Intravenous iron for CAPD populations: proactive or reactive strategies?

Donald Richardson, Cherry Bartlett, Helen Jolly and Eric J. Will

Department of Renal Medicine, St James's University Hospital, Beckett St, Leeds, UK

Abstract

Background. The European best practice guideline [Nephrol Dial Transplant 1999; 14 (Suppl 5)] (5A) for the management of anaemia suggests that >85% of the CAPD population should have a haemoglobin level of >11.0 g/dl.

Methods. We developed and implemented an outpatient-based protocol for intravenous iron sucrose (IV Fe) and erythropoietin (Epo) in CAPD patients showing iron deficiency despite oral iron therapy. We managed a total of 103 patients over 13 months of study. All CAPD patients were included, regardless of co-morbidity. Treatment developed in two phases: in phase 1 (reactive) (months 1–8), patients with markers of iron deficiency (ferritin <100 ng/ml or ferritin 100–500 and percentage hypochromic red cells (%HRC) ≥5) were converted from oral iron to IV Fe (300 mg) and reviewed after 4–8 weeks according to haemoglobin (Hb). In phase 2 (proactive) (months 9–13), the criteria for iron therapy were extended: ferritin <150 ng/ml or ferritin 150–500 and %HRC ≥2. Patients then received IV Fe (200 mg) and were reviewed after 4 weeks according to Hb.

Results. The median haemoglobin increased from 11.0 (Inter quartile range, IQR, 10.1–12.6) g/dl to 11.7 (11.0–12.7) g/dl (P = 0.06). The proportion of patients with absolute iron deficiency (ferritin <100 ng/ml) decreased from 24 to 2%. The percentage of hypochromic red cells (%HRC) decreased from 4 (2–7) to 1 (1–4) (P < 0.01).

Conclusions. An integrated Epo and IV Fe policy increased the number of patients reaching the European guideline from 50 to 75% with no increase in the population median Epo requirements (42 (IQR, 25–95) IU/kg/week vs 45 (27–101) (P = NS)). This study demonstrates the benefit of early (proactive) intervention in achieving population compliance within current guidelines for renal anaemia.

Keywords: clinical governance; erythropoietin; haemoglobin; iron deficiency; iron sucrose; peritoneal dialysis

Correspondence and offprint requests to: Dr Donald Richardson, Renal Research Registrar, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK.

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(11.0 g/dl). The haemoglobin level above which erythropoietin therapy would be decreased was designated the ‘ceiling’. Therapy was decreased in a graded fashion depending on how high the haemoglobin had risen (ceilings of 13 and 15.5 g/dl) (vide infra).

Outpatient blood results were processed to provide recommendations for best subsequent therapy in terms of change to Epo dose or possible intravenous iron replacement. The algorithm used haemoglobin, ferritin and %HRC. Serum ferritin was measured by immunoassay (Bayer Immuno-1). HB and %HRC were measured on a Technicon H*2 automated blood count analyser. Review and alterations to therapy were managed through a single clinician and the CAPD nursing staff. The clinician (D.R.) monitored the recommendations of the algorithm and assessed the patient records for hypertension, resistant iron deficiency, resistant anaemia and raised inflammatory markers. The protocol was followed unless a specific clinical reason for deviation could be detected and recorded.

Oral iron (ferrous sulphate) was used routinely in our CAPD population prior to the study. Patients received 3 × 200 mg/day or the maximum dose they could tolerate. Oral iron was discontinued once the first IV Fe dose had been prescribed. The prior duration of oral therapy varied from weeks to years. No minimum or maximum duration for oral iron therapy was used as a criterion for inclusion in the study.

The algorithms were altered in the light of experience over 13 months and this produced two phases of development. The sets of algorithms are available from the authors on request.

Iron protocols

Phase 1 (0–8 months) (reactive)

Patients with markers of iron deficiency (ferritin <100 ng/ml, or ferritin 100–500 and %HRC ≥5) were converted from oral iron to IV Fe (300 mg diluted in 250 ml, infused initially at 60 ml/h for 10 mins, and then 120 ml/h for 1 h and 180 ml/h if tolerated thereafter) and reviewed after 4–8 weeks according to Hb.

Phase 2 (9–13 months) (proactive)

The criteria for iron therapy were extended: ferritin <150 ng/ml, or ferritin 150–500 and %HRC ≥2. Patients then received IV Fe (200 mg undiluted over 20 min) and were reviewed after 4–8 weeks according to Hb. In phase 2, the lower dose was used, undiluted and over a shorter time period to allow a reduction in the patient attendance time.

