Effect of the Angiotensin-converting Enzyme Inhibitor Enalapril on Post-transplant Erythrocytosis

Seiji MARUBAYASHI, Hiroyuki YAMAMOTO, Satoshi SHIBATA, Yasuhiro FUDABA, Yoshihiro MIYATA, Kazuyuki FUKUMA, Kazuro OKADA, Takao HINOI, Masahiro IKEDA, Takashi MAEDA, Yoshiro OSHIRO and Kiyohiko DORI

The Second Department of Surgery, Hiroshima University School of Medicine, 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan

ABSTRACT

Post-transplant erythrocytosis (PTE) is increasingly recognized as a complication of kidney transplantation. In this study we report the effect of the angiotensin-converting enzyme (ACE) inhibitor enalapril on hematocrit (Ht) and erythropoietin in four patients with PTE. Four renal allograft recipients with Ht greater than 51% were studied. Treatment was initiated with enalapril administered orally at a dose of 2.5 mg/day. All the patients had an increase of hemoglobin (Hb) (17.7 ± 0.64 g/dl), Ht (54.5 ± 1.29 %) and red blood cell count (REC) (584 ± 19.2 × 10^12/µl). All patients responded to enalapril in 8 weeks with a significant decrease of Hb, Ht, and REC. In one patient, the downward trend was more rapid and sustained, and treatment had to be discontinued to prevent the development of anemia. Serum erythropoietin showed normal in all four patients and remained unchanged during the study, even after discontinuation of enalapril treatment. Serum creatinine remained relatively stable throughout the study. These results suggest that PTE may not be dependent upon circulating erythropoietin and that enalapril treatment may be an effective treatment of PTE without renal dysfunction.

Key words: Erythrocytosis, Renal transplantation, Angiotensin converting enzyme inhibitor

MATERIALS AND METHODS

Four renal allograft recipients with Ht greater than 51% were studied. No evidence for secondary polycythemia was found in any of the patients based on clinical features, a pulmonary function test, and transplant ultrasound examinations. The cause of end-stage renal disease was chronic glomerulonephritis in three patients and immunoglobulin A nephropathy in one patient (Table 1). Treatment was initiated with enalapril (Renivase, Banyu, Tokyo, Japan) administered orally at a dose of 2.5 mg/day. All patients were on a standard maintenance immunosuppressive regime of cyclosporine, steroid, and azathioprine, mizoribine or RS 61443. All patients had a stable renal function (mean serum creatinine 1.35 ± 0.25 mg/dl). Arterial blood gas showed O2 saturation above 96%. No patient had hepatic dysfunction, renal artery stenosis, or iron depletion. Serum erythropoietin was measured by a radioimmunoassay (RIA) using antihuman urine erythropoietin antibody (Mitsubishi-kagaku Kit erythropoietin, RIA). Ht, hemoglobin (Hb), red blood cell count (RBC) and serum creatinine were measured by standard laboratory methods. All data, unless otherwise stated, are presented as means ± SD. Statistical
Table 1. Transplant erythrocytosis

<table>
<thead>
<tr>
<th>No.</th>
<th>Gender/Age</th>
<th>Cause of renal failure</th>
<th>Transplant Type</th>
<th>Duration (months)</th>
<th>Pre-trial Systolic BP/diastolic BP (mmHg)</th>
<th>8 weeks Systolic BP/diastolic BP (mmHg)</th>
<th>Erythropoietin (mU/ml)</th>
<th>Pre-trial</th>
<th>8 weeks</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>M/45</td>
<td>CGN</td>
<td>LR</td>
<td>23</td>
<td>120/90</td>
<td>100/60</td>
<td>34.2</td>
<td>27.6</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M/21</td>
<td>CGN</td>
<td>LR</td>
<td>10</td>
<td>142/78</td>
<td>100/70</td>
<td>14.3</td>
<td>13.1</td>
<td>mild hypotension</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M/48</td>
<td>CGN</td>
<td>CAD</td>
<td>6</td>
<td>110/70</td>
<td>100/78</td>
<td>11.9</td>
<td>21.5</td>
<td>none</td>
<td></td>
</tr>
</tbody>
</table>

