Angiotensin-converting enzyme inhibitor-induced anemia and treatment for erythrocytosis in renal transplant recipients

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Erythrocytosis is not rare in renal transplant recipients, and phlebotomy is still the main treatment. Recently, the occurrence of angiotensin-converting enzyme (ACE) inhibitor induced anemia in patients on chronic hemodialysis and in renal transplant recipients has been reported. We herein report 5 transplant recipients whose hematocrit levels decreased while taking ACE inhibitors, including 2 patients treated with ACE inhibitors for erythrocytosis. The individual mean hematocrit values ranged from 35.0% to 54.7% before treatment and from 27.6% to 42.0% after treatment. The hematocrit level in the 2 patients with erythrocytosis decreased from 54.7% to 39.8% and 47.5% to 27.6%, respectively. Anemia improved after discontinuation or dosage reduction of the drugs. The patients were given the same immunosuppressive drugs, and had good renal function. ACE inhibitor-induced conspicuous anemia was not observed in the transplant recipient who received a kidney from a twin sibling and had not been taking any immunosuppressive drugs, nor in the 8 other patients with diabetes mellitus or chronic glomerulonephritis who served as controls. We conclude that ACE inhibitor-induced anemia may frequently arise in an immunosuppressed state. Based on these events, the ACE inhibitor can be used as a potent drug for erythrocytosis in post-transplant recipients.

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Key words: renal transplantation, erythrocytosis, anemia, angiotensin-converting enzyme inhibitor

Introduction

Angiotensin-converting enzyme (ACE) inhibitors are widely used in the treatment of hypertension, and congestive heart failure. Hypertension in many transplant patients is refractory to treatment, often requiring high doses of three or four drugs. Hypertension is more common when native kidneys are in situ because they are the source of hypersecretion of renin. The ACE inhibitors are particularly important in the management of posttransplant hypertension [1]. However, the occurrence of ACE inhibitor induced anemia in renal transplant recipients treated for hypertension has been reported [2–5].

On the other hand, erythrocytosis is a common complication of renal transplantation, afflicting 4% to 17% of allograft recipients [6, 7]. A phlebotomy is still the main treatment for erythrocytosis, and more than 20% of the renal recipients who developed erythrocytosis showed evidence of mild or major embolic events despite repeated phlebotomies [6].

We encountered renal transplant recipients who developed persistent anemia following treatment with ACE inhibitors for hypertension. The previous reports concerning anemia induced by ACE inhibitor in renal transplant patients and our clinical experiences led us to treat posttransplant erythrocytosis with ACE inhibitors. We herein report posttransplant patients who showed anemia while taking ACE inhibitors, including 2 patients treated with ACE inhibitors for erythrocytosis.

Patients and Methods

Between May 1990 and July 1993, 8 patients were treated with ACE inhibitors for hypertension, proteinuria or erythrocytosis. Of these 8 patients, 3 were excluded because ACE inhibitor treatment commenced from the early posttransplant period. The remaining 5 patients

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(4 males and 1 female) were included in this study. Clinical characteristics of the 5 patients are shown in Table 1. The patients were aged between 27 and 48 years (mean age 36.0 years). All 5 patients had received living-related renal transplantation, of whom 4 received treatment with enalapril and 1 with alacepril. The etiology of renal failure was chronic glomerulonephritis (CGN) in 1, gouty nephropathy in 1, and unknown in 3. Four patients were receiving prednisone, azathioprine and cyclosporine. One patient had no immunosuppressive drugs during the period because of having a renal transplantation from a twin sibling. The clinical conditions of all patients were stable in renal transplant function as measured by the plasma creatinine concentration, with no evidence of gastrointestinal bleeding.

Red blood cell (RBC), hemoglobin, and hematocrit values were assessed before, during, and after ACE inhibitor-treatment, whereas serum erythropoietin (EPO) levels were only determined when necessary. Blood pressure and serum creatinine were checked at 2-week intervals.

**Control group**

Eight patients who were treated by enalapril for proteinuria were evaluated as controls. The clinical characteristics of the patients are shown in Table 2. The cause of proteinuria was CGN in 4, diabetes mellitus in 3, and single kidney due to a nephrectomy for tuberculosis in 1. All renal functions measured by plasma creatinine concentration were normal.

