may have a beneficial effect in preventing Epo-induced hypertension; however, they must never be instituted when hypertension has already developed. In this case, I recommend, as Dr Dorhout Mees does, to check and try to reduce blood volume as the first step for controlling blood pressure increases.

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Oral vitamin D3 pulse therapy for overt secondary hyperparathyroidism at pre-dialysis stage

Sir,

Secondary hyperparathyroidism (2 HPT) is still an important complication of patients suffering from chronic renal failure. Our long-term observation on haemodialysis patients revealed that high serum parathyroid hormone (PTH) at the start of haemodialysis is a significant risk factor for the development of overt 2 HPT [1]. Therefore prophylactic treatment from pre-dialysis stage is necessary in some patients; however, we experienced a case that showed an aggravation of 2 HPT despite daily vitamin D3 administration. These situations prompted us to start a clinical trial of oral pulse treatment (Tx) in patients developing overt 2 HPT from early stages of renal failure. We performed a non-randomized study to compare the clinical efficacy of oral pulse Tx with that of low-dose 1,25(OH)2D3 Tx (Conventional Tx). Oral pulse Tx was done with 1,25(OH)2D3 (4 μg) twice a week, and conventional Tx was done with daily administration of 1α(OH)2D3 (0.25 μg).

Forty patients having a serum PTH concentration more than 140 pg/ml (twice the upper normal range) were recruited into the study from a total population of 130 patients. Twenty-nine patients were treated with conventional Tx, while 11 patients were treated with pulse Tx. All patients enrolled in this study had at least 6 months observation period prior to this study. The study protocol consisted of an initial 4-week control period and a 12-week treatment period. All patients completed the study. Serum creatinine, calcium, phosphorus, alkaline phosphatase (Al-P), PTH levels and 24-h creatinine clearance were monitored at the interval of every 4 weeks. Pharmacokinetic study of oral 1,25(OH)2D3 was done in pulse Tx group at the time of initiation of pulse Tx and at the end of treatment phase (12 weeks). This test was done with the infusion of calcium gluconate at a rate of 3 mg/kg per hour of elemental calcium, and we determined the half reduction point. This term was defined as that calcium concentration which caused a 50% decline in PTH levels from basal level of PTH levels during each infusion.

The results of this study are shown in Table 1. Overall reduction in serum PTH over time was significant (P = 0.0001). Though the reduction of PTH was found in all cases of pulse Tx group, four patients (14%) of the conventional Tx group did not show the reduction during treatment period. The response of PTH over time was significantly different between the two groups (significant interaction existed for treatment with time; P=0.0001). Regarding serum calcium increments, the response of serum calcium over time was identical, irrespective of Tx (P=0.74). Regarding with serum phosphorus, we found an overall increase over time (P=0.0001), but the response of serum phosphorus over time (interaction) was significantly different between two groups (P=0.004). This finding demonstrates that the increase of serum phosphorus was more dramatic in the conventional Tx group. According to these changes, the increase of calcium and phosphorus product was more dramatic in conventional Tx group (interaction; P=0.008).

The effect on residual renal function evaluated by serum creatinine and the values of creatinine clearance was identical between two groups; however, the slope of reciprocal serum creatinine over time revealed that it was aggravated only in the conventional Tx group. (the values of slope in conventional Tx were before treatment: -1.89 ± 1.41 x 10-6 μmol/l per day; during treatment: -3.21 ± 2.05 x 10-6 μmol/l per day; P=0.001, and those of pulse Tx were -1.79 ± 1.61 x 10-6 μmol/l per day and -1.51 ± 4.26 x 10-6 μmol/l per day respectively)

Pharmacokinetic study revealed that individual time concentration curve was variable for each patient (Figure 1). The average T+ was 18.6 ± 9.7 h and AUC (0-4g) was 2092 ± 952 pg/ml per hour. Some patients did not return to the basal level even at 48 h after administration. Calcium increase of PTH secretion test revealed that the half reduction point of serum calcium as well as that of PTH decreased after pulse Tx. The results from this non-randomized clinical trial indicated that oral pulse Tx was more potent for suppressing PTH secretion than conventional Tx. Though our study was not randomized and the number of patients enrolled in pulse Tx was small, the percentage reduction of PTH was stronger in the pulse Tx group than in the conventionalTx group. Indeed, some patients enrolled in the conventional Tx group did not show the reduction of serum PTH. Furthermore, we experienced a case who developed an aggravation of 2 HPT in spite of the increase of vitamin D3 dose. Therefore we believe that pulse Tx might be one option when conventional Tx fails to suppress PTH hypersecretion.

