thirty-eight patients entered each treatment group. The numbers of patients withdrawn from the study and the reasons for this are shown in Figure 1. Seventeen patients receiving placebo and six patients receiving calcitriol developed bone disease. An actuarial survival analysis showing withdrawals for bone disease (Figure 2) shows that significantly more patients receiving placebo developed

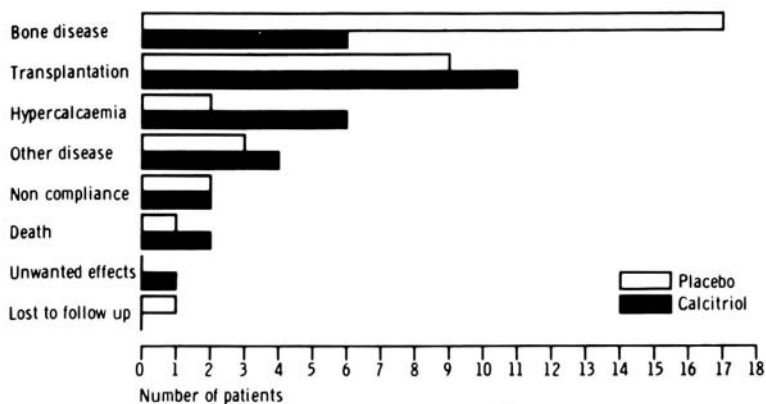


Figure 1. Reasons for withdrawal from trial, including bone disease

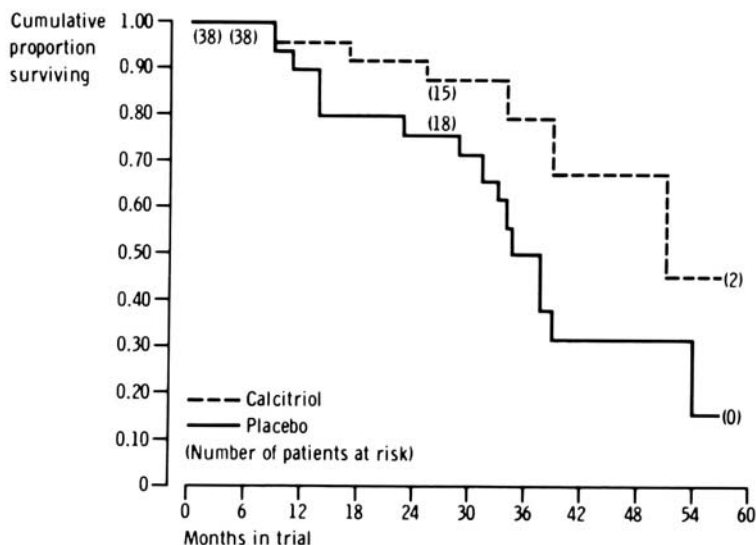


Figure 2. Actuarial survival analysis showing withdrawals from trial for bone disease

bone disease than patients receiving calcitriol ($p < 0.05$, generalised Wilcoxon (Breslow) test).

Before treatment the two groups did not differ significantly with respect to plasma calcium, serum parathyroid hormone and plasma alkaline phosphatase. During treatment, plasma calcium (normal 2.1–2.6mmol/L) rose significantly ($p < 0.01$; Wilcoxon matched pairs signed rank test) in patients receiving calcitriol (Figure 3). Serum parathyroid hormone (normal $< 120\text{pg/ml}$) rose in patients

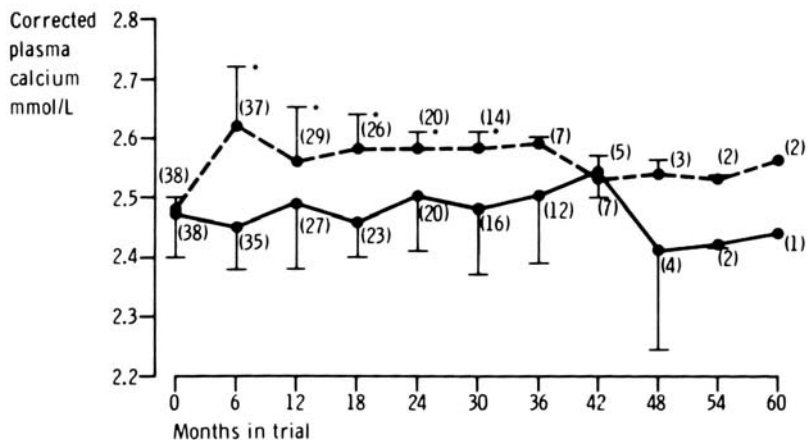


Figure 3. Median (\pm half mid-quartile range) plasma calcium for each six month period of the trial. ● - - - ● calcitriol; ● — ● placebo; (number of patients). *Significant difference between groups $p < 0.05$ (Mann Whitney U test)