**Statistics**

The results are expressed as mean values ± SD. Statistical analysis was made by paired t test. A statistical significant level was defined as p < 0.05.

**Results**

The individual mean hematocrit values before treatment ranged from 35.0% to 54.7% and after treatment from 27.6% to 42.0% (Fig. 1a). No episodes of clinically apparent rejection were noted in any of the patients, and no significant change in serum creatinine level, leukocyte

### Table 1. Clinical characteristics of transplant recipients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/ Gender</th>
<th>Etiology of renal failure</th>
<th>——ACE inhibitor therapy——</th>
<th>Immunosuppressant (mg/day)</th>
<th>Creatinine (mg/dl)</th>
<th>Erythropoietin (ng/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dose (mg/day)</td>
<td>Duration (months)</td>
<td>pretreatment</td>
<td>posttreatment</td>
</tr>
<tr>
<td>32/M</td>
<td>Unknown</td>
<td>enalapril 10→5</td>
<td>PD:10</td>
<td>1.1</td>
<td>1.1</td>
<td>21.9–23.9</td>
</tr>
<tr>
<td>27/F</td>
<td>CGN</td>
<td>enalapril 5</td>
<td>PD:10</td>
<td>1.1</td>
<td>0.8</td>
<td>27.2</td>
</tr>
<tr>
<td>48/M</td>
<td>Gouty nephropathy</td>
<td>enalapril 5</td>
<td>PD:10</td>
<td>1.4</td>
<td>1.4</td>
<td>N/A</td>
</tr>
<tr>
<td>43/M</td>
<td>Unknown</td>
<td>enalapril 5</td>
<td>None</td>
<td>0.8</td>
<td>0.8</td>
<td>9.1–20.8</td>
</tr>
<tr>
<td>30/M</td>
<td>Unknown</td>
<td>alacepril 50</td>
<td>PD:8.75→7.5</td>
<td>1.1</td>
<td>1.1</td>
<td>22.0</td>
</tr>
</tbody>
</table>

CGN: chronic glomerulonephritis, PD: prednisolone, CS: cyclosporine, AZ: azathioprine

N/A: not applicable

### Table 2. Clinical characteristics of patients with proteinuria

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/ Gender</th>
<th>Etiology of proteinuria</th>
<th>——ACE inhibitor therapy——</th>
<th>Creatinine (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dose (mg/day)</td>
<td>Duration (months)</td>
</tr>
<tr>
<td>T.O.</td>
<td>50/F</td>
<td>CGN</td>
<td>enalapril 5</td>
<td>5</td>
</tr>
<tr>
<td>T.K.</td>
<td>48/M</td>
<td>CGN</td>
<td>enalapril 5</td>
<td>6</td>
</tr>
<tr>
<td>S.Y.</td>
<td>43/F</td>
<td>CGN</td>
<td>enalapril 5</td>
<td>5</td>
</tr>
<tr>
<td>T.F.</td>
<td>55/F</td>
<td>CGN</td>
<td>enalapril 5</td>
<td>3</td>
</tr>
<tr>
<td>M.K.</td>
<td>72/M</td>
<td>Diabetic nephropathy</td>
<td>enalapril 5</td>
<td>7</td>
</tr>
<tr>
<td>K.C.</td>
<td>74/F</td>
<td>Diabetic nephropathy</td>
<td>enalapril 10→5</td>
<td>9</td>
</tr>
<tr>
<td>T.C.</td>
<td>28/F</td>
<td>Diabetic nephropathy</td>
<td>enalapril 5</td>
<td>8</td>
</tr>
<tr>
<td>Y.S.</td>
<td>64/M</td>
<td>Post rt. nephrectomy</td>
<td>enalapril 5</td>
<td>5</td>
</tr>
</tbody>
</table>

CGN: chronic glomerulonephritis.
or platelet counts occurred during the administration of the ACE inhibitor. In the control group, the individual mean hematocrit values before enalapril treatment ranged from 33.6% to 43.6% and after treatment from 32.1% to 43.1% (Fig. 1b). The mean ± SD hematocrit of kidney transplant recipients with ACE inhibitor-treatment significantly decreased from 44.1 ± 4.5% to 34.6 ± 6.3%, however, the change in hematocrit of the control group was not significant (Fig. 1c).

