Long-Term Follow-Up of Acute Renal Failure Caused by Angiotensin Converting Enzyme Inhibitors

Alain Wynckel, Bertin Ebikili, Jean-Pierre Melin, Christine Randoux, Sylvie Lavaud, and Jacques Chanard

Angiotensin converting enzyme (ACE) inhibitors are useful in the treatment of hypertension and heart failure. However, acute renal failure (ARF) may occur in patients who are taking these drugs in situations associated with decreased glomerular filtration pressure, such as dehydration caused by acute diarrhea or diuretic therapy.

Sixty-four patients who were admitted to the intensive care unit for ARF associated with ACE inhibitor therapy were followed for more than 5 years. In this historical retrospective study, we documented that 45 patients were treated for hypertension (group I) and 19 were treated for heart failure (group II). Their mean age was 71.2 ± 11.6 years. Patients with ARF presented with overt dehydration in 91% and 84% of the cases in groups I and II, respectively. Hypovolemia was caused by diuretics or gastrointestinal fluid loss. Bilateral artery-renal stenosis or stenosis in a solitary kidney was documented in 22% and 10% of patients in groups I and II, respectively. The probability of survival was 91% and 49% at 1 year and 64% and 18% at 5 years, for groups I and II, respectively. Acute renal failure required hemodialysis in seven patients, but none of them became dialysis dependent. In the subgroup of patients with preexisting chronic renal failure, all the patients except for one who belonged to group II died within 2 years. In both groups, after resolution of ARF, plasma creatinine concentration returned to baseline level and the course of renal function was not significantly worsened.

In conclusion, ARF associated with ACE inhibitors is likely to occur in many patients without renal artery stenosis after unexpected dehydration, especially in older patients with congestive heart failure. In both groups of patients, in the absence of preexisting chronic uremia, recovery of renal function occurred without sequelae, even after an episode of acute tubular necrosis requiring dialysis. Am J Hypertens 1998; 11:1080–1086 © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: Acute renal failure, angiotensin converting enzyme inhibitors, hypertension, heart failure, renal artery stenosis.

Received December 5, 1997. Accepted March 25, 1995.
From the Service de Néphrologie, Centre Hospitalier et Universitaire, Reims, France.

Address correspondence and reprint requests to Professeur J. Chanard, Service de Néphrologie, Centre Hospitalier et Universitaire, 45, rue Cognacq Jay, 51092 Reims Cédex, France.
Antagonism of the renin-angiotensin system has been shown to be beneficial against the deleterious consequences of hypertension and heart failure. Angiotensin converting enzyme (ACE) inhibitors are now widely used and well tolerated. Acute renal failure (ARF) is their major complication, directly related to the hemodynamic consequences of ACE inhibition. Acute renal failure is induced by reduction of intrarenal perfusion pressure associated with blocking of the angiotensin II-induced resistance at the efferent glomerular arteriole. Patients with bilateral renal artery stenosis are particularly at risk of ARF. More recently, with the extensive prescription of ACE inhibitors in patients with congestive heart failure, ARF has been documented in the absence of renal artery stenoses and the role of hypovolemia and negative sodium balance has been described. Only anecdotal reports of ARF caused by acute interstitial nephritis or renal artery thrombosis have also been quoted.

Correction of hypovolemia by infusion of salt and water is usually followed by an increase in blood pressure and recovery of urine output. The increased plasma creatinine concentration rapidly returns to baseline level, indicating that the transient episode of ARF was not complicated by organic damage. However, sustained hypotension can induce protracted renal insufficiency, especially in older patients, reflecting acute tubular necrosis and potentially irreversible renal damage. It has been questioned whether or not ARF caused by ACE inhibitors could induce late renal atrophy and worsen the course of chronic renal failure. Because of the lack of information on this subject, we undertook a retrospective study of patients who had had ARF associated with ACE inhibitors that had been severe enough to require admission to the intensive care unit.

PATIENTS AND METHODS

Sixty-four patients who had ARF while they were taking ACE inhibitors were prospectively followed for more than 5 years to determine if they had renal sequelae. Patients were included in the study if they had been admitted to the intensive care unit because of hypotension and their baseline plasma creatinine concentration had doubled in less than 48 h to a value greater than 200 μmol/L. Patients with the following concomitant clinical conditions were excluded: sepsis, trauma or surgery, recent acute myocardial infarction, obstructive nephropathy, dysproteinemia, and exposure to nephrotoxic drugs or radiocontrast material.

