Adequacy of dialysis reduces the doses of recombinant erythropoietin independently from the use of biocompatible membranes in haemodialysis patients

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Abstract

Background. The effect of the adequacy of dialysis on the response to recombinant human erythropoietin (rHuEpo) therapy is still incompletely understood because of many confounding factors such as iron deficiency, biocompatibility of dialysis membranes, and dialysis modality that can interfere.

Methods. We investigated the relationship between Kt/V and the weekly dose of rHuEpo in 68 stable haemodialysis (HD) patients (age 65 ± 15 years) treated with bicarbonate HD and unsubstituted cellulose membranes for 6–343 months (median 67 months). Inclusion criteria were HD for at least 6 months, subcutaneous rHuEpo for at least 4 months, transferrin saturation (TSAT) > 20%, serum ferritin > 100 ng/ml, and haematocrit (Hct) level targeted to 35% for at least 3 months. Exclusion criteria included HBsAg and HIV positivity, need for blood transfusions or evidence of blood loss in the 3 months before the study, and acute or chronic infections. Hct and haemoglobin (Hb) levels were evaluated weekly for 4 weeks; TSAT, serum ferritin, Kt/V, PCRn, serum albumin (sAlb), and weekly dose of rHuEpo were evaluated at the end of observation. No change in dialysis or therapy prescription was made during the study.

Results. The results for the whole group of patients were: Hct 35 ± 1.2%, Hb 12.1 ± 0.6 g/dl, TSAT 29 ± 10%, serum ferritin 204 ± 98 ng/ml, sAlb 4.1 ± 0.3 g/dl, Kt/V 1.33 ± 0.19, PCRn 1.11 ± 0.28 g/kg/day, weekly dose of rHuEpo 123 ± 76 U/kg. Hct did not correlate with Kt/V, whereas rHuEpo dose and Kt/V were inversely correlated (r = −0.49; P < 0.0001). Multiple regression analysis with rHuEpo as dependent variable confirmed Kt/V as the only significant variable (P < 0.0002). Division of the patients into two groups according to Kt/V (group A, Kt/V ≤ 1.2; group B, Kt/V ≥ 1.4), showed no differences in Hct levels between the two groups, while weekly rHuEpo dose was significantly lower in group B than in group A (group B, 86 ± 33 U/kg; group A, 183 ± 95 U/kg, P < 0.0001).

Conclusions. In iron-replete HD patients treated with rHuEpo in the maintenance phase, Kt/V exerts a significant sparing effect on rHuEpo requirement independent of the use of biocompatible synthetic membranes. By optimizing rHuEpo responsiveness, an adequate dialysis treatment can contribute to the reduction of the costs of rHuEpo therapy.

Keywords: adequacy; anaemia; biocompatibility; Epo dose; haemodialysis

Introduction

The main pathogenetic factor causing anaemia in chronic renal failure is the reduced synthesis of erythropoietin (Epo) by the diseased kidneys [1]. The introduction of recombinant human Epo (rHuEpo) therapy in the last 10 years has dramatically changed anaemia treatment. Its great efficacy in correcting anaemia in a dose-dependent manner has been demonstrated both in the original [2] and subsequent clinical trials [3,4]. Many factors are known to blunt the optimal response to rHuEpo therapy in these patients: iron deficiency, acute or chronic infections, hyperparathyroidism, and aluminium toxicity [5–7]. So far, the contribution of the dialysis dose per se on the rHuEpo dose needed to correct anaemia has not been fully addressed even if this is an important issue for many reasons. Inadequate dialysis is still a prominent clinical problem and contributes to increased morbidity and mortality in haemodialysis patients [8,9]. The direct effect of the adequacy of dialysis on the response to rHuEpo therapy is incompletely understood due to many confounding factors such as iron deficiency, dialysis modality, and biocompatibility of dialysis membranes [10] that can interfere. In order to separate the effect of dialysis adequacy per se from the effects of dialysis modality
and membrane biocompatibility on the response to rHuEpo therapy, we investigated the relationship between the dose of rHuEpo and the dose of dialysis in a group of 68 haemodialysis (HD) patients on stabilized rHuEpo therapy with adequate iron stores, treated with bicarbonate dialysis and unsubstituted cellulosic membranes.

Patients and methods

Sixty-eight uraemic patients (43 men, 25 women), mean age 65 ± 15 years (range 20–89 years) on regular chronic HD for 6–343 months (median 67 months) were selected from a total population of 167 patients treated at our Institution. All of them were treated by bicarbonate HD thrice weekly with 1.3–1.8 m² unsubstituted cellulosic membranes (Fresenius Hemoflow E 35; Bellco NT 1808). The duration of the dialysis procedure ranged from 180 to 270 min (median 240 min). Blood flow rate ranged from 250 to 350 ml/min (median 300 ml/min). Dialysate flow rate was 500 ml/min. Dialysate fluid composition was sodium 140 mmol/l, potassium 2–3 mmol/l, calcium 1.5–1.75 mmol/l, bicarbonate 35 mmol/l, acetate 4 mmol/l and glucose 1 g/l.

