1α-OH VITAMIN D₃ INCREASES PLASMA ALUMINIUM IN HAEMODIALYSED PATIENTS TAKING Al (OH)₃

A Fournier, R Demontis, Y Tahiri, *M Herve, Ph Moriniere, †A Leflon, Z Abdull-Massih, H Atik, S Benelmouffok

Hôpital Nord, *Société de Mathématiques appliquées à la Recherche Médicale et Biométrique, †Laboratoire de Biochimie, Amiens, France

Summary

1α-OH vitamin D₃ at the dose of 6μg per week was given for four weeks to 16 stable patients on chronic haemodialysis with a low dialysate aluminium while taking a constant dose of Al(OH)₃. A significant increase of their plasma aluminium was observed while on 1α(OH)D₃ therapy and during the six weeks following. This increase correlated with the cumulative dose of Al(OH)₃ and duration on dialysis but not with the recent dose of Al(OH)₃. The increase in plasma aluminium observed with 1α(OH)D₃ and after its discontinuation is more likely to be due to aluminium redistribution than to increased intestinal aluminium absorption. This effect indicates the need for close monitoring of plasma aluminium in uraemic patients treated with 1α(OH)D₃.

Introduction

Prevention of hyperparathyroidism is based on the correction of hyperphosphataemia by aluminium containing phosphate binders and the correction of persistent hypocalcaemia by administration of calcium supplements and pharmacological doses of vitamin D or physiological doses of 1α-hydroxylated metabolites of vitamin D [1]. Hyperaluminaemia is frequent in this population and, even in the absence of high water concentrations, may lead to clinically significant bone disease or encephalopathy [1]. Vitamin D metabolites may increase plasma aluminium indirectly by increasing the need of Al(OH)₃ in order to control hyperphosphataemia [1]. Whether or not vitamin D metabolites may directly increase plasma aluminium has not been adequately studied. Experimentally Drueke et al [2] have observed higher plasma aluminium contrasting with lower liver aluminium content in uraemic rats intoxicated by oral Al(OH)₃ when they were taking 1,25(OH)₂D₃. Clinically de Vernejoul has reported an increase of plasma aluminium in four of five uraemic patients taking pharmacological doses of 25(OH)D₃ [3].

390
We have studied the effect of 1αOH vitamin D₃ on plasma aluminium in uraemic patients taking a constant dose of Al(OH)₃ but not exposed to high aluminium dialysate.

Patients and methods

Patients

Sixteen patients (9 men and 7 women; 42–72 years) on chronic haemodialysis were selected because they needed a constant dose of Al(OH)₃ (0.5–4g; mean 2g per day) for control of their plasma phosphate between 1–2mmol/L, while their plasma calcium was <2.5mmol/L. They had been on haemodialysis for 2–108 months (mean = 43 months) and their dialysate aluminium had always been <0.3μmol/L due to reverse osmosis treatment of the water.

Treatment protocol

After three weeks observation 1α(OH)D₃ was given for four weeks at the dose of 6μg weekly, the drug being given at the end of each dialysis. After 1α(OH)D₃ discontinuation follow-up was continued for two weeks in the 16 patients and for eight weeks in six patients. Throughout this study, the dose of Al(OH)₃ has been kept constant.

Analytical methods

Before the first dialysis of each week the following plasma concentrations were measured throughout the study: Calcium, proteins and phosphate by autoanalyser technique. Aluminium by inductively coupled plasma emission spectrometry (normal range 0.46±0.15μmol/L; detection limit 0.15μmol/L) [4].

Plasma PTH was measured in only six patients with an antibody specific to the middle region of the molecule (normal range 80–220pg/ml) [5], at the end of the control period and of the 1α(OH)D₃ administration, then four to eight weeks after 1α(OH)D₃ discontinuation.

Statistical methods

Significance of the changes of plasma parameters compared to the control period was assessed by analysis of variance, pooling the data of the control period and then the data of successive two week periods. Association between plasma aluminium increase and parametric variables was looked for with simple regression and covariance analysis.