Table 1 shows the main demographic characteristics of these patients. Their mean age was 71.2 ± 11.6 years (range, 40 to 90 years), 39 were male and 25 female, 21 had established chronic renal failure (plasma creatinine ≥ 133 μmol/L), and 13 had non-insulin-dependent diabetes mellitus (NIDDM).

The patients were separated into two groups according to the indication for ACE inhibition therapy. Group I included 45 patients treated for hypertension and group II consisted of 19 patients treated for congestive heart failure, classified as grade III–IV of the New York Heart Association (NYHA) classification. In all patients, ACE inhibitors had been prescribed for more than 2 weeks by a general practitioner and were considered effective and well tolerated. The following drugs induced ARF: captopril, enalapril, lisinopril, trandolapril, quinapril, cilazapril, and ramipril. Dehydration was noted in 89%, resulting from loop diuretic use (77%) or gastrointestinal fluid losses (56%). The risk factor of hypovolemia was similarly distributed in the two groups (Table 2).

Patients were followed up for 5 years. The decline of renal function was assessed by plasma creatinine concentration. The presence of renovascular disease was investigated by Doppler echography and renal scintigraphy.
tigraphy with captopril in all cases. Renal angiography was performed in 25 patients. They were selected on positive echographic findings (n = 8) and on positive or doubtful isotopic results (n = 9). In spite of negative results using noninvasive procedures, renal angiography was also performed in eight additional patients because they had moderate to severe hypertension or were waiting for a cardiac transplantation. Endovascular dilatation of arterial stenosis was performed when indicated.

Statistics Results are expressed as mean ± SD; differences between the patients with and without heart failure, with respect to the studied variables, were evaluated using the χ² test with Yates correction for qualitative variables. The Student’s t test was used for quantitative variables. Cumulative event rates were estimated by the Kaplan-Meier method and survival curves were used to display the results graphically. The log-rank (Mantel-Cox) was used to compare event rates between clinical groups.

RESULTS

Clinical Presentation Table 2 shows the main clinical characteristics of the patients. Hypotension was present in all and was corrected after administration of fluid and electrolytes, intravenously. When compared with baseline values, systolic blood pressure decrement was not statistically different between the two groups: 25.9 ± 13.6 mm Hg and 23.9 ± 10.1 mm Hg in groups I and II, respectively. Orthostatic hypotension was noted in 22% of group I patients and 47% of group II patients (P < .05). Dehydration was present in 91% and 84% of the patients in group I and II, respectively. Oliguria (urine output <500 mL/day) was documented in all the patients and lasted at least 48 h. In four (9%) patients in group I and in three (16%) in group II, emergency hemodialysis was required to control acidosis and hyperkalemia. Three-quarters of the patients had been treated with diuretics and 56% had severe diarrhea that had induced a mean body weight loss of 2.8 ± 0.5 kg. Three patients were receiving nonsteroidal antiinflammatory drugs. Clinical chemistry as presentation did not differ significantly between the two groups, except for the plasma potassium concentration, which was 6.1 ± 1.5 mmol/L in patients with heart failure and 5.3 ± 1.3 mmol/L in hypertensives (P < .05), as shown in Table 3. This difference is explained by the prescription of potassium-sparking diuretics in 12 of 19 patients of group II and in 4 of 45 of group I.

Renal artery stenosis greater than two-thirds of the lumen was found in 22% of the group I patients (with hypertension) and in 10% of the group II patients (with heart failure). In four patients renal artery stenosis was bilateral, and in two the stenosis occurred in a solitary kidney. In all instances, the stenoses were associated with diffuse atheromatous vascular lesions. Fourteen (31%) patients in group I and seven (36%) in group II had chronic renal failure before the acute functional deterioration induced by ACE inhibition.

Patient Survival Three patients died within 1 month of onset of ARF, one in group I and two in group II. During the following 5 years, 23 additional patients died. In summary, death occurred in 13 patients of group I and in 13 of group II. At presentation, the mean age of the patients who died was 75.0 ± 11.5 years, whereas it was 68.2 ± 10.5 years in those who survived. Actuarial survival rate is indicated in Figure 1 for group I and group II patients. The probabilities of patient survival were 91% and 49% at 1 year, 79% and 43% at 2 years, 76% and 35% at 3 years, and 64% and 18% at 5 years for groups I and II, respectively. The likelihood of survival as established by calculated half-life was 98 months and 11 months in groups I and II, respectively.

