Intermittent High-Dose Oral 1,25-Dihydroxyvitamin D₃ for Secondary Hyperparathyroidism in Hemodialysis Patients

Takashi Akiba, Ryoiti Ando, Ken-ichi Shioyama, Renjiro Kuriyama, Yoshiko Chida, Jyugoro Ono, Satoshi Kurihara, Masanobu Hoshino, Kazuyoshi Togashi, Fumiaki Marumo.

ABSTRACT

We attempted to confirm whether intermittent high-dose oral 1,25-dihydroxyvitamin D₃ (PULSE) suppressed parathyroid hormone (PTH) secretion, inhibited parathyroid cell proliferation, and increased bone mass in uremic patients (Pts). Twenty two long-term hemodialysis Pts with secondary hyperparathyroidism were given 3.4 ± 0.8 µg 1.25 dihydroxyvitamin D₃ twice a week for 9.5 ± 3.3 M. The size of parathyroid gland (PT) was estimated by echography and computed tomography every 3 months. Bone mineral density of the radius (BAD) was measured by single photon absorptiometer (Norland SPA 26).

Findings were:

<table>
<thead>
<tr>
<th></th>
<th>Before PULSE</th>
<th>6 months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca (mg/dl)</td>
<td>9.96 ± 1.18</td>
<td>11.15 ± 1.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P (mg/dl)</td>
<td>5.17 ± 1.83</td>
<td>5.78 ± 1.11</td>
<td>n.s.</td>
</tr>
<tr>
<td>Alk-Pase (IU)</td>
<td>373 ± 385</td>
<td>167 ± 79</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>HS-PTH (ng/ml)</td>
<td>49.9 ± 31.5</td>
<td>8.01 ± 3.83</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>I-PTH (pg/ml)</td>
<td>563 ± 453</td>
<td>165 ± 101</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

The volumes of 22 PT detected by echography in 11 Pts before and after PULSE were 363 ± 385 and 434 ± 462 cm³ (n.s.), respectively. In 6 Pts before the PULSE therapy began and after 11.OM of PULSE, The BAD values were measured in 6 Pts before and after 11.OM of PULSE. They were 0.388 ± 0.115 and 0.398 ± 0.093 g/cm² (n.s.), respectively.

We conclude that at this dose schedule, PULSE suppresses PTH secretion, but does not decrease PT size or increase the bone mass.

Key words
renal osteodystrophy,
secondary hyperparathyroidism,
hemodialysis, 1,25-dihydroxyvitamin D₃.
Introduction

Renal osteodystrophy is one of main complications which decrease the physical activity of hemodialysis patients. For more than ten years, the active vitamin D metabolites, 1,25-dihydroxyvitamin D₃, and 1 alpha-hydroxyvitamin D₃, has been used in supplementation of 1,25 dihydroxyvitamin D₃ deficiency (1), (2), (3); this has led to strikingly improved secondary hyperparathyroidism in chronic hemodialysis patients (3). However, in spite of these drugs, secondary hyperparathyroidism has not yet been perfectly controlled and parathyroidectomy is still relevant for secondary hyperparathyroidism in hemodialysis patients (4).

In 1984, Slatopolsky and colleagues reported that intravenous administration of 1,25 dihydroxyvitamin D₃ could suppress serum parathyroid hormone levels in secondary hyperparathyroidism (5). Andress and his colleagues reported that long-term intravenous 1,25 dihydroxyvitamin D₃ could improve renal osteodystrophy (6).

Intravenous preparations of 1,25(OH)₂D₃ are not available in Japan. We therefore used intermittent high dose oral 1,25(OH)₂D₃ in the treatment of severe hyperparathyroidism as an alternative to parathyroidectomy (7). In this study, we attempted to determine whether oral 1,25-dihydroxyvitamin D₃ could suppress parathyroid secretion, induce involution of parathyroid hyperplasia, and recover the bone loss due to secondary hyperparathyroidism. We also tried to elucidate the effects of aluminum intoxication on the response of intermittent oral high dose 1,25 dihydroxyvitamin D₃ therapy.

Methods

Twenty two long term hemodialysis patients with moderate to severe secondary hyperparathyroidism were the subjects of this study. Their cause of end-stage renal disease was chronic glomerulonephritis. Prior to the study, they had been given physiological doses of an active vitamin D metabolite (0.5–1 µg/day 1,25–dihydroxyvitamin D₃ or 1 alpha-hydroxyvitamin D₃) for more than six months. Regular dialysis of four hours duration was carried out three times a week with cellulose triacetate membrane dialyzer of surface area 1.5m². Dialysate, composed of water treated by reverse osmosis, contained 2.5–3.5 mEq/l calcium and bicarbonate buffer. Details of the purposes and the risks of the experiments were explained to the patients and their informed consent was obtained.

Four microgram of 1,25 dihydroxyvitamin D₃ was administered per os twice a week at the end of dialysis. The drug was given by hospital staff to confirm its correct administration. Dose of 1,25-dihydroxyvitamin D₃ was decreased when mild hypercalcemia (serum calcium concentration >11.0mg/dl) occurred. In cases of severe (serum calcium concentration >13.0mg/dl) or symptomatic hypercalcemia, 1,25-dihydroxyvitamin D₃ administration was temporarily stopped and was re-commenced with a reduced dose of 0.5 µg/day when calcium concentration decreased to a normal range.

The phosphate binder was changed from hydroxyaluminum gel to calcium carbonate at the start of the study. The dose of calcium carbonate was 3 g/dl at the start of the study and were changed to maintain pre-dialysis serum phosphate levels <6.5mg/dl. If hyperphosphatemia (>6.5 mg/dl) was not controlled by a maximum of 6 g/day calcium carbonate, up to 3 g/day of hydroxyaluminum gel was added.

Total serum calcium, phosphate concentration, and alkaline phosphatase activities were measured by routine autoanalyzer methods. Ionized calcium concentrations were measured by sodium-potassium-calcium ion analyzer Nova 6 (Technicon Japan, Tokyo). Immunoreactive parathyroid hormone concentrations were determined with a c-terminal PTH assay kit (C-PTH, Baxter), a highly sensitive PTH assay kit (HS-PTH, Yamasa), and a two-site radiometric PTH assay kit (Intact PTH, Allegro). Their immunorecognition sites were C-terminal (53–84) for C-PTH, mid region (44–68) for HS-PTH, and both C-terminal (53–84) and N-terminal (1–34) for Intact PTH. Serum aluminum concentrations were measured by flameless atomic absorptiometer.

Special consent was obtained when necessary for bone survey by x-ray, quantitative computer