PTE onset occurs at a median of 16 months after renal transplantation (6 months to 25 months) (Table 1). All the patients had an increase of Hb (17.7 ± 0.64 g/dl), Ht (54.5 ± 1.29 %) and RBC (584 ± 19.2 × 10^4/µl) (Fig. 1). The median PTE period prior to enalapril therapy was 9.8 months (1 month to 21 months). One of four patients had mild hypertension requiring calcium channel blocker. All patients responded to enalapril in 8 weeks with a significant decrease of Hb, Ht, and RBC (Fig. 1). Most patients exhibited a time-dependent drop in Ht as the treatment continued, although the rate and pattern of drop varied. In one patient (No. 1), the downward trend was more rapid and sustained, and treatment had to be discontinued to prevent the development of anemia (Fig. 2). In another patient, treatment was discontinued due to mild hypotension (No. 3). The rate of Ht rebound following the discontinuation of enalapril also varied from patient to patient (Fig. 2). In patient No. 1, in whom Ht was measured within 4 weeks after the discontinuation of treatment, Ht promptly rebounded back within this short interval, while in another patient the recovery was more gradual (No. 3). Serum erythropoietin showed normal in all four patients (19.5 ± 10.1 mU/ml; normal range: 12.5 to 34.5 mU/ml) and remained unchanged during the study (21.6 ± 6.19 mU/ml), even after discontinuation of enalapril treatment. Mean serum creatinine at onset of PTE was 1.35 mg/dl and it remained relatively stable throughout the study (mean Cr; 1.34 mg/dl). No venesections were performed during the study and no thromboembolic episodes occurred.

DISCUSSION

PTE has been reported in association with acute and chronic rejection, renal artery stenosis and hydronephrosis, but in most cases the pathogenesis remains poorly understood. Our study confirms previous reports on the efficacy of ACE inhibition analysis was performed by analysis of variance to compare the experimental groups. Differences were considered to be statistically significant if the p value was less than 0.05.
in lowering the Ht in post-renal transplant patients who developed erythrocytosis\textsuperscript{1,2,3,8}. It is known to occur with well-matched kidneys with good function and higher pre-transplant Ht\textsuperscript{4,10,12}. Some studies suggest that increased circulating levels of erythropoietin are present in PTE.

In the current analysis, PTE occurred most frequently in the first year post-transplant. Wickre et al\textsuperscript{8} reporting on 53 patients with PTE noted an incidence of 17.3\%, with a mean time of onset post-transplant of 17 months (range 3–90 months). A similar line of evidence was also reported by Glicklich et al\textsuperscript{6}. We did not perform red cell mass and plasma volume studies to confirm the presence of true erythrocytosis prior to starting our study. These investigations are not routinely performed on our unit prior to treatment of patients with an elevated Ht. In addition, patients with relative erythrocytosis (stress erythrocytosis) due to reduced plasma volume rather than true erythrocytosis may also have an increased risk of thromboembolic complications and thus treatment is still warrant-ed\textsuperscript{1}.

Several reports have shown that administration of the ACE inhibitor enalapril to patients with PTE effectively reduced the levels of erythropoietin and Ht\textsuperscript{5,12,38}. The mechanism whereby ACE inhibitors decrease the erythropoietin and Ht in patients with PTE is not well known; however, three possible mechanisms are suggested. First, ACE inhibitors have been shown to increase renal plasma flow, thus, the hypoxic stimulus to erythropoietin formation might be diminished. Second, decreased renal oxygen consumption by ACE inhibitors might also reduce the stimulus to erythropoietin production. Third, angiotensin II may exert a direct stimulatory effect on erythropoietin production leading to a reduced formation under ACE inhibition\textsuperscript{13,37}. Animal studies have shown angiotensin II infusion to cause a rise in plasma erythropoietin levels\textsuperscript{9}. Hypoxia and renin cause an increase in erythropoietin levels in rats, which is abolished by an ACE inhibitor but still occurs if angiotensin II is also infused\textsuperscript{8}. However, as shown in the present study, there are patients in whom the Ht level decreases after enalapril administration independent of changes in the circulating concentration of erythropoietin. In addition, the Ht level increased again after withdrawal of enalapril with no change in the erythropoietin level. These results suggest that PTE may not be dependent upon circulating erythropoietin. A number of cytokines and growth factors other than erythropoietin have been shown to affect erythropoiesis\textsuperscript{9,11,23}. Interleukin-3 and granulocyte-macrophage colony stimulating factor have been demonstrated to have stimulatory effects on erythropoiesis\textsuperscript{12,29}, whereas tumor necrosis factor-\alpha has an inhibitory effect on red-cell precursor proliferation and differentiation which is believed to have an important role in the pathogenesis of anemia associated with chronic inflammatory disease\textsuperscript{30}. It is possible that the effect of ACE inhibitors in PTE may be mediated via one or more of these systems, though this remains unproved at present\textsuperscript{5}.

In summary, we have shown that ACE inhibitor therapy is an effective treatment of PTE without renal dysfunction. However, one patient developed anemia which necessitates frequent monitoring of the Ht during treatment. The exact mechanisms underlying the beneficial effect of ACE inhibitors on PTE should be further investigated.

(Received May 26, 1998)
(accepted July 30, 1998)

REFERENCES