Epo protocol

All erythropoietin was administered by the subcutaneous route. Patients who remained anaemic (Hb <11.0 g/dl) despite satisfactory markers for stored iron (as defined in each phase) were commenced on Epo (starting dose: 1000 IU ×3 per week) or received monthly incremental doses of Epo (increased by 1000 IU/dose administered, with an upper limit set at 300 IU/kg/week [3]). Epo doses were decreased in a similar stepwise manner when the Hb >13.0 g/dl. Above 15.5 g/dl, the Epo dose was halved to the nearest 1000 IU/dose delivered. At doses of 3000 IU/week, any decrement was of 1000 IU/week.

Epo dose was not increased if the patient was hypertensive (diastolic BP >99 mmHg). Blood pressure would be controlled and anaemia treatment considered at the subsequent review date. When an Hb of 11.0 g/dl was achieved, iron replacement continued according to protocol but there was no further increase in Epo therapy.

Statistics

Statistical significance was assessed using the U-Mann–Whitney test for unpaired non-parametric data. Differences in variance were tested for using the F test (variance ratio test).

Results

The outcome for Hb, ferritin, %HRC and Epo doses is given in Table 1. All results are given as median and inter-quartile ranges. A total of 81 of the 103 CAPD patients received at least one intravenous iron infusion during the 13 months of study. No adverse reactions to iron sucrose were encountered during this period. In phase 1, a mean of 18% of the CAPD population received an iron infusion (300 mg) each month. In phase 2 this increased to 35% receiving a lower dose infusion (200 mg) each month. During the study, a mean of 15% of patients did not require Epo. The proportion of patients with absolute iron deficiency (ferritin <100 ng/ml) decreased from 24% (16/68) to 2% (1/66) (Figure 1). The number of patients reaching the European Renal Association guideline (>11.0 g/dl) increased from 51 to 76% (Figure 2) with no increase in the population Epo requirements (median 42 (IQR, 25–95) IU/kg/week vs 45 (27–101) (P = NS)). The percentage of patients with a Hb ≥10.0 g/dl (UK Renal Association recommendation [3] 85% >10.0 g/dl) increased from 78 to 92% (no 90 day exclusion). The prevalence of functional iron deficiency assessed using %HRC decreased (median 4 (IQR, 2–7) to 1 (1–4) (P <0.01)), particularly during phase 2 (ending month 13; Figure 3).

The Hb distribution was narrowed at the end of phase 2 (Figure 2) but this was not statistically significant (F test: SD 1.93 and 1.49, n1: 71, n2: 66, P = 0.1). In the context of the US criteria (target haematocrit 33–36%): at the end of the second phase, 20% (n = 13) of Hb values were >13.0 g/dl (Hct 39%). However, 46% (n = 6) of these patients were not on Epo at all and another 23% (n = 3) had values >13.0 in at least one of the preceding 2 months. The remaining 31% (three patients) with Hb persistently >13.0 g/dl had Epo dose decrements made in each of the three preceding months with a resultant mean Epo dose of 2000 IU/week. The inference is that only three of 66 patients (4.5%) at 13 months had rolling Hb values >13.0 g/dl, with consequences for reimbursement of Epo costs in the US healthcare environment.
Table 1. The outcome for Hb, ferritin, %HRC and Epo doses is given below (all results are given as median and inter-quartile ranges (*P* value for U-Mann–Whitney test))

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Hb (g/dl)</th>
<th>Ferritin (ng/ml)</th>
<th>HRC (%HRC)</th>
<th>Epo (IU/kg/week)</th>
<th>Epo (IU/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.0 (10.1–12.6)</td>
<td>240 (107–390)</td>
<td>4 (2–7)</td>
<td>42 (25–95)</td>
<td>3000 (2000–6000)</td>
</tr>
<tr>
<td>8</td>
<td>11.7 (10.6–12.8)</td>
<td>225 (147–429)</td>
<td>3 (1–7)</td>
<td>43 (23–71)</td>
<td>3000 (2000–4000)</td>
</tr>
<tr>
<td>13</td>
<td>11.7 (11.0–12.7)</td>
<td>317 (193–497)</td>
<td>1 (1–4)</td>
<td>45 (27–101)</td>
<td>3000 (2000–6000)</td>
</tr>
</tbody>
</table>

