High dose enalapril impairs the response to erythropoietin treatment in haemodialysis patients

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Abstract

Background. The resistance to recombinant human erythropoietin (rHuEpo) therapy in haemodialysis (HD) patients has multifactorial aetiologies: erythropoietin insufficiency, dialysis insufficiency, iron deficiency, and secondary hyperparathyroidism. Angiotensin-converting enzyme (ACE) inhibitors induce anaemia in patients with essential hypertension, congestive heart failure, chronic renal insufficiency, and renal transplants. Data exist suggesting that ACE inhibitors impair erythropoiesis in HD patients. Therefore the aim of this study was to investigate the impact of enalapril on rHuEpo requirement.

Methods. In the present prospective non-randomized study of 12 months, we compared the effects of enalapril and nifedipine on rHuEpo requirement in 40 hypertensive patients receiving rHuEpo for more than 6 months on maintenance haemodialysis. Twenty normotensive rHuEpo-dependent patients served as a control group. All patients with severe hyperparathyroidism or iron deficiency were excluded.

Results. The mean (±SD) haemoglobin concentration was >10 g/dl in all groups. The mean weekly rHuEpo dose increased in the enalapril group (P < 0.0001 vs before) and remained constant in the nifedipine and control groups (P = NS vs before). Statistically, there was no differences with regard to iPTH levels, dialysis parameters, iron status, and underlying renal diseases among all groups.

Conclusion. High-dose enalapril increases rHuEpo requirement and should be reserved for dialysis patients with hypertension uncontrollable with other antihypertensive medications or dialysis patients with cardiac failure.

Key words: anaemia; enalapril; erythropoietin requirement; haemodialysis

Introduction

Anaemia, a consistent clinical feature of end-stage renal disease, is efficiently treated with recombinant human erythropoietin (rHuEpo) [1–4]. Development and aggravation of hypertension has been documented as the most relevant side-effect of rHuEpo treatment with an incidence of up to 30 to 40% of treated patients [1,2]. Risk factors for hypertension include pre-existing hypertension, severe anaemia at initiation, rapid increment in haematocrit levels, high intravenous rHuEpo doses, and the presence of native kidneys [2]. The mechanisms involved in the development of hypertension secondary to rHuEpo include loss of hypoxic dilatation and increases in blood viscosity, blood volume, activation of the renin-angiotensin system, endothelin levels, vascular calcium uptake, or platelet-dependent mitogenic action [2]. In the majority of haemodialysis patients, rHuEpo-induced hypertension is successfully controlled by water and sodium removal during dialysis, subcutaneous administration of rHuEpo, lower target haemoglobin levels and progressive attainment of this target, or conventional antihypertensive therapy [1–4].

Enalapril maleate, a non-sulph-hydryl angiotensin-converting-enzyme (ACE) inhibitor, is a pro-drug whose pharmacological activity is dependent on its de-esterification in the liver to its active diacid metabolite, enalaprilat. Enalaprilat excretion occurs primarily via the urine and secondarily via the bile. The mean peak serum concentrations of enalapril and enalaprilat are greater and delayed in patients with chronic renal insufficiency. Steady-state enalaprilat serum levels are not achieved in haemodialysis (HD) patients because HD effectively reduces enalaprilat serum levels with a dialysis clearance of enalaprilat amounting to more than 50 ml/min [5]. A strong link exists between enalapril serum levels and ACE inhibition, but not with the haemodynamic effects. Thus the optimum dosage of enalapril has not been determined [5]. However, 2.5 mg/day, 5 mg/day, or 5–40 mg/day of enalapril were successfully used to reduce blood pressure in HD patients without significant untoward events [5,6].

ACE inhibitors are widely used in the treatment of hypertension, left ventricular dysfunction, diabetic nephropathy, and renal post-transplant erythrocytosis, and in preventing the progression of established renal disease of diverse causes [7–23]. Anaemia has been reported as a side-effect of ACE inhibitors in normal
volunteers and in patients with essential hypertension [7], heart failure [8], chronic renal insufficiency [9], ESRD on maintenance HD [10], or renal transplants [14].

However, little is known about the impact of high-dose enalapril on rHuEpo requirement in HD patients with anaemia. Therefore, the present prospective, unblinded, non-randomized study was designed to evaluate rHuEpo dosing in rHuEpo-dependent HD patients with hypertension treated with enalapril or nifedipine, compared to normotensive patients treated with rHuEpo who served as a control group for 12 months of follow-up.

