Effects of Oral Paricalcitol on Hyperparathyroidism and Proteinuria in Peritoneal Dialysis Patients

Severe secondary hyperparathyroidism (HPT) is a complication of chronic kidney disease (CKD). Paricalcitol is a selective vitamin D receptor activator (VDRA) with efficacy in the treatment of hyperparathyroidism and with fewer side effects (such as hypercalcemia and hyperphosphatemia) than are seen with calcitriol (1). In addition to their usefulness in the treatment of HPT, the VDRAs have shown anti-inflammatory pleiotropic effects (2), antifibrotic properties (3), and inhibitory effects on the renin–angiotensin–aldosterone system (4,5). Paricalcitol is a selective VDRA used in the treatment of HPT secondary to CKD with very good results (6–9). The pleiotropic effects already mentioned have been attributed to this drug, with evidence of antiproteinuric action in patients with CKD stages 2–4 (10–13).

Many patients treated with peritoneal dialysis (PD) maintain residual renal function for a long time, which is one of the advantages of the PD technique compared with hemodialysis. The availability of paricalcitol for oral use allows for easier treatment of HPT in PD patients and, at the same time, for an investigation into whether its proven effects on proteinuria in patients with a moderate grade of renal failure also translate into effectiveness in patients with end-stage renal disease treated with PD.

Methods
We prospectively studied 18 patients with CKD being treated with PD [11 men, 7 women; 6 with diabetes; mean age: 60.2 ± 13.9 years (range: 29–75 years); mean PD duration: 20.6 months (range: 3–58 months)] who also had HPT with intact parathyroid hormone (iPTH) levels higher than 200 pg/mL, and who were not already being treated with vitamin D analogs. Depending on iPTH level, the patients were given oral paricalcitol at initial doses of 1–2 μg daily (1 μg for PTH < 500 pg/mL and 2 μg/day for...
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PTH > 500 pg/mL). In this group of patients, 7 were receiving treatment with angiotensin converting-enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) before the treatment with paricalcitol started.

Before and at 1 and 3 months after the administration of paricalcitol, we determined serum Ca, serum P, iPTH, high-sensitivity C-reactive protein, serum albumin, and proteinuria in 14 patients with residual renal function (24-hour urine collection). Proteinuria was measured by the colorimetric pyrogallol red method, and iPTH was analyzed using Immulite 2500 iPTH kits (Siemens Healthcare Diagnostics, Eschborn, Germany).

Statistical analysis
Data are expressed as mean and standard deviation. Comparisons used the Student t-test and Mann–Whitney test according to the nature of the variables. A Spearman rank correlation (ρ) was used to assess correlations between variables. Analysis of variance was used, as appropriate, to determine the degree of association between variables. A value of ρ < 0.05 was considered statistically significant. Data were analyzed using the SPSS software package (version 16.0 for Windows: SPSS, Chicago, IL, U.S.A.).

Results
After treatment with paricalcitol, iPTH levels decreased very significantly in the 1st month to 295 pg/mL from basal values of 670 pg/mL (ρ < 0.001). The fall in iPTH level at the 1st month after the start of paricalcitol was so strong in some patients that it was necessary to reduce the paricalcitol doses in 7 patients to half the initial level. Despite that change, mean iPTH levels at the 3rd month were even lower than they had been in the 1st month (Table I). With paricalcitol treatment, proteinuria declined throughout the study (ρ = 0.043), with the difference between the basal and the 1st month values being significant (1.68 g/L vs. 1.41 g/L, ρ < 0.006, Table I), but nonsignificant at the 3rd month, after the reduction in paricalcitol dose in some of the patients. When the data for the 8 patients with residual renal function and no modification of their original dose of paricalcitol were analyzed separately, the reduction in proteinuria was also significant at the 3rd month (Table I). Treatment with ACEIs and ARBs was not modified during the study, and no differences in proteinuria were observed between the patients who received those agents and those who did not. No correlation was found for the decline in iPTH and proteinuria levels with diabetes status, age, sex, or time on PD. Serum Ca and P levels increased significantly from basal values, but the Ca values remained in the normal range (Table II). No changes were found in levels of high-sensitivity C-reactive protein and serum albumin (Table II). One patient complained of anorexia and vomiting, but symptoms disappeared with a reduction in the paricalcitol dose.