Discussion

Oral iron is associated with gastrointestinal side effects and is poorly absorbed in renal failure. This may be through intolerance, non-compliance [4], malabsorption [5] or through the excessive blood loss [6] that occurs with the use of an extra-corporeal circuit. Intravenous iron dextran has been shown to increase the haemoglobin response to Epo compared to oral iron or no iron therapy in a randomized controlled study [7] in haemodialysis patients. However, intravenous iron is more expensive than oral iron and has the added potential complications of anaphylaxis, cardiac toxicity and an increase in infective complications [8]. Side-effects consisting of metallic taste, nausea, vomiting, headache and hypotension are more commonly recognized. Intravenous iron sucrose has been demonstrated as an effective [9,10] and safe [11] supplement for the treatment of iron deficiency in haemodialysis patients and peritoneal dialysis patients [12]. Iron therapy can now be delivered to those with signs of absolute or functional iron deficiency (as assessed by ferritin and %HRC [9]). This allows tailoring of iron therapy to those that may be expected to respond, and reduces the potential complication of iron overload by reducing or discontinuing therapy in those that are unlikely to respond. Certain discrimination of iron deficiency or iron overload has proved difficult if not impossible without resort to bone marrow examination. Currently the best available tests are ferritin and the percentage of hypochromic red cells in the circulation. In normal subjects, serum ferritin is an accurate indicator of the total reticuloendothelial iron store [13]. Absolute iron deficiency in normal subjects is currently defined by a serum ferritin < 20 μg/l. In renal failure the threshold for serum ferritin that defines iron
deficiency has been found to be at a greater level than in normal subjects (50–100 ng/ml) [14,15]. An upper limit ferritin level of 500 ng/ml for iron therapy has been proposed to avoid iron overload [16], there being little evidence in the literature of benefit from intravenous iron therapy above this level.

Functional iron deficiency is diagnosed when there is a normal serum ferritin concentration, but insufficient iron available to meet the needs of erythropoiesis. Red cell hypochromia of >10% has been proposed as a marker of functional iron deficiency but response to intravenous iron at lower levels has been documented [9]. Indeed the upper limit for %HRC is 2.5%. %HRC can also be increased secondary to factors other than iron deficiency. Prolonged sample storage (more than a few hours), sepsis, inflammation and haemolysis are all associated with higher values. The European guidelines [1] (6A and B) for assessing and optimizing iron stores suggest that the ferritin should be maintained at >100 ng/ml, and the %HRC <10%. It is suggested that it is necessary to aim for optimal levels of ferritin at 200–500 ng/ml and %HRC <2.5%. Using a %HRC of ≥5% and a ferritin level of <100 ng/ml as the criteria for intravenous iron therapy in the reactive phase (1) of our study had no effect on %HRC as an outcome measure (Figure 3). An effect was noted in a reduction in absolute iron deficiency (ferritin <100 ng/ml) during this phase (24 to 8%) (Figure 1).

In the proactive phase (2), the use of a %HRC of ≥2 as the criterion for intravenous iron therapy decreased iron deficiency as measured by %HRC. In addition it produced a right shift in the ferritin outcome without the risk of toxicity (less than 2% >800 µg/ml at month 1 and 13). The ferritin outcome was largely the result of activity directed at normalizing the %HRC and was not the result of any desired ferritin outcome other than ≥150 ng/ml.

We have demonstrated that improvement in the haemoglobin outcome is possible through the systematic use of an outpatient intravenous iron programme. This improvement has been achieved by increasing the proportion of HRC values below the value of 10%, previously suggested as a marker of iron deficiency in renal patients. Here the proactive approach to the treatment of iron deficiency at all degrees of severity (phase 2) has shown benefit over merely reacting to absolute iron deficiency and/or gross functional iron deficiency once it has developed (phase 1).

In the context of cholesterol lowering therapy the ‘prevention paradox’ is described, wherein more ischaemic events are prevented and more lives saved by treating the patient groups with ‘normal’/minimally elevated values than in treating only those with markedly elevated values. This occurs because although the relative benefits of treatment for any individual with a markedly increased cholesterol are greater, the number of individuals with ‘normal’/minimally raised cholesterol at lesser risk is greater still. Although our experience with intravenous iron is not a randomized controlled study, the proactive approach to normalization of %HRC in the CAPD population showed greater benefit in terms of improvements in %HRC and ferritin outcome. Indeed, restricting intravenous iron therapy to those individuals with %HRC >10% would result in <10% of our CAPD population being offered this treatment at any one time (Figure 1), resulting in no opportunity for influencing the prevalence of iron deficiency in the group as a whole. These results are entirely consistent with our studies in a large haemodialysis population [17].

These data indicate for ferritin and %HRC, in particular, just how far the ‘aim’ must exceed the desired (target) outcome in the systematic management of renal anaemia in CAPD patient groups. Waiting for clearly pathological levels to develop in either variable before beginning therapy does not produce a satisfactory outcome. Further work is necessary to define the characteristics of the most effective system for managing renal anaemia in CAPD cohorts.

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References
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