Original Article

Regular low-dose intravenous iron therapy improves response to erythropoietin in haemodialysis patients

J. E. Taylor, N. Peat, C. Porter and A. G. Morgan
Renal Unit, Nottingham City Hospital, Nottingham, UK

Abstract

Background. Erythropoietin (Epo) is an effective but expensive treatment for anaemia in patients with chronic renal failure. Hyporesponsiveness to Epo, particularly in haemodialysis patients, is most commonly due to a functional iron deficiency, which is difficult to monitor reliably.

Methods. Forty-six stable haemodialysis patients, receiving Epo therapy, were commenced on regular low-dose intravenous iron (sodium ferric gluconate complex) at a dose of 62.5 mg/5 ml given as a slow injection post-dialysis twice weekly, weekly, or fortnightly, according to their serum ferritin levels. Haemoglobin, serum ferritin, Epo dose, and iron dose were measured at 6-weekly intervals over a 6-month period.

Results. At the beginning of the study, 12 patients in the group had ferritin levels of less than 100 µg/l, and were thus considered to potentially have an absolute iron deficiency. The study group was therefore split into two subgroups for the purpose of analysis, i.e. the 12 patients with ferritin levels of less than 100 µg/l at the start of the study or ‘low ferritin group’, and the remaining 34 patients with ferritin levels of greater than 100 µg/l at the start of the study or ‘normal ferritin group’.

In the low ferritin group (n=12), intravenous iron therapy increased serum ferritin levels, and produced a significant rise in haemoglobin, and a significant reduction in Epo dose. (Ferritin pre-iron, median (range) 68 (20–96) µg/l; post-iron, 210.5 (91–447) µg/l, P<0.003, Wilcoxon. Haemoglobin pre-iron, 10.05 (8.2–11.9) g/dl; post-iron, 11.0 (9.9–11.9) g/dl, P<0.03. Epo dose pre-iron, 9000 (4000–30000) i.u./week; post-iron, 6000 (2000–10000) i.u./week, P<0.05.)

Similar results were obtained in the normal ferritin group (n=34) following intravenous iron therapy, with significant increases in serum ferritin levels and haemoglobin concentrations, and a significant reduction in Epo dose. (Ferritin pre-iron, 176 (103–519) µg/l; post-iron, 304.5 (121–792) µg/l, P<0.0001. Haemoglobin pre-iron, 9.85 (6.5–12.8) g/dl; post-iron: 11.25 (9.9–13.3) g/dl, P<0.0001. Epo dose pre-iron, 6000 (2000–15000) i.u./week; post-iron, 4000 (0–15000) i.u./week, P<0.005.)

Conclusion. Regular intravenous iron supplementation in haemodialysis patients improves the response to Epo therapy.

Key words: erythropoietin; intravenous iron; haemodialysis

Introduction

Recombinant human erythropoietin (Epo) is a highly effective treatment for anaemia in patients with chronic renal failure, the majority of patients responding to doses of less than 200 i.u./kg per week. The commonest cause of a poor response to Epo is the lack of an adequate supply of iron to meet the demands of enhanced erythropoiesis [1]. This is particularly a problem in haemodialysis patients, where blood losses due to dialysis, venepuncture, and gastrointestinal bleeding, may amount to up to 6 litres a year [2]. Detection of iron deficiency in these patients may be difficult, since there are no reliable markers available for clinical use. Measurement of serum ferritin, which reflects storage iron, is the most widely used test of iron deficiency, and a level of less than 100 µg/l is a good marker of absolute iron deficiency in dialysis patients. Serum ferritin levels may, however, be spuriously raised during infections and inflammatory episodes, and even when normal do not rule out the possibility of a functional iron deficiency, i.e. where there is a failure to mobilize iron stores sufficiently for erythropoiesis. Transferrin saturation determines the amount of circulating iron, but this test shows marked diurnal variation and is thus less reliable [3]. Detection of the percentage of hypochromic red cells is a good indicator of the use of iron for erythropoiesis; however, this test requires technology which is not currently available in many centres [4].
Given the drawbacks in detecting particularly functional iron deficiency, the implications are that lesser degrees of this condition may go unnoticed and result in unnecessary overuse of expensive Epo. Since the losses of iron in haemodialysis patients are probably in small amounts, but frequently, the purpose of this study was to investigate the tolerability, and impact on Epo responsiveness, of regular low-dose intravenous iron replacement.

**Subjects and methods**

Forty-six haemodialysis patients, median age 67 years (range 24–82 years), 31 male, 15 female were studied. All patients were receiving Epo therapy for anaemia solely due to renal failure, and had been on this treatment for at least 6 months, with a stable Epo dose for at least 3 months. No patient had evidence of infection, malignancy, liver disease, or any chronic inflammatory condition which may impair their response to Epo. All patients had ferritin levels of less than 600 µg/l prior to commencing treatment with intravenous iron, and had not received a blood transfusion within the preceding 6 months. All patients were taking oral iron supplements, and had not received intravenous iron in the 3 months prior to commencement of the study.