In patients with preexisting chronic renal failure, the prognosis was significantly worse, as illustrated in figure 2 (logrank test, P = .001). This difference was significant in both groups of patients (P = .02 for group I and P = .01 for group II). In surviving patients with preexisting normal renal function, plasma creatinine concentration remained stable throughout the study (Figure 3).

Two patients with chronic renal failure at time of ARF required regular hemodialysis 3 years later. This endpoint would be expected in the normal course of the disease. The episode of ARF was reversible in each and did not exacerbate the rate of progression of the chronic renal failure. In group II patients, changes in renal function paralleled cardiac failure and all died within 2 years, except for a successful heart transplant recipient. Univariate analysis of the effect of NIDDM on the course of chronic uremia showed a higher mortality in the diabetic patients (P < .02).

| TABLE 3. CLINICAL BIOCHEMISTRY AT TIME OF ADMISSION TO INTENSIVE CARE UNIT |
|---------------------------------|-------------------|-------------------|
| Baseline plasma creatinine (μmol/L) | 128 ± 53          | 146 ± 104         |
| Maximum plasma creatinine (μmol/L) | 584 ± 356         | 581 ± 312         |
| Maximum blood urea level (mmol/L)  | 37.2 ± 15.8       | 40.9 ± 16.9       |
| Plasma Na level (mmol/L)          | 134 ± 7           | 133 ± 5           |
| Plasma K⁺ level (mmol/L)          | 5.3 ± 1.3         | 6.1 ± 1.5*        |
| Plasma bicarbonate level (mmol/L) | 19 ± 7            | 19 ± 6            |

*P < .05.
Renal Function Follow-Up None of the seven patients who required hemodialysis in the acute phase of renal failure became dialysis dependent. Their renal function had returned to baseline level when checked up 1 month later. The mean plasma creatinine concentrations are shown in Table 4, indicating a similar slight increase with time in both groups.

DISCUSSION

Acute renal failure is a well-established potential complication of ACE inhibitor treatment, which occurs in patients with renal artery stenosis. Its occurrence in patients with heart failure but without obvious renal artery stenosis is increasing, as ACE inhibitors are increasingly used to treat this condition.\textsuperscript{16,17} The clinical presentation of ARF ranges from transient oliguria, and as often-unrecognized increase of the plasma creatinine concentration, to overt anuria. The incidence of significant azotemia complicating therapy with ACE inhibitors remains uncertain. Up to one-third of patients with bilateral renal-artery stenosis may exhibit a rise in plasma creatinine after starting therapy.\textsuperscript{8} In patients with hypertension or heart failure but without renal artery stenosis, the incidence......
of ARF is unknown. During the past 5 years, ARF caused by ACE inhibitors accounted for 9% of all the cases of ARF requiring hospitalization in the renal intensive care unit in our institution. Eleven percent of these patients required hemodialysis, indicating that renal impairment caused by ACE inhibitors is not always functional and reversible, and that protracted hypotension in this situation may induce acute tubular necrosis.¹⁸

Dehydration associated with gastrointestinal fluid loss or the use of high doses of loop diuretics were the major risk factors for ARF during ACE blockade. In this situation, a fall in glomerular filtration pressure is expected because the homeostatic adaptation of the renin-angiotensin system is impaired. The risk can be minimized by prompt vascular refilling, especially in older subjects with an impaired thirst threshold.¹⁹ One of the most interesting findings of this study was that significant bilateral or unilateral renal artery stenosis was present in only 19% of the patients. This figure excluded smaller degrees of atheromatous narrowing of the renal artery, which could not be identified by conventional noninvasive radiologic procedures, as renal arteriography was not systemically performed. Nevertheless, some reports have described renal failure associated with ACE inhibitors in patients with angiographically normal renal arteries and have postulated diffuse small-vessel disease of the kidney, as might be seen in severe nephrosclerosis.⁹–¹¹ Conversely, patients with proven renal artery stenosis have not developed ARF when they were treated with ACE blockers.²⁰ A negative sodium balance caused by diuretics may be an essential pathogenic factor for ARF in that situation. Mandal et al¹² have documented that the addition of diuretics potentiates ACE-inhibitor–induced ARF in 33% of the patients treated with additional diuretics and in 2.4% of those not taking diuretics. In an analysis of 104 patients with heart failure treated with a combination of diuretics and ACE inhibitors, Packer et al¹⁶ documented ARF in 33%, a result similar to our findings. Frequently, as in the present series, histologic data are not available, as there is general agreement that renal biopsy in elderly patients with diffuse cardiovascular symptoms and

