Improved haemoglobin levels with reduced frequency of administration of epoetin alfa

Glen Allen, Ann Kruger, Rajiv Juneja, George Passaris & Jeffrey A. Barbara

Abstract
In January 2004, at the Flinders Medical Centre (FMC) 95 patients were receiving erythropoietin, either three times a week intravenous (IV) Eprex (Group A) or two times a week IV Eprex (Group B). Group B patients had measurably improved haemoglobin levels of 12.2 g/dl even with reduced Eprex dosage of 8,875 U/Wk compared to Group A patients with haemoglobin levels of 11.3 g/dl and associated Eprex dosage of 13,696 U/Wk. In May 2004, most haemodialysis (HD) patients at FMC were changed over to a twice a week Eprex dosing regimen and audited prospectively until the end of 2004. Analysis of data from this group of patients at the end of 2004 showed sustained haemoglobin levels at lower Eprex dosing. Ferritin and transferrin saturation (Tsat) levels remained satisfactory indicating adequate iron repletion during this period. Cost and safety benefits were made with less Eprex administered and reduced nursing intervention required.

This Eprex regimen was maintained successfully in our dialysis population from 2004 onwards with data measured prospectively from 2008, indicating that the vast majority of patients were given IV Eprex two times a week with haemoglobin levels of 11.8 g/dl and associated Eprex dosage of 10,696 U/Wk comparable with the previous results from the patient cohort receiving twice-weekly Eprex in 2004 (Group B).

Keywords
Erythropoietin, haemoglobin, Eprex.

Introduction
Recombinant human erythropoietin (r-HuEPO) is used to correct anaemia associated with chronic renal failure in patients undergoing maintenance haemodialysis (HD) (Bommer et al., 1987; Schaefer & Schaefer, 1992). Patients suffering from renal anaemia have been shown to experience increased morbidity, mortality, hospitalisation, impaired cardiac function and lower quality of life with related health care costs (Thomas, 2006). The cost of erythropoietin-replacement therapy is significant but is balanced by savings due to the improvement in patient health outcomes (Besarab et al., 1999; Crawford et al., 2002).

Erythropoietin is administered either by intravenous (IV) or subcutaneous (SC) route usually two to three times weekly in many dialysis centres (Churchill et al., 2007). In our dialysis population at the Flinders Medical Centre (FMC) epoetin alfa (Eprex) was administered via the SC route with a number of studies indicating a smaller dose of epoetin was required to achieve adequate haemoglobin if applied subcutaneously (Besarab et al., 1992; Nissenson 2000; Besarab et al., 2002). The efficacy of Eprex was optimised by ensuring adequate patient iron repletion with intermittent intravenous iron therapy based on a modified iron status protocol (Barbara et al., 2006) but required a significant increase in the dose of Eprex to achieve target haemoglobin levels (Barbara et al., 2006) in agreement with other studies on SC versus IV epoetin dosage (Besarab et al., 1992; Besarab et al., 2002; Galliford et al., 2005). A number of studies have highlighted the difficulty of assessing the optimal frequency of Eprex dosing in HD patients with some studies suggesting that reducing the frequency of administration will lead to unsatisfactory haemoglobin outcomes, especially with once-weekly dosing (Geddes & Woo, 2003; Messa et al., 2005) while others suggest that reducing the frequency does not alter the responsiveness of the patient to Eprex (Weiss, 2000; McDougall, 2002).

In our study we compared the efficacy of twice-weekly IV Eprex with thrice-weekly IV Eprex in our dialysis population by evaluating haemoglobin levels in these patients and determining the cost benefits of placing patients on a reduced frequency regimen.

Methods
Ninety-five patients were dialysed in an in-centre or satellite HD facility for the duration of the clinical study period (Table 1). The duration of dialysis and the number of treatments per...
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included in the study (January 2004 – December 2004). Doses of Eprex were administered via IV, either three (Group A) or two times per week (Group B) and these dosages were revised monthly based on target haematologic parameters (Barbara et al., 2006). Monitoring of iron status in the HD population was evaluated using a modified iron repletion protocol as described in a previous study (Barbara et al., 2006). All patients were supplemented with oral folic acid, multi-B vitamin and vitamin C.

Table 1. Age and gender characteristics of the HD population in 2004.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69.6 (14.8)</td>
<td>67.5 (13.2)</td>
<td>72.0 (16.0)</td>
</tr>
<tr>
<td>Range</td>
<td>28–92</td>
<td>28–92</td>
<td>39–92</td>
</tr>
<tr>
<td>Number</td>
<td>95</td>
<td>50</td>
<td>45</td>
</tr>
</tbody>
</table>

Values represent mean (SD).