Subjects and methods

We evaluated patients from five haemodialysis centres who had been on maintenance haemodialysis for more than 6 months and who were treated with antihypertensive drugs and rHuEpo for more than two months with a haemoglobin concentration ≥10 g/dl.

We excluded all patients with folate or vitamin B12 deficiency, serum aluminium >40 μg/l, serum ferritin <200 μg/l, intact parathyroid hormone (iPTH) >300 pg/ml, active bleeding lesions, haematological diseases, active untreated infections, malignancies or other causes of inflammation, and those taking bone-marrow suppression medications. All patients were matched with respect to age, sex, subjacent renal disease, duration on HD, dialysis parameters, intact parathyroid hormone levels, haemoglobin concentrations, iron status, and rHuEpo dose before starting this study.

Forty hypertensive patients fulfilled these criteria, and 20 rHuEpo-dependent patients without hypertension served as a control group. Patients were divided into one of three classifications based on treatment regimen: those who had enalapril plus rHuEpo (n = 20, enalapril group); nifedipine plus rHuEpo (n = 20, nifedipine group); and rHuEpo (n = 20, control group). The initial doses of enalapril and slow-release nifedipine were 5 and 20 mg/day respectively. The doses of enalapril and nifedipine were increased to adequately control the (BP <140/90 mmHg). When maximal doses (20 mg/day for enalapril or 40 mg/day for nifedipine) of initial medications were reached, atenolol was added in order to control the high blood pressure more adequately.

Intravenous iron infusion (average dosage 50–100 mg/week) was used to maintain serum ferritin ≥400 μg/l and transferrin saturation ≥25%, and the rHuEpo dose was adjusted monthly to maintain haemoglobin >10 g/dl.

Dialysis programme

All patients underwent conventional haemodialysis three times a week (range 4–5 h/session), using bicarbonate-buffered dialysate and cellulosic membrane, and were managed to maintain their Kt/V (urea) >1 and protein catabolic rate (PCR) at 1–1.2 g/kg/day (Table 2).

Measurements

Haemoglobin level, haematocrit, absolute reticulocyte count, serum ferritin, and transferrin saturation were monitored monthly. Intact parathyroid hormone (iPTH), serum albumin by nephelometry, and serum aluminium were measured quarterly. Kt/V (urea) according to Daugirdas [26] and protein catabolic rate (PCR) according to Gotch and Sargent [27] were calculated monthly.

Statistical analysis

The end-point of the study was the effect of enalapril or nifedipine on rHuEpo requirements in haemodialysis patients over time. Statistical analysis was performed with Chi-square or Fisher’s test as appropriate. All data are presented as means ± standard deviation. Univariate analysis was used to identify differences among the three group. All P values were two-tailed and a P value ≤0.05 was considered statistically significant.

Results

Patient characteristics and laboratory data are summarized in Tables 1 and 2. The majority of patients in all groups had ESRD secondary to diabetic nephropathy, hypertensive nephropathy, or glomerular nephropathy (Table 1). One patient in the enalapril group was omitted due to cough attributed to ACE inhibitor therapy, and two patients in the nifedipine group were excluded because of pitting oedema of the lower extremities attributed to nifedipine in the first case and a severe inflammatory syndrome in the second. Two patients in the control group received renal grafts and were also excluded.

Fifteen patients were treated with 20 mg of enalapril; four patients with 10 mg of enalapril, and 18 patients were on 40 mg of nifedipine. Four patients in the enalapril group and five patients in the nifedipine group also received atenolol to maintain blood pressure within the normal range.

There was no statistically significant difference among the three groups in terms of age, sex, duration on haemodialysis, blood pressure, Kt/V, PCR, serum albumin, iPTH, iron status, absolute reticulocyte count, or haemoglobin values. Average haemoglobin concentrations were 10.6 ± 0.4 g/dl, 10.7 ± 0.2 g/dl, and 10.8 ± 0.3 g/dl before and 10.5 ± 0.3 g/dl.

