THE INFLUENCE OF 1 ALPHA-HYDROXYCHOLECALCIFEROL ON LEFT VENTRICULAR FUNCTION IN END-STAGE RENAL FAILURE

R J S McGonigle, A D Timmis, J Keenan, D E Jewitt, M J Weston, V Parsons

King's College Hospital, London, United Kingdom

Summary

This study was designed to assess the influence of 1α-hydroxycholecalciferol on left ventricular function in end-stage renal failure. Twelve patients, all of whom were on regular haemodialysis, were investigated. M-mode echocardiography and systolic time intervals were used to derive indices of left ventricular function. Measurements were performed before and six weeks after treatment with one microgram daily of 1α-hydroxycholecalciferol. Fractional fibre shortening increased from 34.6 to 37.6% (p < 0.025) and mean velocity of fibre shortening increased from 1.21 to 1.32 cm/sec (p < 0.01). These changes were associated with a fall in the mean plasma parathyroid hormone concentration from 1883 to 1123 ng/L (p < 0.0025) and a rise in magnesium concentration from 0.89 to 1.06 mmol/L (p < 0.0025); plasma calcium increased from 2.59 to 2.70 mmol/L but this change was not significant.

Our results indicate that 1α-hydroxycholecalciferol improves left ventricular function in end-stage renal failure by influencing both the turnover or secretion of parathyroid hormone and the metabolism of calcium and magnesium ions.

Introduction

Heart failure is a frequent complication of end-stage renal disease [1,2] though the mechanisms are not always clear. A specific uraemic cardiomyopathy [3,4] has been suggested but it remains a doubtful entity [1,5]. However, the possibility that parathyroid hormone (PTH) may be the 'uraemic toxin' [6] is supported by the recent finding that parathyroidectomy improves left ventricular function in uraemic patients with secondary hyperparathyroidism [7]. 1α-hydroxycholecalciferol (1α(OH)D₃) is a synthetic vitamin D analogue which is readily absorbed from the gastrointestinal tract and hydroxylated to 1,25-dihydroxycholecalciferol (1,25(OH)₂D₃) in the liver; (1,25(OH)₂D₃) is the metabolically active form of vitamin D, and is deficient in uraemia. Treatment with 1α(OH)D₃ has been shown
to suppress PTH secretion in renal failure, and corrects the proximal myopathy associated with osteomalacia. We decided therefore to investigate the influence of this hormone on left ventricular function in patients with end-stage renal failure.

Patients and methods

Twelve patients aged 29 to 53 years (mean 44 years) were studied after informed consent had been obtained. All had Cimino-Brescia fistulas and had been on regular haemodialysis for periods ranging from 8 to 67 months (mean 28 months). Dialysis was performed for between 15 and 20 hours each week using flat-plate ‘Kiils’ or hollow-fibre dialysers; the dialysis schedule in individual patients remained unchanged throughout the study. The majority of patients were on treatment with phosphate binders and all received iron and Orvite therapy. None of the patients had received vitamin D supplements prior to the study, however one patient was on labetalol therapy and another was on amiodarone. Four patients had early skeletal evidence of hyperparathyroidism radiologically, and two had severe left ventricular failure. In none of the group was there a history suggestive of coronary heart disease.

After initial measurements of serum biochemistry and left ventricular function had been taken, the patients were treated with 1µg daily of 1α(OH)D₃ over a six week period, and the measurements were then repeated. We were careful to investigate individual patients with the same time relationship to dialysis, both before and after treatment, thereby excluding the direct effects of haemodialysis on left ventricular function [8].

Investigations

Routine haematological and biochemical investigations, including plasma magnesium concentrations, were performed. PTH was measured by radioimmunoassay using an anti-bovine PTH antiserum and bovine PTH as a standard (Miss D Jackson, Institute of Child Health, London) [9]. 25-hydroxycholecalciferol was measured using a competitive protein binding method [10]. Body weight, blood pressure and heart rate were recorded. The cardiothoracic ratio was calculated from the chest radiograph.