Patients from Group A had their Eprex dosage reduced from three times to two times weekly from May 2004 until the end of December 2004 and the effectiveness of this dosage regimen was evaluated by comparing the results of Group A from the first period of four months (thrice-weekly Eprex) to the second period of eight months (twice-weekly Eprex). There were two patients who suffered from either cardiac insufficiency or peripheral vascular disease and remained on high doses of Eprex thrice weekly.

Analysis of data from the dialysis patient population (n=119, Table 2) in 2008, indicated that 12 patients were receiving Eprex three times weekly (Group C), and 92 patients two times weekly (Group D) and 10 patients were receiving Eprex once a week (Group E) and five patients did not require Eprex (Group F). Iron status protocol and vitamin supplementation was identical to that provided in the 2004 study.

Table 2. Age and gender characteristics of the HD population in 2008.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.5 (14.0)</td>
<td>69.1 (12.8)</td>
<td>65.4 (15.3)</td>
</tr>
<tr>
<td>Range</td>
<td>20–91</td>
<td>35–88</td>
<td>20–91</td>
</tr>
<tr>
<td>Number</td>
<td>119</td>
<td>67</td>
<td>52</td>
</tr>
</tbody>
</table>

Values represent mean (SD).

Blood specimens were collected from patients routinely each month and measured for haemoglobin, ferritin, Tsat (all groups) and albumin and CRP (Groups C, D, E & F). Results were collated over each study period and averaged for each patient.

Statistics

Data are presented as Mean (SEM). Differences in mean haemoglobin, Eprex dose, ferritin and Tsat were analysed by unpaired (Group A versus Group B patients) or paired t-tests (Group A patients). Results from Groups C, D, E and F were analysed with analysis of variance and between group significance tested with Scheffé’s post hoc pair-wise method.

Results

In the first quarter of 2004, 95 HD patients received either three times a week IV Eprex or two times a week IV Eprex. Comparison of these two groups of patients showed that Group A patients (three times a week) had significantly lower mean Haemoglobin value of 11.3 g/dL compared to 12.2 g/dL of Group B patients (two times a week) (p<0.001, Table 3).

Mean Eprex dose was significantly higher at 13,696 U/Wk in Group A patients compared to 8,875 U/Wk in Group B patients (p<0.001, Table 3). Mean ferritin and Tsat were not significantly different between groups, with values indicating satisfactory iron repletion in both sets of patients. Thus Group B patients were receiving reduced Eprex dosage with measurably greater haemoglobin and sustained iron repletion.

Table 3. Effect of Eprex dosing protocol on haemoglobin levels in two groups of patients on HD at FMC and satellites during January to April 2004.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Haemoglobin (g/dl)</th>
<th>Eprex (U/Wk)</th>
<th>Ferritin (ug/L)</th>
<th>Tsat (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A 3x weekly before May 2004</td>
<td>11.3 (0.3) n=23</td>
<td>13,696 (901) n=23</td>
<td>454.0 (46.3) n=23</td>
<td>25.4 (2.3) n=23</td>
</tr>
<tr>
<td>Group B 2x weekly before May 2004</td>
<td>12.2 (0.1) n=72</td>
<td>8,875 (472) n=72</td>
<td>439.2 (46.4) n=72</td>
<td>28.0 (1.2) n=72</td>
</tr>
</tbody>
</table>

Unpaired t-test p-value p<0.001 p<0.001 p=0.87 p=0.29

Values represent mean (SEM).