Though recent reports suggest that low-dose vitamin D3 treatment is not harmful to residual renal function [2-4], the danger of vitamin D3 administration on residual renal function has been previously reported [5]. Both hypercalcaemia and hyperphosphataemia were considered to be causative factors [5]. Our study demonstrated that the time-dependent increase in serum creatinine was identical between two Tx groups, but an aggravation of slope during treatment period was found only in the conventional Tx group. According to these results, we conclude that the effect of oral pulse Tx on residual renal function is minimal and less harmful than that of conventional Tx. We hypothesize that the more dramatic increases in phosphorus and (Ca)x(P) product found in
Table 1. Changes in various parameters during treatment

<table>
<thead>
<tr>
<th>Term</th>
<th>Group</th>
<th>Start of treatment</th>
<th>After 12 weeks treatment</th>
<th>Interaction between two treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH (pg/ml)</td>
<td>P</td>
<td>424 ± 65</td>
<td>120 ± 25***</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>239 ± 10</td>
<td>130 ± 7***</td>
<td>*</td>
</tr>
<tr>
<td>Al-Pase (IU/l)</td>
<td>P</td>
<td>208 ± 67</td>
<td>133 ± 40***</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>178 ± 10</td>
<td>140 ± 9***</td>
<td></td>
</tr>
<tr>
<td>Total calcium (mmol/l)</td>
<td>P</td>
<td>2.1 ± 0.3</td>
<td>2.2 ± 0.2*</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>2.1 ± 0.2</td>
<td>2.2 ± 0.2*</td>
<td></td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>P</td>
<td>1.42 ± 0.24</td>
<td>1.58 ± 0.26***</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1.38 ± 0.18</td>
<td>1.91 ± 0.20***</td>
<td></td>
</tr>
<tr>
<td>(Ca) x (P) product (mg²/dl²)</td>
<td>P</td>
<td>36.2 ± 5.5</td>
<td>43.2 ± 7.9***</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>36.2 ± 6.5</td>
<td>47.5 ± 6.5***</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mmol/l)</td>
<td>P</td>
<td>45.8 ± 18</td>
<td>55.7 ± 20.2***</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>444 ± 80</td>
<td>570 ± 90***</td>
<td></td>
</tr>
<tr>
<td>24-h creatinine clearance (/day)</td>
<td>P</td>
<td>26.1 ± 7.3</td>
<td>20.7 ± 9.6***</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>27.9 ± 6.5</td>
<td>20.7 ± 6.8***</td>
<td></td>
</tr>
</tbody>
</table>

Changes in various parameters between start of treatment and after 12 weeks treatment are shown. Statistical analysis by repeated-measures two-way ANOVA. P values of time-dependent changes are shown for the values after treatment, and those of interaction between treatment are shown in the right-hand column. */><0.05; **/><0.01; ***/><0.001. P, pulse Tx; C, conventional Tx.

Fig. 1. Pharmacokinetic study of orally administered 1,25(OH)₂D₃. The upper part shows the average data and the lower part the individual data.

conventional Tx group is the reason for the aggravation of slope.

Concerning with the pharmacokinetics of 1,25(OH)₂D₃, our results were almost same with those reported by Salusky et al. [6]. But the duration of time that the serum 1,25(OH)₂D₃ exceeded the normal range was 22 h and it was longer than the results reported by Salusky et al. (12 h) [6]. We speculate that this sustained elevation of serum 1,25(OH)₂D₃ might be one cause of the time-dependent rise in serum calcium in pulse Tx group. With regards to the most effective route (intravenous or oral) and dose (physiological or pharmacological), Quarles et al. conducted a prospective study [7], and concluded that the suppressing effect on PTH secretion was the same between intravenous and oral routes in spite of different pharmacological profiles. Our results reconfirmed the clinical usefulness of oral pulse Tx on suppressing PTH secretion. But we now consider that oral pulse Tx once per week might be advantageous to avoid the increase in serum calcium and phosphorus based on the results of pharmacokinetic study.

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Placement of central venous catheters by overinsertion of guide wires: low complication rate in 1527 central venous access devices

Sir,

Symptomatic dysrhythmia induced by a guide wire and