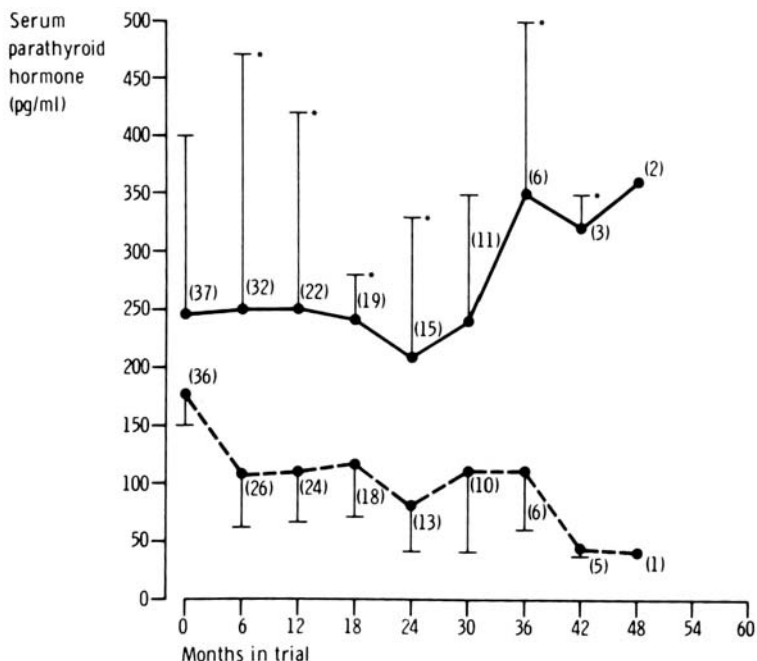


Figure 4. Median (\pm half mid-quartile range) serum parathyroid hormone during the trial. ● - - - ● calcitriol; ● — ● placebo; (number of patients). *Significant difference between groups $p < 0.05$ (Mann Whitney U test)

receiving placebo and fell significantly ($p < 0.025$; Wilcoxon matched pairs signed rank test) in those receiving the active drug (Figure 4). Plasma alkaline phosphatase (normal $< 100\text{U/L}$) rose in patients receiving placebo; initially it fell in patients receiving calcitriol, but later rose to above pre-treatment levels (Figure 5).

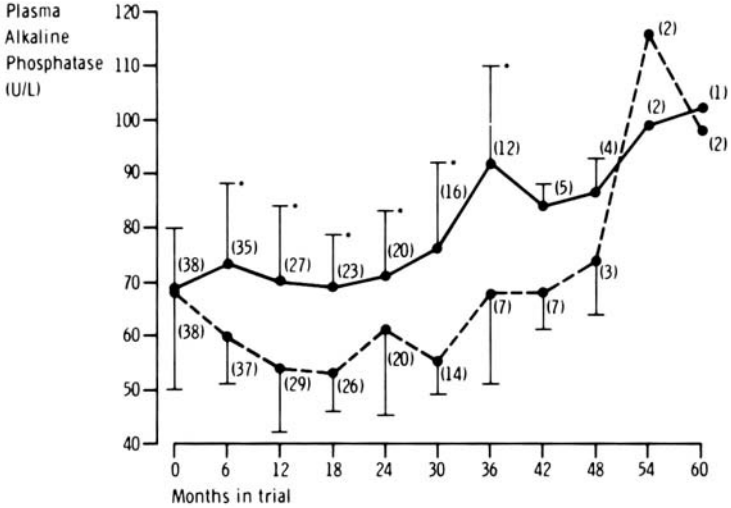


Figure 5. Median (\pm half mid-quartile range) plasma alkaline phosphatase for each six month period of the trial. ● - - - ● calcitriol; ● — ● placebo; (number of patients). * Significant difference between groups $p < 0.05$ (Mann Whitney U test)

During the trial significant differences between the two groups ($p < 0.05$; Mann Whitney U test) for plasma calcium, serum parathyroid hormone and plasma alkaline phosphatase were observed (see Figures 3–5).

Assessment of radiological deterioration or improvement during the trial showed no significant differences between the two groups.

Discussion

The value of vitamin D therapy in preventing the development of bone disease will depend on its efficacy and toxicity. Hypercalcaemia (the most important unwanted effect) was frequent, severe and prolonged initially, but after the change in protocol was infrequent and mild. We have shown that significantly more patients receiving placebo developed bone disease and that serum parathyroid hormone fell significantly in patients receiving calcitriol and was significantly lower than in patients receiving placebo. It is concluded that calcitriol delays and may prevent the development of metabolic bone disease in patients receiving regular haemodialysis therapy.

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