In May 2004, 21 patients from Group A had a change in Eprex dosing frequency from three times a week IV to twice-weekly, whilst maintaining the same total weekly dose and were followed from May until the end of that year. In the next eight-month period, mean haemoglobin levels increased, although not significantly, from 11.2 to 11.6 g/dL (p=0.10, Table 3). Mean Eprex dose in this group of patients was decreased, although not significantly (p=0.57, Table 4), from 12,619 to 12,253 U/Wk. Mean ferritin decreased slightly from 468.6 to 430.6 ug/L, a change which was not significant (p=0.37, Table 4), while mean Tsat levels were sustained above 25% with values not significantly altered (p=0.63, Table 4) from 26.6% with Eprex three times per week to 25.6% on a regimen of two times per week. Cost savings to the renal unit with the reduction in dosing frequency could be measured at $9.74/week/patient, with a cost of $241.50/week (three times a week) compared to $231.76/week (two times a week).
Investigation of the HD population at the FMC in the year 2008 indicated that the vast majority of patients received Eprex twice weekly and that the target haemoglobin level was being achieved with a reduced Eprex dose. Pairwise comparison (Scheffe’s test) showed that haemoglobin was significantly lower in patients given thrice-weekly Eprex compared to other Groups (C versus D, E and F; p<0.0001, p<0.0001, p<0.0001 respectively, Table 5). Patients requiring thrice-weekly Eprex were almost invariably suffering from comorbidities which reduced the effectiveness of Eprex. These comorbidities included gastrointestinal bleeding, malignancy and infection. Not surprisingly, the Eprex weekly dosage was found to be significantly higher in Group C compared to other Groups (Scheffe’s test p<0.0001 C versus D, and E, Table 5). Mean CRP (C reactive protein) values measured across groups were significantly different (p<0.005 ANOVA) with pairwise comparison indicating CRP in thrice-weekly Group C (66.2 (8.6) n=9) was significantly elevated compared to the once-weekly Group E (18.3 (8.0) n=7, Scheffe’s test p=0.014). However, CRP was not measured routinely as part of standard monthly blood tests in all patients. There were no significant differences between groups (C, D, E & F) in respect to ferritin, transferrin saturation and serum albumin (Table 5).

### Table 4. Effect of Eprex dosing protocol on haemoglobin levels in Group A patients receiving HD at FMC and satellite centres during 2004 and Group B patients after May 2004.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Haemoglobin (g/dL)</th>
<th>Eprex (U/Wk)</th>
<th>Ferritin (ug/L)</th>
<th>Tsat (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A 3x weekly before May 2004</td>
<td>11.2 (0.2) n=21</td>
<td>12,619 (471) n=21</td>
<td>468.6 (40.5) n=21</td>
<td>26.6 (2.8) n=21</td>
</tr>
<tr>
<td>Group A 2x weekly after May 2004</td>
<td>11.6 (0.2) n=21</td>
<td>12,253 (793) n=21</td>
<td>430.6 (33.6) n=21</td>
<td>25.6 (1.7) n=21</td>
</tr>
<tr>
<td>Paired t-test p-value Group A 3x vs 2x Eprex</td>
<td>NS p=0.10</td>
<td>NS p=0.57</td>
<td>NS p=0.37</td>
<td>NS p=0.63</td>
</tr>
<tr>
<td>Group B 2x weekly after May 2004</td>
<td>12.1 (0.1) n=69</td>
<td>9,107 (475) n=69</td>
<td>411.3 (22.5) n=69</td>
<td>26.4 (0.8) n=69</td>
</tr>
<tr>
<td>Unpaired t-test p-value Group A vs Group B 2x Eprex</td>
<td>p&lt;0.05</td>
<td>p&lt;0.002</td>
<td>NS p=0.67</td>
<td>NS p=0.64</td>
</tr>
</tbody>
</table>

Values represent mean (SEM).

### Table 5. Effect of Eprex dosing protocol on biochemical and haematological markers in patients receiving HD at FMC and satellite centres during 2008.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Haemoglobin (g/dL)</th>
<th>Eprex (U/Wk)</th>
<th>Ferritin (ug/L)</th>
<th>Tsat (%)</th>
<th>Alb (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group C 3x weekly</td>
<td>9.6 (0.3) N=12</td>
<td>28,000 (853) N=12</td>
<td>493.9 (100.1) N=12</td>
<td>22.4 (4.9) N=12</td>
<td>32.3 (1.6) N=12</td>
</tr>
<tr>
<td>Group D 2x weekly</td>
<td>11.8 (0.1) N=92</td>
<td>10,696 (713) * N=92</td>
<td>417.7 (32.9) N=92</td>
<td>23.8 (1.1) N=92</td>
<td>35.0 (0.4) N=92</td>
</tr>
<tr>
<td>Group E 1x weekly</td>
<td>12.4 (0.3) N=5</td>
<td>1,950 (157) * N=10</td>
<td>277.0 (69.0) N=10</td>
<td>19.9 (3.0) N=10</td>
<td>36.4 (1.0) N=10</td>
</tr>
<tr>
<td>Group F No Eprex</td>
<td>12.0 (0.6) N=5</td>
<td>0 N=5</td>
<td>194.8 (68.7) N=5</td>
<td>17.0 (1.8) N=5</td>
<td>36.0 (1.9) N=5</td>
</tr>
<tr>
<td>ANOVA F-Test p-value</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>NS p=0.16</td>
<td>NS p=0.45</td>
<td>NS p=0.12</td>
</tr>
</tbody>
</table>

Values represent mean (SEM).