Table 1. Clinical data (mean ± SD)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Enalapril group</th>
<th>Nifedipine group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>46.3 ± 21.7</td>
<td>48.2 ± 23.1</td>
<td>52.1 ± 14.7</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>11/9</td>
<td>10/10</td>
<td>10/10</td>
</tr>
<tr>
<td>Cause of renal failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Duration on HD (months)</td>
<td>34 ± 29</td>
<td>36 ± 27</td>
<td>29 ± 41</td>
</tr>
<tr>
<td>Pretrial weight (kg)</td>
<td>56.9 ± 31.2</td>
<td>55.3 ± 25.1</td>
<td>57.3 ± 35.8</td>
</tr>
<tr>
<td>12-month weight (kg)</td>
<td>56.4 ± 31.3</td>
<td>55.1 ± 25.6</td>
<td>57.8 ± 31.9</td>
</tr>
<tr>
<td>Pretrial SBP (mmHg)</td>
<td>177 ± 14</td>
<td>172 ± 16</td>
<td>125 ± 13</td>
</tr>
<tr>
<td>12-month SBP (mmHg)</td>
<td>132 ± 19</td>
<td>130 ± 17</td>
<td>124 ± 8</td>
</tr>
<tr>
<td>Pretrial DBP (mmHg)</td>
<td>91 ± 15</td>
<td>92 ± 14</td>
<td>77 ± 5</td>
</tr>
<tr>
<td>12-month DBP (mmHg)</td>
<td>80 ± 13</td>
<td>78 ± 14</td>
<td>78 ± 4</td>
</tr>
</tbody>
</table>
Table 2. Basic biological data and dialysis parameters (mean ± SD)

<table>
<thead>
<tr>
<th>Enalapril group</th>
<th>Nifedipine group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretrial haemoglobin (g/dl)</td>
<td>10.6 ± 0.4</td>
<td>10.7 ± 0.2</td>
</tr>
<tr>
<td>Pretrial serum ferritin (µg/l)</td>
<td>10.5 ± 0.3</td>
<td>10.4 ± 0.2</td>
</tr>
<tr>
<td>12-month haemoglobin (g/dl)</td>
<td>10.2 ± 0.2</td>
<td>10.1 ± 0.2</td>
</tr>
<tr>
<td>12-month serum ferritin (µg/l)</td>
<td>475 ± 321</td>
<td>457 ± 356</td>
</tr>
<tr>
<td>Pretrial transferrin saturation (%)</td>
<td>31.4 ± 9.5</td>
<td>29.7 ± 5.6</td>
</tr>
<tr>
<td>Pretrial parathyroid hormone (pg/ml)</td>
<td>31.4 ± 9.5</td>
<td>29.7 ± 5.6</td>
</tr>
<tr>
<td>12-month transferrin saturation (%)</td>
<td>34.6 ± 14.7</td>
<td>32.8 ± 12.1</td>
</tr>
<tr>
<td>12-month parathyroid hormone (pg/ml)</td>
<td>245 ± 147</td>
<td>234 ± 121</td>
</tr>
<tr>
<td>Pretrial serum albumin (g/l)</td>
<td>41.1 ± 3.2</td>
<td>40.2 ± 3.4</td>
</tr>
<tr>
<td>12-month serum albumin (g/l)</td>
<td>42.3 ± 5.4</td>
<td>41.4 ± 4.1</td>
</tr>
<tr>
<td>Pretrial Kt/V (urea)</td>
<td>1.31 ± 0.24</td>
<td>1.39 ± 0.21</td>
</tr>
<tr>
<td>12-month Kt/V</td>
<td>1.32 ± 0.29</td>
<td>1.35 ± 0.23</td>
</tr>
<tr>
<td>Protein catabolic rate (g/kg)</td>
<td>1.29 ± 0.19</td>
<td>1.24 ± 0.21</td>
</tr>
<tr>
<td>12-month protein catabolic rate (g/kg)</td>
<td>1.26 ± 0.21</td>
<td>1.23 ± 0.18</td>
</tr>
</tbody>
</table>

10.4 ± 0.2 g/dl, and 10.3 ± 0.2 g/dl at 1 year in the enalapril, nifedipine, and control groups respectively. Figure 1 compares the mean weekly rHuEpo dose subcutaneously administered to the three groups. To maintain a similar haemoglobin level, the enalapril group received 84 ± 14 IU/kg/week before and 138 ± 10 IU/kg/week at 1 year (P < 0.0001 vs before), 86 ± 7 IU/kg/week before and 77 ± 5 IU/kg/week at 1 year in the nifedipine group (P < 0.0001 vs enalapril at 1 year), and 79 ± 11 IU/kg/week before and 80 ± 9 IU/kg/week in the control group (P < 0.0001 vs enalapril at 1 year).

However, there were no statistically significant differences between the nifedipine group and control group (P = NS).

The mean monthly individual intravenous ferric hydroxide polymaltose dose was 212 ± 61 mg in the enalapril group, 194 ± 53 mg in the nifedipine group, and 197 ± 47 mg in the control group. Again, there were no statistically significant differences among the three groups (P = NS). None of the patients received transfusions during the study.