Patients were assigned to receive intravenous ferric gluconate complex 62.5 mg/5 ml (Rhône-Poulenc, Germany) twice weekly (ferritin <100 µg/l), weekly (ferritin 100–250 µg/l), or fortnightly (ferritin 250–600 µg/l), according to their serum ferritin level. The ferric gluconate complex was given as a slow injection through the fistula needle at the end of dialysis. Oral iron supplements were discontinued. Haemoglobin, serum ferritin, Epo dose, and intravenous iron dose were reviewed for each patient at 6-weekly intervals over a 6-month period. Epo doses were adjusted by plus or minus 30–50% in order to maintain haemoglobin levels of 11–13 g/dl for male patients, and 10–12 g/dl for female patients.

Table 1. Changes in haemoglobin, ferritin, erythropoietin dose and intravenous iron dose over a 6-month period of treatment in 34 patients with an initial ferritin of > 100 µg/l.

<table>
<thead>
<tr>
<th></th>
<th>Pre haemoglobin (g/dl)</th>
<th>Post haemoglobin (g/dl)</th>
<th>Pre ferritin (µg/l)</th>
<th>Post ferritin (µg/l)</th>
<th>Pre erythropoietin (x 1000 i.u./wk)</th>
<th>Post erythropoietin (x 1000 i.u./wk)</th>
<th>Pre iron (ml/wk)</th>
<th>Post iron (ml/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>9.85</td>
<td>11.25</td>
<td>176</td>
<td>204.5</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>Range</td>
<td>6.5–12.8</td>
<td>9.9–13.3</td>
<td>103–519</td>
<td>121–792</td>
<td>2–15</td>
<td>0–15</td>
<td>2.5–10</td>
<td>0–5</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.005</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Haemoglobin (g/dl)**

![Fig. 1. Changes in haemoglobin concentrations in 34 patients with initial ferritin levels of > 100 µg/l (normal ferritin group), and in 12 patients with initial ferritin levels of < 100 µg/l (low ferritin group), following 6 months treatment with intravenous iron.](image-url)
Statistical analysis

None of the measured variables could be assumed to have normal distributions, hence results are expressed as medians and ranges, and non-parametric tests (Wilcoxon rank sum tests) were used to determine statistical significance. A $P$ value of less than 0.05 was considered significant.

Results

Thirty-four patients had ferritin levels of greater than 100 μg/l (normal ferritin group), and the remaining 12 patients had ferritin levels of less than 100 μg/l (low ferritin group) at the start of the 6-month study period. In both the normal ferritin group and the low ferritin group, intravenous iron therapy was associated with significant increments in haemoglobin (Tables 1 and 2, Figure 1) and serum ferritin levels (Tables 1 and 2, Figure 2), and significant reductions in Epo dose (Tables 1 and 2, Figure 3). One patient, in the normal ferritin group, stopped Epo during the last month of the study, and required only intravenous iron to maintain a satisfactory haemoglobin. The median dose of intravenous iron at the start of the study was 5 ml twice weekly for the low ferritin group, and 5 ml weekly for the normal ferritin group. By the end of the 6-month treatment period, the median intravenous iron dose was 5 ml fortnightly for both groups (Tables 1 and 2). In the normal ferritin group, two patients had their intravenous iron discontinued during the last month of the study because their ferritin levels exceeded 600 μg/l.

In the normal ferritin group, nineteen patients had haemoglobins of less than 10 g/dl before receiving

<table>
<thead>
<tr>
<th></th>
<th>Pre haemoglobin (g/dl)</th>
<th>Post haemoglobin (g/dl)</th>
<th>Pre ferritin (μg/l)</th>
<th>Post ferritin (μg/l)</th>
<th>Pre erythropoietin (x 1000 i.u./wk)</th>
<th>Post erythropoietin (x 1000 i.u./wk)</th>
<th>Pre iron (ml/wk)</th>
<th>Post iron (ml/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>10.05</td>
<td>11.00</td>
<td>68</td>
<td>210.5</td>
<td>9</td>
<td>6</td>
<td>10</td>
<td>2.5</td>
</tr>
<tr>
<td>Range</td>
<td>8.2–11.9</td>
<td>9.9–11.9</td>
<td>20–96</td>
<td>91–447</td>
<td>4–30</td>
<td>2–10</td>
<td>5–10</td>
<td>1.25–10</td>
</tr>
<tr>
<td></td>
<td>0.03</td>
<td>0.003</td>
<td>0.003</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Changes in haemoglobin, ferritin, erythropoietin dose and intravenous iron dose over a 6-month period of treatment in 12 patients with an initial ferritin of <100 μg/l

![Graph showing changes in serum ferritin concentrations in patients with initial ferritin levels of >100 μg/l (normal ferritin group), and in patients with initial ferritin levels of <100 μg/l (low ferritin group), following 6 months treatment with intravenous iron.](image)
intravenous iron. Although there was no significant fall in Epo dose in this subgroup, haemoglobin concentrations increased significantly to over 10 g/dl in all cases (Table 3). The other 15 patients in the normal ferritin group had haemoglobins of greater than 10 g/dl at the beginning of the study. In this subgroup, there was no significant change in haemoglobin with intravenous iron supplementation, however, Epo doses decreased significantly (Table 4).