The systolic time intervals of the cardiac cycle were measured by conventional means [11] using a fibreoptic multichannel recorder (Cambridge Scientific Instruments Ltd). The ratio of the pre-ejection period (PEP) to the left ventricular ejection time (LVET) was used as an index of left ventricular function.

Measurements of the left ventricular end-diastolic diameter (DD) and end-systolic diameter (DS) were made from the M-mode echocardiogram using a Smith-Kleine Ekosector III. Recordings were taken at a level just below the mitral valve leaflets and only those containing clear simultaneous echoes of the septum and posterior wall were used for analysis. Patients with paradoxical septal motion were excluded from the study. Indices of left ventricular function were derived as follows: Fractional fibre shortening (FS) = 100 × (DD−DS)/DD%

Mean velocity of fibre shortening (Vcf) = (DD−DS)/(DD × LVET) circ/sec.

Student’s ‘t’ test was used for statistical comparisons.
TABLE I. Effects of 1α-hydroxycholecalciferol on biochemical, haematological and clinical variables. (Values are mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>PTH</th>
<th>Calcium</th>
<th>Magnesium</th>
<th>Alkaline phosphatase</th>
<th>Albumin</th>
<th>Urea</th>
<th>25(OH)D₃</th>
<th>Haemoglobin</th>
<th>Body weight</th>
<th>Systolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ng/L</td>
<td>mmol/L</td>
<td>mmol/L</td>
<td>g/L</td>
<td>mmol/L</td>
<td>µg/L</td>
<td>g/dl</td>
<td>g/dl</td>
<td>kg</td>
<td>mmHg</td>
</tr>
<tr>
<td>Before treatment</td>
<td>1883±226</td>
<td>2.59±0.08</td>
<td>0.89±0.06</td>
<td>108±21</td>
<td>42.7±1.2</td>
<td>23.7±2.9</td>
<td>27.5±9</td>
<td>8.5±0.67</td>
<td>60.37±1.98</td>
<td>155±5</td>
</tr>
<tr>
<td>After treatment</td>
<td>1123±289</td>
<td>2.70±0.06</td>
<td>1.06±0.05</td>
<td>100±20</td>
<td>43.2±1.0</td>
<td>22.7±2.7</td>
<td>29±6</td>
<td>8.4±0.67</td>
<td>60.1±1.97</td>
<td>166±7</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0025</td>
<td>NS</td>
<td>&lt;0.0025</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

PTH = parathyroid hormone; 25(OH)D₃ = 25-hydroxycholecalciferol; NS = not significant; p = significant

TABLE II. Effects of 1α-hydroxycholecalciferol on left ventricular function and ventricular dimensions. (Values are mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>FS %</th>
<th>Vcf circ/sec</th>
<th>PEP/LVET</th>
<th>DD cm</th>
<th>DS cm</th>
<th>CTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>34.6±3.1</td>
<td>1.21±0.02</td>
<td>0.35±0.02</td>
<td>5.4±0.2</td>
<td>3.6±0.2</td>
<td>0.52±0.02</td>
</tr>
<tr>
<td>After treatment</td>
<td>37.6±3.2</td>
<td>1.32±0.08</td>
<td>0.33±0.02</td>
<td>5.5±0.2</td>
<td>3.5±0.2</td>
<td>0.52±0.02</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.025</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

CTR = cardiothoracic ratio; NS = not significant; FS = fractional fibre shortening; Vcf = mean velocity of fibre shortening; DD = left ventricular end-diastolic diameter; DS = left ventricular end-systolic diameter; PEP/LVET = ratio of the pre-ejection period to the left ventricular ejection time
Results

The influence of 1α(OH)D₃ therapy on plasma biochemistry is summarised in Table I. A 40% reduction in the mean plasma PTH concentration (p<0.0025) from 1883 to 1123ng/L (normal values 250–450ng/L) was associated with a 19% increase in plasma magnesium concentration (p<0.0025). Other variables, including the endogenous production of 25-hydroxycholecalciferol, and plasma calcium concentration were not significantly altered.