Discussion

In this study we have shown that high-dose enalapril can lead to substantial and sustained increase in rHuEpo requirement of haemodialysis populations. The mean rHuEpo dose increased significantly after 1 year of treatment with ACE inhibitors (P < 0.0001). To maintain the same level of haemoglobin, the group of patients treated with enalapril needed a higher dose of rHuEpo than the group of patients treated with nifedipine and the control group over the 1-year study period (P < 0.0001). rHuEpo requirement did not significantly differ between the nifedipine group and control group. Further, the mean rHuEpo dose in enalapril group returned to the baseline value 4 months after discontinuing enalapril (results not shown).

There are many causes for rHuEpo resistance in HD patients, such as functional iron deficiency, secondary hyperparathyroidism, aluminium overload, dialysis insufficiency, blood loss, or inflammatory syndrome [5, 6]. In our study we excluded all patients with any one of these conditions. Good iron status was assessed by transferrin saturation >25% and serum ferritin >400 µg/l, aluminium overload was avoided by using calcium carbonate as the only phosphate chelator, and adequate dialysis was defined by Kt/V > 1, PCR > 1, and serum albumin > 35 g/l. In addition, there was no statistical difference regarding iPTH levels, iron status parameters (hypochromic RBC not measured), haemoglobin levels, and indicators of adequate dialysis among the three groups throughout the trial.
The target haemoglobin level for anaemia treatment was 10–11 g/dl which is the case for the majority of European studies [4,30], while in the USA the upper target haemoglobin limit has been extended to more than 12 g/dl [2]. Adequate dialysis parameters may improve renal failure anaemia and consequently reduce rHuEpo need in HD patients, explaining the relatively low rHuEpo dose of the control and nifedipine groups, similar to that reported by others [31].

We acknowledge that this study has several limitations. First, we studied a relatively small number of patients without randomization, but all patients were matched before beginning the study, the data were all registered prospectively and analysed in comparison with the other groups during the treatment time of 12 months, and factors affecting erythropoiesis other than enalapril were excluded before and during the study. Secondly, it could be argued that the detrimental effect of enalapril therapy on erythropoiesis is related to a high-dose regimen of this agent. To the best of our knowledge, the enalapril dose in the main previous studies in HD patients was within a range of 2.5 to 40 mg/day [7,9,13,23,25]. Although unlikely, this may partially explain the discrepancies between other reports using a relatively lower dose of enalapril [23,25] and our results. However, we cannot rule out the possibility that higher doses of enalapril might have had a harmful effect on red blood cell production in our subjects. Thirdly, the negative effect on erythropoiesis may be specific to enalapril and may not apply to other types of ACE inhibitors. Therefore it is necessary to conduct additional studies with other ACE inhibitors.

The mechanism by which ACE inhibitors alter erythropoiesis remains a subject of debate. In rat studies, angiotensin II infusion produces an increment in plasma erythropoietin levels [28] which is abolished by ACE inhibitors [29]. Angiotensin II may directly or indirectly, via renal hypoxia caused by the vasoconstriction, increase erythropoietin release [15]. However, other studies showed that ACE inhibitors could lower haemoglobin concentrations regardless of plasma erythropoietin levels [16,17,21]. Additionally, Perazella et al. [16] found that erythrocyte survival and plasma volume are not influenced by ACE inhibitors; excluding haemolysis or haemodilution as causing ACE-inhibitor-associated anaemia.

To explain the negative effect of ACE inhibitors on erythrocyte production, one may speculate that ACE inhibitors produce, either an alteration in the control of erythropoiesis with reduced sensitivity to rHuEpo, or an alteration in erythropoietic regulatory factors other than erythropoietin [15]. Recently it has been shown that captopril massively increases the tetrapeptide n-acetyl-seryl-aspartyl-lysyl-proline (Ac-SKDP) plasma levels, which prevents the recruitment of pluripotent haematopoietic stem cells and normal early progenitors into S-phase of the cell cycle by maintaining the Go-phase [32]. Unfortunately we did not measure this tetrapeptide in our patients.

In our subjects one may posit that high-dose enalapril enhances the plasma level of Ac-SKDP and/or lowers renal and extrarenal endogenous erythropoietin production; explaining the refractoriness to rHuEpo therapy.

We conclude that high-dose enalapril increases rHuEpo requirement and should be reserved for HD patients with high blood pressure resistant to other antihypertensive medications or those with congestive heart failure, unless there are specific indications to the contrary.

References

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Received for publication: 25.6.97
Accepted in revised form: 1.12.97