Enalapril and anemia in patients undergoing hemodialysis

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<Abstract>
We evaluated the incidence and progression of anemia in a retrospective study of 18 hemodialysis (HD) patients who were receiving enalapril maleate. Patients were divided into 2 groups based on hematocrit (Ht) changes. In Group A (n=6 patients), the Ht decreased more than 5% ; in Group B (n=12 patients), there was no significant decrease in Ht. We measured hematological parameters, and concentrations of enalapril and erythropoietin (Ep). Hemolytic and/or iron deficiency anemia were ruled out by hematologic evaluation in Group A. The Ep level was lower during treatment than pre-treatment level in Group A, whereas, there was no significant difference in this parameter in Group B.

We recommend that enalapril maleate should be used with caution in patients with a reduced Ht level associated with drug administration. We conclude that enalapril-induced anemia is provoked by the suppression of Ep production.

Introduction
Angiotensin converting enzyme inhibitor (ACEI) has been reported to be especially effective in the treatment of hypertension related to disorders of the renin-angiotensin system. In hemodialysis (HD) patients, it is a well-known fact that the long-term use of captopril1,2 or enalapril3 aggravates the anemia. We evaluated the incidence and severity of anemia in HD patients who were receiving enalapril maleate, which is a long-acting ACEI.

Subjects and Methods
This study was conducted in 18 patients undergoing maintenance HD. They were 12 males and 6 females with the mean age of 49 ranging from 26 to 70 years. None of the patients had had nephrectomy. A single daily oral dose of enalapril maleate, ranging from 1.25 to 7.5 mg/day was administered to control hypertension. Patients were accepted in the study according to the following criteria : 1) receiving maintenance hemodialysis therapy ; 2) blood pressure elevation over 160/95 mmHg ; 3) administered enalapril maleate for 8 weeks or more. We excluded the cases who was administrated erythropoietin agents.

The subjects were subdivided into two groups according to their hematocrit (Ht), retrospectively : Group A : Ht decreased more than 5% (n=6) ; Group B : no significant decrease in Ht (n=12). RBC and hematocrit (Ht) were measured every two weeks before each dialysis treatment. Erythropoietin (Ep) were measured by radioimmunoassay (RIA) before and during enalapril administration in groups A and B, using preserved plasma. The serum concentrations of enalapril maleate were measured by RIA during enalapril therapy. In group A, haptoglobin (Hp), direct and indirect Coombs’ test, vitamin B12, vitamin B12 and folic acid were measured during enalapril treatment to eliminate the possibility of hemolytic anemia, iron deficiency anemia or pernicious anemia. Vitamin B12, vitamin B12, and folic acid were administrated to all subjects at the end of HD treatment to supplement the loss induced by hemodialysis.
Results are expressed as mean±SEM and analyzed by paired and non-paired Student’s t-test.

Results

In the profiles of 6 patients in group A, the age ranged from 35 to 70 (49.8±13.8) years and the duration of HD ranged from 2 to 10 (3.8±3.2) years. The dosages of enalapril maleate ranged from 2.5 to 7.5 (4.79±1.66) mg/day and duration of treatment ranged from 8 weeks to 20 weeks. The causes of end-stage chronic renal failure were chronic glomerulonephritis in one, diabetes mellitus in three, nephrosclerosis in one and unknown etiology in one. On the other hand, in the profiles of 12 patients in group B, the age ranged from 26 to 77 (48.6±14.6) years and the duration of HD ranged from 1 to 9 (5.1±2.7) years. The dosages of enalapril ranged from 1.25 to 7.5 (3.54±1.39) mg/day and duration of treatment ranged from 36 weeks to 1 year. The causes of end-stage chronic renal failure were chronic glomerulonephritis in six, diabetes mellitus in three, nephrosclerosis in one and unknown etiology in two.