Selection criteria

Regular chronic HD treatment for at least 6 months before the study, treatment with subcutaneous (s.c.) rHuEpo for at least 4 months, transferrin saturation (TSAT) ≥ 20%, serum ferritin levels > 100 ng/ml, stable haematocrit (Hct) levels targeted between 32 and 36% for at least 3 months before the study.

Exclusion criteria

Refusal by the patient to participate, known blood dyscrasia or haemoglobinopathy, micro or macrocytosis (mean corpuscular volume < 80 or > 100 µm³), HIV and HBsAg positivity, treatment for any infection with drugs known to affect erythropoiesis, including androgens and angiotensin-converting enzyme (ACE) inhibitors, systemic disease, nephropathy, cachexia. Patients were also excluded if any of the following events had occurred in the 3 months preceding the study: blood loss (gastrointestinal bleeding and/or blood loss from the vascular access), blood transfusions, hospitalizations, infection (fever and leukocytosis).

The selected patients were all those that satisfied the inclusion/exclusion criteria referred above.

The underlying renal diseases were: chronic glomerulonephritis in 11 patients, tubulointerstitial nephritis in 14, diabetic nephropathy in five, nephroangiosclerosis in 13, polycystic kidney disease in nine, and undiagnosed nephropathy in 16; 65/68 patients received regular i.v. iron supplements such as iron gluconate, (mean dose 75 ± 15 mg/week) at the end of HD.

Study protocol

Patients enrolled in the study were prospectively followed for 4 weeks, during which the following parameters were analysed: haemoglobin (Hb), hematocrit (Hct), transferrin saturation (TSAT), serum ferritin, Kt/V, normalized protein catabolic rate (PCrn), serum albumin, C-reactive protein (CRP), serum intact PTH (iPTH), weekly rHuEpo dose/body weight.

Urea kinetic modelling (UKM) was performed mid-week at the start and at the end of the study. Samples for BUN were drawn from the arterial side of the AV fistula at the start, 15 min after the end, and at the beginning of the next dialysis session and processed by auto analyser. The duration of each dialysis session, duration of the elapsed times between dialyses, intra-dialytic weight loss and inter-dialytic weight gain were recorded. All patients were anuric or very oliguric (daily urine volume < 100 ml/24 h). The values for Kt/V and PCrn were the mean of the two tests performed at the start and at the end of observation. Although not recommended by the recently published European Best Practice Guidelines for the management of anaemia in patients with chronic renal failure [11], we decided to evaluate Hb and Hct levels in post-dialysis in order to minimize the differences due to hyperhydration. These parameters were performed weekly and determined by Coulter counter model STKS. iPTH was determined by an immunoradiometric assay for intact parathyroid hormone (Allegro, Nichols Institute, San Juan Capistrano, CA, USA; normal values: 10–65 pg/ml). Serum albumin concentrations were measured by nephelometric assay, other biochemical parameters were assayed by standard laboratory methods. Patients were managed to attain and maintain a Hct level of 35% (Hb level 12 g/dl). During the 4 weeks of follow up no changes in rHuEpo dose or dialytic schedule were made.

Measurements

The following equations were used to calculate the volume of distribution of urea (V), Kt/V, urea generation rate (G), and protein catabolic rate (PCrn). V was calculated according to the formula of Watson and Watson [12]. Kt/V was calculated according to Daugirdas [13]. G, C3*V2 – C2*V1/Tid PCrn, (9.35G + 0.294V1)/(V1/0.58).

C1 and C2 are BUN concentrations at the start and 15 min after the end of dialysis; C3 is the BUN concentration at the beginning of the next dialysis; Td is the dialysis time; Tid is the inter-dialysis time. V1 is the volume of distribution of urea at the end of dialysis; V2 is the volume of distribution of urea at the beginning of the next dialysis session.

Statistics

All the data are expressed as mean ± SD. Linear regression analysis, multiple regression analysis and Student t test for unpaired data were adopted for statistical evaluation. Significant differences were defined by P < 0.05.

Results

The results for the whole group of patients were Kt/V 1.33 ± 0.19 (range 1.02–1.81), Hb concentrations 12 ± 0.6 g/dl, Hct 35 ± 1.2% (range 31–39%), TSAT 29 ± 10%, serum ferritin concentrations 204 ± 98 ng/ml, PCrn 1.11 ± 0.28 g/kg BW/day, serum albumin concentrations 4.1 ± 0.3 g/dl, CRP 7 ± 2 mg/l, serum iPTH 189 ± 142 pg/ml (range 11–490 pg/ml). The mean weekly rHuEpo dose was 123 ± 76 U/kg/week (range 34–354 U/kg/week).
Dialysis adequacy and rHuEpo doses in haemodialysis patients

Discussion

More than 90% of patients with renal anaemia respond in a dose-dependent manner to rHuEpo administration [14] although some of them may require larger doses. Due to the great efficacy of rHuEpo therapy in correcting anaemia and the prominent role of iron deficiency in reducing the rate of response to rHuEpo treatment [15], the role of the dose of dialysis per se on the response to rHuEpo treatment has been largely underestimated. Moreover, recent preliminary results from the United States Renal Data System [16] indicate a correlation between dialysis dose and Hct levels in HD patients treated with rHuEpo. However, in this observational study the Hct was also higher in patients treated with synthetic compared with non-synthetic dialysers, making the evaluation of the separate effects of dialysis adequacy and dialysis membrane very problematic. In order to separate the effect of dialysis adequacy per se from the effect of membrane biocompatibility, we have selected a cohort of patients on regular HD treatment with unsubstituted cellulose membranes, on maintenance s.c. rHuEpo treatment.

