Severe Paradoxical Hypertension With Angiotensin-Converting Enzyme Inhibitors: An Unusual Feature of Renal Artery Stenosis

To the Editor:

Angiotensin-converting enzyme (ACE) inhibitors are frequently used in the treatment of hypertension, heart failure, and renal disease but may cause acute renal failure in patients with renal artery stenosis (RAS).1 We describe a novel adverse effect of ACE inhibitors in patients with advanced chronic kidney disease (CKD) and RAS.

We observed 4 episodes of severe paradoxical hypertension in 3 patients with CKD (Table) and bilateral RAS, during initiation or titration of the ACE inhibitor ramipril (Tritace, Sanofi-Aventis). The etiology of CKD was atherosclerotic renovascular disease in each case. Bilateral, hemodynamically significant RAS had been demonstrated previously with both Doppler ultrasound and renal angiography in all 3 of the patients and magnetic resonance angiography in 2 patients. Blood pressure (BP) measurement using an automated oscillometric device (Dinamap Pro series, GE Healthcare) demonstrated initial transient hypotension or relative hypotension, after administration of ramipril, followed by rebound severe hypertension (Figure 1). This phenomenon occurred in patient 1 after increasing ramipril from 7.5 mg to 10.0 mg; in patient 2 with the addition of 10.0 mg of ramipril; and in patient 3 with the addition of 5.0 mg of ramipril. Only patient 2 was taking an angiotensin receptor blocker. Cessation of ramipril, followed by rebound severe hypertension (Figure 1). This phenomenon occurred in patient 1 after increasing ramipril from 7.5 mg to 10.0 mg; in patient 2 with the addition of 10.0 mg of ramipril; and in patient 3 with the addition of 5.0 mg of ramipril. Only patient 2 was taking an angiotensin receptor blocker. Cessation of ramipril in each case resulted in lower BPs, with reduced requirements for antihypertensive therapy (Figure 2). The phenomenon was recurrent in patient 1 when rechallenged with an ACE inhibitor. This episode was complicated by hypertensive encephalopathy and a generalized seizure, with a BP of 240/120 mm Hg. Two days after the cessation of ramipril, the patient’s systolic BP ranged from 120 to 130 mm Hg on a single antihypertensive.

Other causes for the worsening of hypertension were excluded. The 2 patients on maintenance hemodialysis were considered to be euvoletic on clinical examination. Review of dialysis records in these patients did not reveal orders for extra ultrafiltration, suggesting that they were not volume overloaded. The third patient was weighed daily, and weight decreased by 1.2 kg over several days after the initiation of ramipril, despite worsening hypertension. None of the patients received intravenous infusions during the period of interest. Other antihypertensive medication remained constant during initiation or titration of ramipril, as did the recombinant erythropoietin dose.

We describe severe hypertension apparently secondary to ACE inhibitor therapy in the setting of bilateral RAS and CKD. The mechanism is unclear, but we postulate that, in the setting of fixed afferent obstruction, the additional drop in glomerular pressure induced by ACE inhibitors led to activation of the renin-angiotensin-aldosterone system with resulting rebound hyperreninemia and hypertension. This hypothesis might be supported by the measurement of plasma renin concentration during an observed episode. It is interesting to note that ACE inhibitor therapy precipitated simultaneous acute renal failure in patient 3. This is thought to be mediated by the same process of reduced

Table. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>F</td>
<td>ESRF on hemodialysis</td>
</tr>
<tr>
<td>episode 1</td>
<td>79</td>
<td>M</td>
<td>ESRF on hemodialysis</td>
</tr>
<tr>
<td>episode 2</td>
<td>79</td>
<td>M</td>
<td>ESRF on hemodialysis</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
<td>F</td>
<td>CKD stage 4, eGFR 25 mL/min per 1.73 m²</td>
</tr>
</tbody>
</table>

ESRF indicates end-stage renal failure; F, female; M, male; eGFR, estimated glomerular filtration rate (calculated according to the 4-variable Modification of Diet in Renal Disease formula²).

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glomerular pressure. A similar effect might be expected with angiotensin receptor blockers but not with other antihypertensives, because they lack a vasodilator effect on the efferent arteriole.

Severe paradoxical hypertension may be an adverse effect of ACE inhibitor therapy in the setting of RAS and CKD. Clinicians should be aware of this when treating patients with known or suspected RAS.

**Disclosures**

None.
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