Therapeutic use of continuous subcutaneous infusion of recombinant human erythropoietin in malnourished predialysis anemic patients with diabetic nephropathy

Motoi Sohmiya, Toshiaki Kakiba and Yuzuru Kato

First Division, Department of Medicine, Shimane Medical University, Izumo 693, Japan

(Correspondence should be addressed to M Sohmiya)

Abstract

We compared the effect of recombinant human erythropoietin (rhEPO) administration by continuous s.c. infusion (CSI) with that of a weekly bolus s.c. injection (SBI) in five malnourished predialysis anemic patients with diabetic nephropathy. rhEPO was either continuously infused at a flow rate of 6000 IU per week (36 IU/h) (CSI group) or injected s.c. at a dose of 6000 IU once a week (SBI group) for 4 weeks, in a cross-over comparative study with a washout period of 4 weeks. Mean ± s.d. plasma EPO levels increased from a basal value of 18.0 ± 4.9 mIU/ml to a steady state value of 70.5 ± 38.9 mIU/ml 2 weeks after the start of CSI of rhEPO (P < 0.05). Increases in reticulocyte count above the basal value were greater in the CSI group than the SBI group at 3 weeks after the start of treatment (0.94 ± 0.35% vs −0.03 ± 0.46%, P < 0.05). Increases in Hb concentration above the basal value were much greater in the CSI group than the SBI group at 4 weeks after the start of treatment (2.56 ± 0.77 g/dl vs 0.28 ± 0.62 g/dl, P < 0.05). These findings suggest that rhEPO administration by CSI is more effective than by SBI for improving anemia in malnourished predialysis patients with diabetic nephropathy.

European Journal of Endocrinology

Introduction

Erythropoietin (EPO) production is induced by hypoxic stimuli and modulated by various hormones, nutritional factors and cytokines (1). Chronic renal failure (CRF) is accompanied by anemia in which serum EPO levels are low relative to blood hemoglobin (Hb) concentrations (2–4). CRF patients with diabetic nephropathy are often malnourished and accompanied by a number of metabolic abnormalities, water retention and diabetic vascular complications (5).

Recombinant human (rh)EPO administration is useful for improving not only anemia but also the quality of life in both dialysis and predialysis patients (6–9). rhEPO therapy has been delivered using a number of different dosages and administration methods in anemic patients with CRF during the predialysis period (10–12). However, malnourished patients with diabetic nephropathy often show a poor response to EPO administration.

In the present study, we compared the effect of continuous s.c. infusion (CSI) of rhEPO with that of s.c. bolus injection (SBI) in malnourished predialysis anemic patients with diabetic nephropathy.

Materials and methods

Patients

Five patients with diabetic nephropathy in the predialysis period were studied; their clinical characteristics are shown in Table 1. All patients were diagnosed as having non-insulin-dependent diabetes mellitus with diabetic nephropathy. The mean ± s.d. age was 69.4 ± 9.04 years (range 58–82). Body mass index (BMI), serum albumin and plasma insulin-like growth factor-I (IGF-I) levels were low in all the patients, suggesting undernourishment. Blood pressure and plasma glucose levels were well controlled during the study by diet alone (case 3) or in combination with insulin therapy (cases 1, 2, 4 and 5), although case 3 had been treated with insulin before good control had been gained by diet alone after renal function was impaired.

Study protocol

All patients were admitted to our hospital during the experimental period. Their diet was restricted to a total calorie intake of 30 kcal/kg of ideal body weight, protein...
A clinical study was conducted to evaluate the effectiveness of subcutaneous erythropoietin (rhEPO) administration in treating diabetic nephropathy. The study was conducted in Japan DPC Co., Chiba, Japan, and involved 5 patients with diabetic nephropathy. Informed consent was obtained from all patients. Plasma EPO levels were measured every 2 weeks. Serum creatinine and BUN levels were markedly elevated above normal, whereas blood Hb, serum albumin, iron, and TIBC levels were decreased in all subjects (Table 2). These patients also had decreased plasma IGF-I concentration and BMI, indicating malnutrition, although plasma glucose and HbA1c were well controlled. There were no statistical differences in these variables between the CSI group and the SBI group. No differences in plasma EPO levels were observed between the two groups before the treatment.

Statistical analysis

Statistical analysis of the data was performed by one-way ANOVA in combination with Student’s t-test. P < 0.05 was considered significant.

Results

Serum creatinine and BUN levels were markedly elevated above normal whereas blood Hb, serum albumin, iron and TIBC levels were decreased in all subjects (Table 2). These patients also had decreased plasma IGF-I concentration and BMI, indicating malnutrition, although plasma glucose and HbA1c were well controlled. There were no statistical differences in these variables between the CSI group and the SBI group. No differences in plasma EPO levels were observed between the two groups before the treatment.