Patient M. Y.
A 32-year-old man received a living-related kidney transplant in 1990. Maintenance immunosuppressive medication consisted of 10 mg prednisolone, 100 mg azathioprine, and 175 mg cyclosporine daily. Hypertension was treated with manidipine hydrochloride and clonidine hydrochloride. The RBC, hemoglobin, and hematocrit values prior to enalapril treatment were $524 \times 10^4/\text{ul}$, 17.7 g/dl, and 54.7%, individually. Enalapril 10 mg had been given daily for proteinuria and erythrocytosis since May 6, 1993. The hematocrit and serum creatinine concentrations in relation to enalapril treatment are shown in Fig. 2. Within 70 days since beginning the enalapril treatment, the hematocrit level was decreased to 39.8%. After reducing the dose of enalapril to 5 mg daily, the hematocrit level gradually increased. Peripheral EPO concentrations during enalapril treatment ranged from 21.9 to 23.9 ng/ml (normal 12.0–32.0 ng/ml).

Patient K. T.
A 30-year-old man received a living-related kidney transplant in 1989. Maintenance immunosuppressive medication consisted of 8.75 mg prednisolone, 75 mg azathioprine, and 175 mg cyclosporine daily until July, 1993. Hypertension was controlled with a combination of nifedipine and prazosin hydrochloride. He had several phlebotomies when the hematocrit was over 52%. The RBC, hemoglobin, and hematocrit values immediately prior to alacepril treatment were $474 \times 10^4/\text{ul}$, 15.5 g/dl, and 47.3%. Alacepril was given at a dose of 50 mg daily for erythrocytosis since April 1, 1993. The hematocrit and serum creatinine concentrations in relation to alacepril treatment are shown in Fig. 3. Fifty-seven days after beginning the alacepril treatment, he received 200 mg allopurinol daily for hyperuricemia. Within 4 months, the hematocrit decreased to 25.6%. For progressive anemia, the doses of azathioprine and allopurinol were reduced to 50 mg and 100 mg daily, respectively. The peripheral EPO concentration was 22.0 ng/ml while taking alacepril. Anemia was improved after discontinuation of alacepril.

Other patients
The other 3 patients had enalapril-treatment for hypertension prior to the treatment for erythrocytosis of patients M. Y. and K. T. Their hematocrit values decreased from 35.0% to 29.3%, 40.0% to 34.4%, and 43.3% to 42.0%, respectively. The hematocrit
Hematological toxicity has been observed as a side effect of ACE inhibitor therapy in renal transplant recipients. Patient K.G. who had not been administered immunosuppressive drugs showed a minimal decrease of hematocrit with enalapril treatment. The EPO concentration of this patient was relatively lower than that of other patients taking immunosuppressive drugs.

**Discussion**

Hematological toxicity has been observed as a side effect following the introduction of the prototype compound, captopril, which has a sulfhydryl group. Neutropenia and agranulocytosis are the main concerns in the use of captopril, especially in immunosuppressed patients with collagen vascular disease and renal insufficiency [4, 8, 9]. Alacepril also has the sulfhydryl component. Enalapril has been synthesized without the sulfhydryl group in an attempt to minimize certain adverse reactions, including hematological disturbance. However, a small decrease in hematocrit and hemoglobin frequently occurs during the use of enalapril. A report from the U.S. indicated that 0.1% of patients treated with enalapril developed anemia that resulted in discontinuation of the drug [10]. There have been several reports of decrease in hematocrit and hemoglobin following enalapril treatment in patients with normal kidney function and, more frequently, in hemodialysis and renal transplant patients [2–5, 11, 12]. Therefore, anemia is an important side effect of ACE inhibitor therapy in renal transplant recipients.

Erythrocytosis is not a rare complication after renal transplantation. It was first described more than 20 years ago [13]. Defined as a hematocrit greater than 0.51, it appears most often within the first year after transplantation [6, 7]. Risk factors for posttransplant erythrocytosis are pretransplant hypertension, retention of native kidney, higher pretransplant hematocrit, a rejection-free course and excellent graft function [7], however, the mechanism of this phenomenon remains controversial. Recent reports described that patients with erythrocytosis had inappropriately high systemic levels of EPO [14–16]. This EPO secretion arises mostly from the native kidney, and rarely from the transplanted kidney [15, 16]. Under normal conditions, after an initial high EPO output, a negative feedback mechanism slows down EPO production. In contrast, a defective feedback mechanism with increased EPO production exists at least in some of patients with erythrocytosis [17]. It is important to emphasize, however, not all patients have high levels of EPO [17, 18]. While the levels of EPO elevated in some cases, the levels were lower or normal in others and that posttransplant erythrocytosis is not necessarily associated with elevated serum EPO levels [18]. In our limited experience, the EPO concentration was normal in patients taking the ACE inhibitor. Several mechanisms may exist in the pathogenesis of erythrocytosis after renal transplantation.