---

**TABLE 4. PLASMA CREATININE FOLLOW-UP OF THE PATIENTS WHO HAD ACUTE RENAL FAILURE CAUSED BY ANGIOTENSIN CONVERTING ENZYME INHIBITORS**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Plasma Creatinine (μmol/L)</th>
<th>Baseline</th>
<th>Month 1</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td>134 ± 72</td>
<td>157 ± 89</td>
<td>160 ± 112</td>
<td>143 ± 88</td>
<td>174 ± 177</td>
<td>171 ± 203</td>
<td>113 ± 21</td>
</tr>
<tr>
<td></td>
<td>(n = 64)</td>
<td>(n = 61)</td>
<td>(n = 44)</td>
<td>(n = 36)</td>
<td>(n = 29)</td>
<td>(n = 19)</td>
<td>(n = 13)</td>
<td></td>
</tr>
<tr>
<td>Group I (hypertension)</td>
<td></td>
<td>128 ± 53</td>
<td>150 ± 75</td>
<td>151 ± 80</td>
<td>146 ± 93</td>
<td>181 ± 190*</td>
<td>180 ± 222*</td>
<td>113 ± 22</td>
</tr>
<tr>
<td></td>
<td>(n = 45)</td>
<td>(n = 44)</td>
<td>(n = 37)</td>
<td>(n = 32)</td>
<td>(n = 25)</td>
<td>(n = 16)</td>
<td>(n = 12)</td>
<td></td>
</tr>
<tr>
<td>Group II (heart failure)</td>
<td></td>
<td>146 ± 104</td>
<td>175 ± 119</td>
<td>208 ± 220</td>
<td>120 ± 36</td>
<td>129 ± 31</td>
<td>119 ± 4</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>(n = 19)</td>
<td>(n = 17)</td>
<td>(n = 7)</td>
<td>(n = 4)</td>
<td>(n = 4)</td>
<td>(n = 3)</td>
<td>(n = 1)</td>
<td></td>
</tr>
</tbody>
</table>

* Plasma creatinine was considered as 1000 μmol/L in two patients on chronic hemodialysis.
probable functional and reversible ARF is not ethically justified.

Survival was dependent upon the underlying clinical condition. After 1 year, survival was 91% and 49% in groups I and II, respectively. Half-life survival was nine times shorter in patients with congestive heart failure than in those with essential hypertension. Patients with heart failure in association with chronic renal insufficiency had the poorest prognosis and all the patients (except for one) with both conditions died within 2 years of the ARF episode.

In general, preexisting chronic uremia decreased patient’s half-life survival by a factor of five, when compared with patients with normal renal function; ARF did not significantly worsen the underlying renal insufficiency. Before and 1 month after ARF the mean plasma creatinine was 193 and 227 μmol/L, respectively (P = NS). Regular hemodialysis was only required in two patients 3 years after a complete recovery of ARF and there is no evidence that progression of uremia was altered. At variance with these results, Devoy et al18 described irreversible deterioration in renal function associated with ACE inhibitor therapy in a group of 15 patients with extrarenal vascular disease, of whom 13 had preexisting renal impairment. Nine required dialysis and four who remained dialysis dependent died within 4 weeks of presentation. Patients with NIDDM had a poorer prognosis, especially those with preexisting chronic renal failure. The presence of diffuse microangiopathy is a likely explanation for these results.

In conclusion, the administration of ACE inhibitors in patients with hypertension or severe heart failure may cause ARF in the presence of any condition that will induce acute hypotension. In older patients, dehydration caused by intermittent vomiting and diarrhea is more likely to occur and to produce hemodynamic instability. Acute tubular necrosis occurs more frequently with protracted hypotension. Bilateral renal artery stenosis or stenosis in the artery of a solitary functioning kidney was less frequent than postulated intrarenal diffuse microangiopathy. On clinical grounds, renal impairment caused by ACE inhibitors was totally reversible, and did not induce progressive deterioration in renal function, whether or not the patient had preexisting chronic renal failure. Considering the overall good renal prognosis of ARF in this setting, renal biopsy is not required, even in cases requiring hemodialysis because of acute tubular necrosis. The risk of inducing ARF in patients receiving ACE inhibitors can be minimized by using the smallest effective dose, avoiding agents liable to lower glomerular perfusion pressure. Hypotension and dehydration must be avoided when using diuretics.

REFERENCES