Table 1

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age (years)</th>
<th>Sex</th>
<th>BMI (kg/m²)</th>
<th>HbA1c (%)</th>
<th>IGF-1 (ng/ml)</th>
<th>Blood pressure (mmHg)</th>
<th>Diabetic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>1</td>
<td>74</td>
<td>M</td>
<td>18.3</td>
<td>6.9</td>
<td>95</td>
<td>124</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>M</td>
<td>19.9</td>
<td>6.9</td>
<td>87</td>
<td>158</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>82</td>
<td>F</td>
<td>18.6</td>
<td>6.6</td>
<td>89</td>
<td>134</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>M</td>
<td>19.8</td>
<td>7.2</td>
<td>120</td>
<td>138</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>M</td>
<td>16.0</td>
<td>5.5</td>
<td>66</td>
<td>142</td>
<td>74</td>
</tr>
<tr>
<td>Mean</td>
<td>69.4</td>
<td></td>
<td>18.5</td>
<td>6.6</td>
<td>91.4</td>
<td>139.2</td>
<td>64.0</td>
</tr>
<tr>
<td>SD</td>
<td>9.04</td>
<td></td>
<td>1.58</td>
<td>0.66</td>
<td>19.4</td>
<td>12.5</td>
<td>13.0</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th></th>
<th>CSI group</th>
<th>SBI group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>7.52 ± 0.55</td>
<td>8.20 ± 0.42</td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td>0.56 ± 0.29</td>
<td>0.93 ± 0.48</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>4.00 ± 1.70</td>
<td>4.78 ± 0.75</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>55.0 ± 26.7</td>
<td>60.5 ± 16.6</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.10 ± 0.64</td>
<td>3.40 ± 0.76</td>
</tr>
<tr>
<td>Fe (µg/dl)</td>
<td>57.8 ± 12.5</td>
<td>63.5 ± 27.2</td>
</tr>
<tr>
<td>TIBC (µg/dl)</td>
<td>198.6 ± 4.6</td>
<td>200.5 ± 24.6</td>
</tr>
<tr>
<td>Ferritin (µg/l)</td>
<td>158.2 ± 140.3</td>
<td>177.6 ± 120.8</td>
</tr>
<tr>
<td>Erythropoietin (mIU/ml)</td>
<td>18.0 ± 4.9</td>
<td>22.1 ± 6.6</td>
</tr>
</tbody>
</table>

BUN, blood urea nitrogen.
of rhEPO treatment in the CSI group (Fig. 2, lower panel). On the other hand, in the SBI group, Hb concentration had only increased at 3 weeks, by 0.43 ± 0.48 g/dl. The increase in Hb concentration above the basal value at 4 weeks was higher in the CSI group than in the SBI group (P < 0.05).

Serum iron levels were slightly but not significantly decreased at 2 weeks in both groups. Serum TIBC, ferritin, creatinine and BUN levels were not changed in either group and neither was blood pressure or body weight.

Discussion

EPO is mainly secreted from the perivascular endothelial cells or fibroblasts in the kidney into the circulation (13). The synthesis of EPO is stimulated by hypoxia in the circulation (14). In patients with CRF, however, EPO secretion is relatively reduced compared with blood Hb concentrations (2). Furthermore, in patients with CRF due to diabetic nephropathy, anemia is also affected by metabolic disorders. EPO treatment is often ineffective for diabetic nephropathy (15, 16), but the precise reason for this blunted effect is not clear.

rhEPO treatment has been reported to be useful for improving anemia in predialysis patients with CRF (11, 12) without progression to renal failure (17, 18). Accumulating evidence suggests that SBI of rhEPO is more effective than i.v. administration, as SBI achieves the same effect at lower doses, although there have been some conflicting results (10, 19).

We first compared the effect of rhEPO administration by two different routes, CSI and SBI, in predialysis anemic patients with diabetic nephropathy. Plasma EPO levels were maintained by CSI within the upper normal limit in these subjects, whereas they superphysiologically increased but rapidly returned to basal values in the SBI group when the same total dose of rhEPO was given. Blood Hb concentration and reticulocyte count were more effectively improved by CSI than by SBI. These findings are in line with the report of Pavlovic-Kentera et al. (20) that a modest increase in serum EPO (30–60 mIU/ml) was sufficient to correct anemia in hemodialysed patients.

We conclude therefore that CSI of rhEPO is more useful than SBI for improving anemia in malnourished predialysis anemic patients with diabetic nephropathy.

Acknowledgements

This work was supported in part by grants from the Ministry of Education and Culture, Japan, the Ministry of Health and Welfare, Japan, and the Foundation of Renal Disorders. We also thank Ms A Kanayama for her
technical assistance and Ms A Kawakami for her secretarial help.

References


Received 18 November 1997
Accepted 15 June 1998