Therapy for erythrocytosis is necessary because increased blood viscosity due to erythrocytosis is associated with increased evidence of thromboembolic episodes and hypertension [19]. Repeated phlebotomies, chronic theophylline administration, and native kidney nephrectomy are involved [6, 17, 20, 21]. Aeberhard et al. [14] suggested an observation period of one year with iterative phlebotomies if hematocrit values indicated the need for this approach. They described phlebotomy itself as a contributing factor underlying EPO stimulation if erythrocytosis continues. In fact, our patient K.T. had repeated phlebotomies for over one year before receiving alacepril treatment. Aminophylline, a nonselective adenosine antagonist, was found to decrease significantly the production of EPO [17]. Nephrectomy is performed to reduce EPO production from native kidneys [20, 21].

Based on our own experiments and previous reports of anemia caused by ACE inhibitors in renal transplant recipients and dialysis patients, ACE inhibitors were used to reduce the hematocrit level in our 2 patients with erythrocytosis. In 1990, Islam et al. [18] reported the effect of captopril on erythrocytosis after renal transplantation. Recently, several reports concerning the effect of enalapril on erythrocytosis have been published [16, 19, 22, 23]. There are many possible mechanisms by which ACE inhibitor may correct posttransplant erythrocytosis. ACE inhibitors, having the property to increase renal blood flow and postglomerular vasodilation, may improve renal ischemia and reduce EPO production [18]. In this way, ACE inhibitors may induce posttransplant erythrocytosis. Furthermore, participation of the renin-angiotensin system in erythropoiesis has been suggested. Renin and angiotensin-II increased the production of EPO by causing vasoconstriction and consequently, hypoxia in the rat experiment [24]. In human with end-stage renal disease, angiotensin-II activity was found to correlate with the EPO level [11]. These findings confirm the hypothesis that the ACE inhibitor could worsen the degree of anemia through suppression of angiotensin-II.

![Fig. 3. Hematocrit and serum creatinine levels in relation to alacepril treatment of patient](image-url)
and EPO production.

Grossmann et al. [25] reported that severe anemia was found in renal transplant recipients caused by concomitant therapy with azathioprine and ACE inhibitors. They concluded that the combination of these two drugs should probably be avoided. However, not only azathioprine, but also the immunosuppressive state may have contributed to the effect of the ACE inhibitor on erythropoiesis [3, 4]. In the present study, the control patients and patient K.G. without having an immunosuppressant showed a small fall in hematocrit level compared to the other 4 recipients who had been given immunosuppressive drugs including azathioprine. Because administration of ACE inhibitor to the general hypertensive population only rarely leads to substantial anemia [10], and based on our experience, it is not unreasonable to assume that the effect of ACE inhibitor on the reduction of hematocrit levels may be accelerated by an immunosuppressive condition.

There is general agreement that ACE inhibitors should be used with caution in kidney transplant recipients. This group carries a high risk of developing vascular changes (renal artery stenosis, diffuse arterial lesions caused by chronic rejection, or cyclosporine toxicity) resulting in glomerular hypotension [16]. ACE inhibitors may reduce glomerular filtration by changing the glomerular hemodynamics. Before administration of ACE inhibitors we excluded these clinical conditions in all patients. We did not observe any significant increase in plasma creatinine during ACE inhibitor-treatment. Our study supports other reports [16, 19, 22, 23] showing that the ACE inhibitor can be used safely in renal transplant recipients.

In summary, ACE inhibitor-induced anemia should be considered in renal transplant recipients with a markedly high hematocrit level prior to administration of the ACE inhibitor. The present findings proved that the ACE inhibitor can be safely and effectively used to treat post-transplant erythrocytosis. Further studies are needed to confirm the etiology of posttransplant erythrocytosis, and the mechanism of the effect of ACE inhibitors on reducing hematocrit levels.

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References