Effects of suspending ACE inhibitors and ARBs in advanced chronic kidney disease

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To the Editor,

Renin-angiotensin system inhibition is a commonly used therapeutic measure for slowing the progression of kidney disease in diabetic nephropathy and nephropathies with proteinuria. It has also been established that activation of this system is necessary for maintaining glomerular filtration when renal perfusion is severely impaired, as occurs in ischaemic nephropathy and cases of hypotension and dehydration. In these situations, the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) can deteriorate renal function.

In a recent and very shocking study carried out in patients with advanced chronic renal failure, Ahmed et al showed that halting renin-angiotensin system inhibitor treatment was associated with a relevant and persistent improvement in renal function, with an increase in glomerular filtration rate $>25\%$ in 61.5$\%$ of cases. These results led us to question the adequacy of using these drugs in advanced chronic kidney disease, and we decided to confirm these findings in our own patients.

Between January and June 2011, ACE inhibitors and ARBs were suspended in patients with stage 5 chronic kidney disease that were undergoing pre-dialysis programmes at the Hospital Ramón y Cajal Hospital in Madrid. The study included a total of 14 patients (5 women and 9 men) with a mean age of 68±12 years (range: 42-88 years). The aetiologies of the different cases were diabetic nephropathy (5 cases), nephroangiosclerosis (3 cases) polycystic kidney disease (2 cases), and other (4 cases). Eleven patients were receiving ARBs, one received ACE inhibitors, and the other two received both ARBs and ACE inhibitors. These drugs were replaced with calcium channel blockers or beta blockers. When the renin-angiotensin system inhibitor was suspended, all patients were clinically stable, with no signs or symptoms of heart failure, with blood pressure values under control and fractional sodium excretion ranging between 2$\%$ and 5.6$\%$.

Table 1 summarises the progression of glomerular filtration rate (MDRD-4), proteinuria (proteinuria:creatinine ratio) and serum potassium concentration since the renin-angiotensin system inhibitors were suspended (baseline values) to three months later.

We only observed an increase in glomerular filtration rate $>25\%$ in one patient, and this increase was temporary. Overall, the removal of ACE inhibitor and ARB treatment was associated with an almost statistically significant increase in proteinuria. However, in 5 patients, the increase in proteinuria:creatinine ratio in urine samples was greater than 1mg/mg. There were no changes in serum potassium concentrations. We did not find an increase in blood pressure in any patient following the suspension of renin-angiotensin system inhibitors; however, two patients requested reinstatement of treatment, attesting to a better clinical tolerance. No patients suffered cardiovascular events during the follow-up period.

Our results in patients with stage 5 chronic kidney disease differ from those published by Ahmed et al. Although these drugs may worsen renal function in cases of compromised renal perfusion, the removal of renin-angiotensin system inhibitors failed to provide any relevant benefits in clinically stable patients without signs of dehydration. Even in these advanced phases of renal failure, ACE inhibitors and ARBs have an antiproteinuric effect. We believe that larger studies are needed in order to clarify whether suspending treatment with ACE inhibitors or ARBs in advanced chronic kidney disease impacts glomerular filtration rate, and if so, which patients would benefit from this protocol.

Table 1. Evolution of glomerular filtration rate and proteinuria following suspension of ACE inhibitors and ARBs

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<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>P</th>
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<tbody>
<tr>
<td>Glomerular filtration rate (ml/min/1.73m²)</td>
<td>11.3±2.7</td>
<td>11.4±3.7</td>
<td>0.982</td>
</tr>
<tr>
<td>Proteinuria:creatinine (mg/mg)</td>
<td>2.03±1.64</td>
<td>2.90±2.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Serum potassium (mEq/l)</td>
<td>4.7±0.5</td>
<td>4.6±0.6</td>
<td>0.3795</td>
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ARB: angiotensin receptor blockers; ACE: angiotensin-converting enzyme.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

Microalbuminuria, another use for paricalcitol? Our experience in advanced chronic kidney disease
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To the Editor,
Albuminuria increases the risk of progression of renal failure (RF), even in advanced stages. Renin-angiotensin-aldosterone system (RAAS) inhibitors are the main tool used for reducing albuminuria and slowing the progression of RF, although this treatment is often insufficient. Recently, paricalcitol has been proven effective in reducing albuminuria in certain patients.