Administration of enalapril maleate once daily caused the significant decrease in systolic and diastolic blood pressure in both groups A and B (from 171/98 to 150/76mmHg, p<0.05 and from 174/102 to 154/82mmHg, p<0.05, respectively). There was no remarkable change in body weight gain on each HD therapy during enalapril maleate treatment in group A and B (from 2.5±1.0 to 2.3±1.3kg, from 2.6±1.5 to 2.0±1.7kg, respectively). In all patients in group A whose anemia worsened, the change of Ht is shown in Fig. The Ht decreased from a mean of 28.0±2.4% to 20.2±1.6%, a significant decline (p<0.01) during enalapril maleate therapy. After discontinuance of enalapril maleate, the Ht returned to pre-treatment levels reversibly within two to six months. In contrast, in group B, the values of Ht were not significantly changed. There was no significant difference in the level of pre-treatment Ht between the two groups.

Enalapril maleate lacks biological activity and the diacid metabolite is active compound. Plasma concentrations of the diacid metabolite and enalapril maleate in group A and B were not significantly different. There was no significant correlation between the extent of Ht decrease and the dose of enalapril maleate. During the treatment Ep levels were lower than that in the pre-treatment in group A (p<0.05). After the discontinuation of the drug, Ep levels restored to the pre-treatment levels. In group B, there was not a significant difference in Ep levels between pre-treatment and during treatment. Pre-treatment Ep level did not differ significantly among the groups (Table).

In group A, Coombs’ test was negative, Hp did not decrease and vitamin B₆, vitamin B₁₂, or folic acid concentration exceeded normal values in all cases during enalapril treatment.

Discussion

In HD patients, the long-term use of captopril and enalapril has been known to aggravate anemia. In the present study, we evaluated enalapril maleate, which is a long-acting ACEI. In patients with chronic renal failure, the clearance of enalapril maleate from the serum is delayed because renal clearance is the major route of elimination. It is important to note that the renal clearance of enalapril maleate and its diacid metabolite in patients with chronic renal failure is significantly lower than that in normal controls. Therefore, excessive levels of enalapril can occur in HD patients.

In the present study, anemia worsened in 6 of 18 patients (33%) during treatment with enalapril maleate. The Ht level continued to decrease during treatment and the Ht returned to pre-treatment levels within 2~6 months after the drug was stopped.

There was no difference between in Group A and B the dose of enalapril maleate and the plasma concentration of the diacid metabolite and enalapril. Plasma
concentrations of the diacid metabolite in both groups were much higher than the minimal level to needed for maximal blockage of plasma angiotensin converting enzyme activity\(^7\). Therefore, the possibility exists that factors other than the overdose enalapril lead to anemia in HD patients.

In the present study, we recognized that significant difference between group A and B in the level of Ep and the suppression of Ep production led to anemia in patients given enalapril maleate. Some authors reported that the reduction of renal ischemia by ACEI might partly explain the reduction of Ep production\(^8,9\). Anagnostou et al\(^{10}\) reported that renin and A-II increased the production of Ep by causing vasoconstriction and consequently, hypoxia in the rat experiment. We speculated that (1) enalapril–induced anemia was related to the suppression of Ep production, (2) the effect of enalapril maleate on the production of Ep differed between group A and B and (3) an Ep supplement may be useful therapy in the patients with suppressed Ep production in Group A.

The following conclusions can be drawn from this study. First, the anemia worsened in 6 of 18 HD patients (33%) during enalapril maleate therapy. The suppression of Ep production led to anemia in these patients. Second, since anemia induced by enalapril maleate is reversible, the drug should be discontinued in the patients with progressive anemia.

### Table. Changes in BP, Ht, and serum concentration of Ep, and diacid metabolite and total enalapril by enalapril maleate.

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<th>Group A</th>
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<tr>
<td></td>
<td>treatment</td>
<td>treatment</td>
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<tr>
<td>BP (mmHg)</td>
<td>171/98</td>
<td>150/76*</td>
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<tr>
<td>Ht (%)</td>
<td>28.0±2.4</td>
<td>20.2±1.6**</td>
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<tr>
<td>Diacid</td>
<td>208.2±152.0</td>
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<tr>
<td>metabolite (ng/mL)</td>
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<tr>
<td>Total enalapril</td>
<td>231.7±152.8</td>
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<td>(ng/mL)</td>
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<td>Ep (mU/mL)</td>
<td>21.7±2.78</td>
<td>18.1±4.06*</td>
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*: p<0.05 (compared with pre-treatment level)
**: p<0.01 (compared with pre-treatment level)
#: p<0.05 (compared with group A)

References