Results

The individual data of this study are reported in the thesis of Demontis [6]. Table 1 shows that plasma concentration of aluminium (P Al) increases significantly after two to four weeks of 1αOH vitamin D₃ administration
<table>
<thead>
<tr>
<th>Plasma Concentration (Numbers of patients)</th>
<th>Control Period</th>
<th>Weeks on 1α(OH)D₃ (1 + 2)</th>
<th>Weeks on 1α(OH)D₃ (3 + 4)</th>
<th>Weeks after 1α(OH)D₃ discontinuation (5 + 6)</th>
<th>Weeks after 1α(OH)D₃ discontinuation (7 + 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminium (µmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(16)</td>
<td>(16)</td>
<td>(16)</td>
<td>(16)</td>
<td>(6)</td>
</tr>
<tr>
<td></td>
<td>(16)</td>
<td>(16)</td>
<td>(16)</td>
<td>(6)</td>
<td>(6)</td>
</tr>
<tr>
<td></td>
<td>(16)</td>
<td>(16)</td>
<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
</tr>
<tr>
<td></td>
<td>(16)</td>
<td>(16)</td>
<td>(16)</td>
<td>(6)</td>
<td>(6)</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>1.20 ± 0.25</td>
<td>1.51 ± 0.3*</td>
<td>1.69 ± 0.35**</td>
<td>1.71 ± 0.3**</td>
<td>1.52 ± 0.4*</td>
</tr>
<tr>
<td></td>
<td>2.28 ± 0.06</td>
<td>2.48 ± 0.07</td>
<td>2.54 ± 0.09*</td>
<td>2.38 ± 0.06</td>
<td>2.31 ± 0.06</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.72 ± 0.13</td>
<td>1.86 ± 0.12</td>
<td>1.90 ± 0.11</td>
<td>1.81 ± 0.12</td>
<td>1.31 ± 0.20</td>
</tr>
<tr>
<td></td>
<td>1.33 ± 0.15</td>
<td>1.41 ± 0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH 44–68 (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(only 6 pts)</td>
<td>1375 ± 300</td>
<td>–</td>
<td>654 ± 200**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1173 ± 300*</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>911 ± 150*</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparison versus control period: *p<0.05; **p<0.01
(28 and 43%) and that the increase is still observed during the six weeks following the discontinuation of 1α(OH)D₃. After seven to eight weeks plasma aluminium reaches control values.

Plasma calcium increases significantly during 1α(OH)D₃ administration but the increase is no longer significant 15 days following 1α(OH)D₃ discontinuation. No significant change in plasma phosphate was observed. Plasma PTH measured in only six patients decreased significantly (-50%; p<0.01) at the end of 1α(OH)D₃ administration and the decrease is still present during the eight weeks after 1α(OH)D₃ discontinuation.

The greater plasma aluminium increase (measured during the two weeks following 1α(OH)D₃ discontinuation correlates to the total previously prescribed dose of Al(OH)₃ and to the duration on dialysis (p<0.01 and <0.02 respectively by covariance analysis) but not to the recent dose of Al(OH)₃ nor to age, sex or the nature of nephropathy.

Variations of plasma aluminium (versus control period) positively correlate with plasma calcium variations during 1α(OH)D₃ administration and during the four weeks following 1α(OH)D₃ discontinuation at a borderline significance (p = 0.08). No correlation between plasma aluminium variation and plasma phosphate variation is observed. Significant negative correlations are however observed between variations of plasma aluminium and variations of plasma PTH only during the period of 1α(OH)D₃ administration.

Discussion

1αOH vitamin D₃ induces in stable patients on chronic haemodialysis, not exposed to parenteral aluminium intoxication but taking a constant dose of Al(OH)₃, an increase in their plasma aluminium concentration which lasts six weeks after the drug discontinuation while the effects on plasma calcium resolve within 15 days.

These findings may be explained either by an increase in intestinal absorption of aluminium or by a decreased capacity of tissue storage of aluminium. The fact that plasma aluminium increase is correlated to duration on dialysis and to the cumulative dose of Al(OH)₃ but not to the recent dose of Al(OH)₃ favours the hypothesis of a redistribution of total body aluminium. The experimental data of Druke et al [2] showing that uraemic rats treated with 1,25(OH)₂D₃ accumulate less aluminium in their liver than paired controls when exposed to an oral aluminium load but have higher plasma aluminium values, are consistent with our observation. To determine between the two hypotheses the effect of 1α(OH)D₃ on the plasma aluminium of uraemic patients previously loaded with aluminium but no longer taking aluminium hydroxide, will have to be studied. Which of the hypotheses is eventually proven, the fact that plasma aluminium increases with 1αOH vitamin D₃ should lead to a close monitoring of plasma aluminium when 1α hydroxylated vitamin D metabolites are given to patients previously loaded with aluminium or still taking aluminium containing phosphate binders.
References

3 de Vernejoul MC. Calcif Tissue Int 1983; 35: A49
5 Gueris J, Ferriere C. Pathol Biol 1975; 23: 821