The aim of our study was to assess the usefulness of paricalcitol to reduce albuminuria in patients with stage 4-5 RF.

Method: We included all patients referred to the predialysis unit. Patients were administered paricalcitol at an initial mean dose of 1±0.3Ìg/day orally, adjusted for calcium/phosphorous metabolic parameters. Follow-up continued for at least 6 months, with three visits every 2 months, in which albuminuria, MDRD, and calcium/phosphorous metabolic parameters were registered. Treatment with RAAS inhibitors and hydroferol continued without change. Statistical analysis: we used analysis of variance for comparing the means of quantitative variables, Wilcoxon tests for comparing medians, and chi-square tests to compare percentages.

Results: Our study included a total of 40 patients, 67% males, with a follow-up period of 135-235 days. Baseline MDRD was 19.5±3ml/min. 97.5% of patients had hypertension, and 35% were diabetic. Mean urine albumin-to-creatinine ratio (UACR) was 1932±1641mg/g. Initial calcium/phosphorous metabolism parameters were: calcium: 8.8±0.5mg/dl; phosphorous: 4.5±0.5mg/dl; intact parathyroid hormone (iPTH): 473±143pg/ml. At the start of the follow-up period, 25% of patients received angiotensin-converting enzyme inhibitors, 42.5% angiotensin receptor blockers, 55% hydroferol, and 12.5% calcitriol. During the follow-up period, we observed a significant decrease in MDRD (19.5±3ml/min vs 17.3±3.4ml/min; P=.003). There was also a decrease in iPTH and an increase in calcium, both significant results (473±143pg/ml vs 197±88pg/ml, and 8.84±0.5mg/dl vs 9±0.4mg/dl; P=.00 and P=.01, respectively). We also observed an increase in phosphorous, although this was not significant (4.5±0.5mg/dl vs 4.8±0.6mg/dl; P=.1). UACR decreased over the course of the study from an initial mean value of 1932±1641mg/g to the final mean value of 1417±1284mg/g, a 27% decrease (P=.1). In the group of patients with higher initial UACR values (>3000mg/g), the decrease was significant (4258±944mg/g vs 2786±1630mg/g; P=.03). We observed an increase in patients with normalised albuminuria and a decrease in those with albuminuria >3000mg/g. UACR was not associated with treatment with RAAS inhibitors, hydroferol, or calcitriol. In no cases was suspension of treatment necessary due to altered calcium/phosphorous metabolism or secondary side effects, although 17% of patients required dosage adjustments.

Our study shows that treatment with paricalcitol in this group of patients is associated with a significant decrease in UACR, leading to a higher proportion of patients with normal excretion of albumin, in addition to providing better control of bone metabolism. The effect was greatest and most significant in patients with higher initial albumin excretion levels, which is the group with the highest risk for progression of RF.

It may be that the small sample in our study was insufficient to demonstrate the antiproteinuric effects of this treatment with a greater level of significance. We may not have observed significant results in the control of renal function deterioration because of this same reason. Although it was not an objective of this study, we should also keep in mind the decreased cardiovascular risk associated with reduced UACR.

Conclusion: Paricalcitol can be effective in halting proteinuria in patients with stage 4-5 chronic renal failure disease and controlling secondary hyperparathyroidism. Its efficacy in preventing the progression of RF must be verified in future studies.

Conflicts of interest
The authors affirm that they have no conflicts of interest related to the content of this article.

4. Ruggenenti P, Perna A, Ghezardi G, Benini R, Remuzzi G. Chronic proteinuric nephropathies. Outcomes and response to...