Intravenous ferric gluconate complex was well tolerated, and there were no adverse reactions in any of the patients studied. Similarly there were no disturbances in liver function tests (results not shown).

Table 3. Changes in haemoglobin, ferritin, erythropoietin dose and intravenous iron dose over a 6-month period of treatment in 19 patients with an initial ferritin of > 100 µg/l and an initial haemoglobin of < 10 g/dl

<table>
<thead>
<tr>
<th></th>
<th>Pre haemoglobin (g/dl)</th>
<th>Post haemoglobin (g/dl)</th>
<th>Pre ferritin (µg/l)</th>
<th>Post ferritin (µg/l)</th>
<th>Pre erythropoietin (×1000 i.u./wk)</th>
<th>Post erythropoietin (×1000 i.u./wk)</th>
<th>Pre iron (ml/wk)</th>
<th>Post iron (ml/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>9.00</td>
<td>11.10</td>
<td>176</td>
<td>303</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>P</td>
<td>0.0001</td>
<td>0.05</td>
<td>0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.009</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Changes in haemoglobin, ferritin, erythropoietin dose and intravenous iron dose over a 6-month period of treatment in 15 patients with an initial ferritin of > 100 µg/l and an initial haemoglobin of > 10 g/dl

<table>
<thead>
<tr>
<th></th>
<th>Pre haemoglobin (g/dl)</th>
<th>Post haemoglobin (g/dl)</th>
<th>Pre ferritin (µg/l)</th>
<th>Post ferritin (µg/l)</th>
<th>Pre erythropoietin (×1000 i.u./wk)</th>
<th>Post erythropoietin (×1000 i.u./wk)</th>
<th>Pre iron (ml/wk)</th>
<th>Post iron (ml/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>11.20</td>
<td>11.60</td>
<td>176</td>
<td>306</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>Range</td>
<td>10.1–12.8</td>
<td>9.9–12.5</td>
<td>108–387</td>
<td>204–525</td>
<td>3–12</td>
<td>0–12</td>
<td>2.5–10</td>
<td>0–2.5</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>0.0007</td>
<td>0.0007</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.009</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Intravenous iron in haemodialysis patients

Discussion

This study has shown that in haemodialysis patients receiving treatment with Epo, regular intravenous iron therapy improves the haemoglobin response with a reduction in Epo dose. Our findings are in agreement with those of Granolleras et al. [2], Nyvad et al. [5], and Sunder-Plassmann and Horl [6]. In Granolleras's study, 18 haemodialysis patients were treated with 10 mg iron dextran thrice weekly, intravenously. After 4 months, their haematocrits had risen from 29 to 31%, with a reduction in Epo dose from 66 i.u./kg per week to 46 i.u./kg per week [2]. Iron saccharate was used in the studies of Nyvad et al. [5] and Sunder-Plassmann and Horl [6], and resulted in similar reductions in Epo dosage, by as much as 70% in the latter case. Although oral iron supplementation is easier to administer, there is evidence that it is ineffective in Epo-treated dialysis patients, and that it does not compare with intravenous supplementation [7]. In any case many patients are unable to take oral iron due to gastrointestinal side-effects.

The ideal intravenous iron preparation for use in Epo-treated patients must have a chemical structure that allows it to be taken up by the reticuloendothelial system rather than being deposited in the liver parenchyma, and must not contain the slowly degradable biopolymers so that the incidence of allergic side-effects is minimal. The preparation should also be easy to administer so that large numbers of patients can be treated in a busy dialysis unit. Following the withdrawal of iron dextran by one manufacturer, and the lack of readily available iron saccharate in the UK at the time this study was performed, we used ferric gluconate complex. We found it to be well tolerated, effective, and easy to administer, since it was given as a slow injection at the end of dialysis rather than an infusion requiring dilution in saline and an infusion pump. Experimental studies in mice have indicated that iron saccharate preparations are probably the safest and most effective form of intravenous iron [8], although these require dilution and infusion in current commercially available forms.

In conclusion, regular low-dose intravenous iron supplementation in haemodialysis patients improves the response to Epo. In our patients the average saving on the cost of Epo was £14.43 per patient per week, with an average expenditure on ferric gluconate complex of £1.60 per patient per week.

References


Received for publication: 18.9.95
Accepted in revised form: 29.1.96