Fig. 1. Correlation between Kt/V and weekly Epo dose.

Hct did not correlate with Kt/V ($P=\text{NS}$), whereas rHuEpo dose and Kt/V were inversely correlated ($P<0.0001$) (Figure 1).

Table 1 shows the results of the multiple regression analysis. Considering the weekly rHuEpo dose as dependent variable, it was evident that the only parameter that correlated with the rHuEpo dose was Kt/V.

Table 2 shows the results of the comparison of Hct and weekly rHuEpo dose after the division of the patients into two groups according to Kt/V values (group A, Kt/V ≤1.2; group B, Kt/V ≥1.4). Hct did not differ between the two groups, while weekly rHuEpo dose was significantly higher in patients in group A compared with those in group B.

Table 1. Multiple regression analysis. Dependent variable: weekly rHuEpo dose

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>$t$ statistic</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kt/V</td>
<td>308.85</td>
<td>1.76</td>
<td>0.002</td>
</tr>
<tr>
<td>PCRn</td>
<td>−165.30</td>
<td>−3.28</td>
<td>0.194</td>
</tr>
<tr>
<td>Age</td>
<td>0.16</td>
<td>0.24</td>
<td>0.81</td>
</tr>
<tr>
<td>Dialysis age</td>
<td>0.00</td>
<td>−0.02</td>
<td>0.98</td>
</tr>
<tr>
<td>S. albumin</td>
<td>22.6</td>
<td>0.81</td>
<td>0.42</td>
</tr>
<tr>
<td>iPTH</td>
<td>−0.02</td>
<td>−0.37</td>
<td>0.71</td>
</tr>
<tr>
<td>CRP</td>
<td>−0.80</td>
<td>−0.22</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Table 2. Comparison between haematocrit and weekly rHuEpo dose after the division of the patients into two groups according to Kt/V values

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Kt/V ≤1.2)</td>
<td>(Kt/V ≥1.4)</td>
<td></td>
</tr>
<tr>
<td>patients</td>
<td>patients</td>
<td></td>
</tr>
<tr>
<td>($n=21$)</td>
<td>($n=18$)</td>
<td></td>
</tr>
<tr>
<td>Hct (%)</td>
<td>35 ±1.5</td>
<td>NS</td>
</tr>
<tr>
<td>rHuEpo dose</td>
<td>183 ±95</td>
<td>0.0001</td>
</tr>
<tr>
<td>(U/kg/Week)</td>
<td>35 ±1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>86 ±33</td>
<td></td>
</tr>
</tbody>
</table>

Our data confirm and expand the observations by Ifudu et al. [19] although with some important differences. These authors showed that Hct and the dose of dialysis, evaluated by the urea reduction ratio (URR), were directly correlated. However, unlike our study, patients were treated with a fixed dose of rHuEpo and Hct was an independent variable. In addition, a group of patients were assigned to standard (URR = 61%) or...
high-dose (URR = 72%) dialysis while receiving a fixed rHuEpo dose. While at the start of observation Hct was similar in both groups, Hct at the end of observation was significantly higher in the high-dose group compared to the other. However, the increased dose of dialysis was achieved by changing both the dialysis membrane and the duration of dialysis treatment. For this reason the study design made it difficult to distinguish between the effects of dose of dialysis per se and dialyser type. In our study this problem has been completely overcome by the fact that all patients were dialysed with unsubstituted celluloseic membranes, and the dialysis schedule was not changed during the study. Moreover, as previously described, we made every possible effort to exclude patients with known causes of resistance to rHuEpo treatment, in particular those with iron depletion, aluminium overload, severe hyperparathyroidism, acute or chronic infections as evaluated by the absence of red blood cell microcytosis, serum intact PTH levels > 500 ng/ml, and elevated RCP levels.

For this reason our study population is clearly a positively selected population. However, even under these circumstances, a very strong influence of Kt/V on the dose of rHuEpo to be given to maintain the target Hct was evident also in patients with Kt/V values ≥ 1.4, well above the recommended goal for dialysis adequacy [18]. This strongly suggests a significant role for some dialysable low-molecular-weight inhibitor/s of erythropoiesis, like spermine and/or polyamine, in determining such a relative resistance to rHuEpo [20,21].

In conclusion, our study clearly indicates that in HD patients treated with rHuEpo in the maintenance phase, Kt/V exerts a significant sparing effect on rHuEpo requirement independent of the use of biocompatible synthetic membranes. By optimizing rHuEpo responsiveness, an adequate dialysis treatment can contribute to a reduction of the costs of rHuEpo therapy.

References


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