Discussion
A reduction in proteinuria accompanying the decline in iPTH level after administration of oral paricalcitol in CKD patients treated with PD is the main finding of the present study. Similar results have been described in patients with lesser damage to renal function [stages 2 – 4 CKD (10–13)]. Our study was performed in patients with high levels of iPTH such that the initial paricalcitol doses were appropriate; doses were corrected as necessary in some of the patients who experienced a large iPTH response. In some earlier studies, iPTH levels were in the normal range, and although it was not reported, there could have been a risk of adynamia because the relatively high doses of vitamin D analogs used. The efficacy of paricalcitol for HPT has been reported in CKD patients not on dialysis and in patients treated with hemodialysis and PD (6–9). Our results confirm those reports at 1 and 3 months in patients on PD. Although a lower rise in serum Ca and P has been described with the use of paricalcitol rather than calcitriol (1), we observed an increase in both parameters, although values for serum Ca remained within the normal range. The rise of serum Ca and P in our patients require us to be cautious with the use of Ca-based phosphate binders and to maintain rigorous follow-up of Ca and P levels in the patients.

The reduction in proteinuria seen with the administration of vitamin D analogs such as calcitriol (14) and paricalcitol (10–13) has been related to an inhibitory action of these selective VDRAs on the renin–angiotensin–aldosterone system, based on a description of their appearance in several tissues, including the kidney (1). The behavior of an analog of vitamin D, 1,25(OH)2D3, as a novel negative endocrine regulator of the renin–angiotensin system
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(15) and the anti-inflammatory action of paricalcitol in lowering C-reactive protein (11) are probably other mechanisms involved in the decline of proteinuria in response to paricalcitol. Even though we found no correlation between the decline in iPTH and the reduction in proteinuria, the significant decline in proteinuria at the 3rd month in only those patients whose paricalcitol doses were not changed may reflect a dose-dependent antiproteinuric effect of paricalcitol. The regular use of ACEIs and ARBs as renoprotective drugs, with an antiproteinuric effect in patients with varying degrees of renal damage (16–18), is considered as an excellent way to preserve or slow the progression of renal disease. The similar effect of paricalcitol on proteinuria that was described in patients with CKD stages 2 – 4 and that we describe here in patients on PD, including those using ACEIs and ARBs, allows us to consider paricalcitol as a potential new tool in the prevention of CKD progression.

**Conclusions**

Our results seem to indicate that, besides its efficiency in the treatment of HPT in PD patients, paricalcitol is also able to reduce proteinuria in PD patients who still have residual renal function.

**Disclosures**

Dr. Coronel has received speaker’s honoraria from Baxter Healthcare, Fresenius Medical Care, and Abbott Laboratories. Dr. Cigarrán has received speaker’s honoraria from Abbott Laboratories and Shire. The other authors have no financial conflicts of interest to declare.

**References**


**Table I** Parathyroid hormone and proteinuria before and after paricalcitol treatment in peritoneal dialysis patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal</th>
<th>Treatment month</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPTH (pg/mL)</td>
<td>670±318</td>
<td>295±147</td>
<td>&lt;0.001</td>
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<tr>
<td>Proteinuria (g/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1.68±2.0</td>
<td>1.41±1.5</td>
<td>&lt;0.006</td>
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<tr>
<td>Patients with unchanged dose</td>
<td>3.1±2.7</td>
<td>2.1±2.1</td>
<td>0.04</td>
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<tr>
<td>Proteinuria (g/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with unchanged dose</td>
<td>5.0±6.1</td>
<td>2.3±2.1</td>
<td>0.012</td>
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</tbody>
</table>

iPTH = intact parathyroid hormone.

**Table II** Biochemical parameters before and after paricalcitol treatment in peritoneal dialysis patients

<table>
<thead>
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<th>Variable</th>
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<th>p Value</th>
</tr>
</thead>
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<tr>
<td>Ca (mg/dL)</td>
<td>9.1±0.7</td>
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<tr>
<td>P (mg/dL)</td>
<td>5.2±0.8</td>
<td>5.7±1.2</td>
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<td>hsCRP (mg/dL)</td>
<td>0.50±0.53</td>
<td>0.60±0.69</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.46±0.39</td>
<td>3.44±0.44</td>
<td>NS</td>
</tr>
</tbody>
</table>

hsCRP = high-sensitivity C-reactive protein; NS = nonsignificant.

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