Though only two patients had severe left ventricular impairment (FS<25%; Vcf<1 circ/sec; PEP/LVET>0.45), indices of left ventricular function for the entire group improved (Table II). The increments in FS and Vcf (8% and 9% respectively) were significant but the small reduction in PEP/LVET failed to achieve significance. Left ventricular dimensions and cardiothoracic ratio did not change. There was also no difference in body weight, haemoglobin and plasma albumin concentrations indicating that the improvement in left ventricular function was not related to variations in plasma volume.

Discussion

Multiple factors may contribute towards the development of heart failure in chronic renal disease [1–3]. These include hypertension, pericarditis, plasma volume overload and coronary artery disease. Occasionally, however, the degree of heart failure is out of proportion to the severity of these predisposing factors. In such cases, myocardial suppression by metabolic toxins is frequently invoked. The identity of these toxins remains unclear but recent work by Drücke suggests that PTH may play an important role [7]. Our results lend some support to this. PTH levels were considerably elevated in all 12 of our patients, typical of the majority of patients on dialysis, though only four had radiographic evidence of skeletal damage. Although 1α(OH)D₃ reduced plasma concentrations of PTH, levels remained high and this may have been due to the propensity of the immunoassay to recognise biologically inactive fragments. However, plasma PTH does correlate with indirect indices of bone cell turnover (osteoblastic activity) indicating that the PTH concentrations have some biological relevance [12]. It is not clear if 1α(OH)D₃ (or its active metabolite) improved left ventricular function by a direct influence on myocardial contractility due to its effect on calcium and magnesium metabolism or, whether the reduction in PTH is itself responsible for the beneficial cardiac effects.

Plasma calcium concentrations in our patients showed no significant changes as a result of 1α(OH)D₃ therapy. But vitamin D increases calcium uptake by the sarcoplasmic reticulum and also increases the concentration of troponin C (the calcium-binding component of the troponin complex) in striated muscle, demonstrated experimentally in rachitic rabbits [13,14] and is likely to have a similar action in the heart. Increasing intramyocardial calcium would enhance the inotropic state of the heart [15] and might in part account for our findings.

1,25(OH)₂D₃ acts on the intestine to increase absorption of both calcium and magnesium. The rise in plasma magnesium concentration was probably responsible, in part, for the suppression of PTH secretion in our patients [16,17]. Though
magnesium undoubtedly influences myocardial automaticity [18], its effects on ventricular function are uncertain.

Depletion of cardiac magnesium has been suggested as an important common pathway in the pathogenesis of cardiomyopathic disease of diverse aetiologies [20,21]. However, ionised magnesium has also been shown to compete with calcium for the troponin binding sites, which then might impair tension development and consequently compromise myocardial contractility [22,23].

This study demonstrates that treatment with 1α(OH)D₃ improves left ventricular function in end-stage renal disease, though the mechanisms remain speculative. Greater improvements in left ventricular function may have occurred with more prolonged therapy.

References

1 Lewis BS, Milne FJ, Goldberg B. Br Heart J 1976; 38: 1229
3 Prosser D, Parsons V. Nephron 1975; 15: 4
5 Gueron M et al. Nephron 1975; 15: 2
6 Massry SG, Goldstein DA. Clin Nephrol 1979; 11: 181
7 Druèke T et al. Lancet 1980; 1: 112
11 Weissler AM, Harris WS, Schoenfield CD. Circulation 1968; 37: 149
13 Curry OB et al. Nature 1974; 249: 83
15 Nayler WG. Am Heart J 1963; 65: 404
18 Ghani MF, Rabam M. Am Heart J 1977; 94: 600
19 Iseri LT, Freed J, Bures AR. Am J Med 1975; 58: 837
21 Wherat AF, Perloff JK. Circulation 1973; 47: 915
22 Page E, Polinent PI. J Physiol 1972; 224: 121
23 Shine KI. Am J Physiol 1979; 237: H413

Open Discussion

RITZ (Heidelberg) The indices you reported are dependent on preload, after load and frequency of heart rate. You gave information on after load and blood pressure which rose so these should affect the indices in opposite directions. Preload is unchanged, but you failed to mention heart rate. Was this constant or did you eliminate this effect by introducing the correction of Weissler?

McGONIGLE We used Weissler's method of correction.

RITZ I owe to Dr Haussler the information that there are no 1,25 receptors on striated muscle. This contrasts with the morphological evidence, and we reported
biochemical evidence for 1,25 effects on skeletal muscle and there is unpublished information from our department by Professor Taber on diminished sarcoplasmic calcium transport on myocardium in uraemia. So there are effects of 1,25 on muscle although there are no receptors, which makes the results very difficult to interpret.

WARREN (Portsmouth, United Kingdom) I wonder whether you could kindly tell us what was the standard deviation of repeated measurements of fractional fibre shortening and your other parameters when made under standard conditions at intervals of six weeks in dialysis patients without intervention? You have shown us changes which are quantitatively very small although statistically significant. We cannot really assess the importance of those unless we know how reproducible your measurements are.

McGONIGLE The measurements are a sum of 20 cardiac cycles and are therefore reproducible.

WARREN I would like to ask you what were the results when you did those measurements, at six week intervals under standard conditions without any treatment? In other words what is the reproducibility of the method?

McGONIGLE We did not think it necessary to perform these repeated measurements.

WARREN So do you think there is any biological significance at all in a change of only eight or nine percent?

McGONIGLE The measurements improved in all patients except two whose parathyroid hormone levels did not fall and these two patients underwent parathyroidectomy, and consolidated the data.

In these two patients, parathyroid hormone levels fell after parathyroidectomy and measurements of left ventricular function consequently improved. They further confirm our results of treatment with vitamin D suggesting that the possible mechanism of vitamin D action was by reducing parathyroid hormone levels.

WARREN I was really trying to make a general point, and that is that those of us in renal medicine who try to measure cardiovascular variables have to be very critical about the way in which we use techniques with which we are often, perhaps, not as expert as the cardiologists. I speak from personal experience and I think you would need to know the answer to that question, as to the variability of your method, before really interpreting the results that you gave us.

DRÜEKE (Paris) To the preceding comments: statistics is a method to exclude the intervention of spontaneous variations or variations due to method. If there is really no effect then you should not find any difference by statistical analysis, as 12 patients is quite a good number. I agree with you that in very rare instances
you could see an effect by chance which in fact does not exist but generally statistics are there for excluding just those random differences.

Did you try to correlate the improvement of ventricular performance with the decrease in parathyroid hormone concentration?

McGONIGLE We did not look at them individually, but the last slide did show that the patients whose parathyroid hormone levels did not fall with vitamin D therapy did fall when they underwent parathyroidectomy.

RITZ May I inject a note of caution in assuming that parathyroid hormone is negatively inotropic. There is work recently forthcoming from the UCLA Department of Dr Kurokawa who in acute experiments employing papillary muscle of a cat, if I remember correctly, shows an acute positive inotropic effect of parathyroid hormone. Something which is logical if one takes into account the ability of parathyroid hormone to translocate calcium from the extracellular into the intracellular compartment. So although Dr Drüeke showed clearly that in the chronic state parathyroid hormone does presumably have a negative inotropic effect, there is experimental evidence to the contrary.

JAHN (Strasbourg) Your calcium level rises from 2.59 to 2.70. Calcium per se has an inotropic effect. Have you made injections of calcium to see if calcium gives the same modifications of the parameters you measured with echocardiography.

McGONIGLE We have not done those experiments, however the change in calcium was not significant.