*Scheffe’s pairwise test p<0.002 C versus D, E & F Groups of patients.

**Scheffe’s pairwise test p<0.0001 C versus D & E Groups of patients.

### Discussion

Optimal erythropoietin therapy maintains near normal haemoglobin levels and has been demonstrated to reduce the incidence of cardiovascular morbidity and repeated blood transfusions (Galliford et al., 2005; Dimkovic 2001) whilst improving patient physical wellbeing and prolonging life on HD (Portoles et al., 2007). However, the administration of erythropoietin needs to be cost-effective under the constraints of modern medical practice (Mundinger et al., 2004).

The efficacy of IV Eprex was investigated in this study of HD patients in 2004 and 2008 in our dialysis centre. The preferred route of dosing was IV due to the previously documented risk of pure red cell aplasia with SC Eprex. In addition, this IV regimen was favoured by clinical staff due to the ability to deliver the Eprex during HD sessions and so ensure strict compliance (Nissenson, 2000).

Accepted practice in a majority of dialysis centres in the early history of erythropoietin replacement therapy had determined that Eprex be delivered intravenously three times a week during the thrice-weekly HD schedule via easy access to this venous line (Besarab et al., 1992). When administration was modified to the SC route in a number of studies, the frequency of administration was investigated with once-weekly dosing being as effective in maintaining haemoglobin levels as thrice-weekly dosing with a concomitant reduction in total weekly epoetin and hence it was more cost-effective (Besarab et al., 1999; Weiss et al., 2000). The longer circulating half-life of erythropoietin and maintenance of the minimal threshold concentration of
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erthropoietin required for effective erythropoiesis in the SC mode may explain this benefit (Nisenson, 2000; Galliford et al., 2005).

Although there is some evidence that IV administration can be as effective as SC especially when iron-repletion protocols are strictly enforced (Pizzarelì et al., 2006), when our unit commenced IV Eprex following reports of pure red cell aplasia with Eprex SC, 13.7% more Eprex was required via IV route compared to SC even with carefully managed iron-replete dialysis patients (Barbara et al., 2006). This was in accord with previous studies, indicating an increased dose of Eprex is required via IV compared to SC route, ranging from 15% to 50% (Besarab et al., 1992; Galliford et al., 2005; Furuland et al., 2005).

Reduction in the frequency of IV Eprex has also been investigated with conflicting results on the efficacy of treatment on haemoglobin outcomes (Geddes & Woo, 2003; Messa et al., 2005; Pizzarelì et al., 2006). In 2004 it was noted in our dialysis population that a significant number of patients were receiving IV Eprex twice-weekly and this protocol was achieving acceptable haemoglobin outcomes, whereas the thrice-weekly group of patients was requiring an increased dose of Eprex (54%) with a resultant lower haemoglobin level (7%). We decided to switch the thrice-weekly group of dialysis patients to twice-weekly and determine the efficacy of this protocol. Mean haemoglobin was increased in Group A patients but not significantly – 11.6 g/dL compared to 11.2 g/dL – with a reduction in dose of Eprex 12,253 U/Wk compared to 12,619 U/Wk (also not statistically significant).

Data from our HD population in 2008 revealed that the majority of patients were being maintained on twice-weekly IV Eprex with maintenance of mean haemoglobin levels at 11.8 g/dL and a mean Eprex dosage of 10,696 U/Wk. Ferritin and Tsat outcomes were commensurate with satisfactory iron repletion. Thus the cost-benefit of reducing Eprex administration, both in the acquisition of epoetin alfa and allocation of resources to control and administer doses to patients on HD, represented a significant saving in nursing workload in our unit.

A small group of patients (Group C) who were required to be on an augmented, thrice-weekly Eprex dose of 28,000 U/Wk had a lower mean haemoglobin of 9.6 g/dL compared to the twice-weekly group. Factors such as chronic bleeding, malignancy and infection had increased their resistance to erythropoietin therapy, in accord with reports of inflammatory and nutritional markers being associated with refractory anaemia (Locatelli et al., 2005; Dmńkovic, 2001). Mean CRP was elevated in Group C, indicating a possible inflammatory role while the mean albumin result in Group C was lower than the other groups, suggestive of nutritional deficiency.

In contrast, Group E patients (n=10) on once-weekly Eprex (1,950 U/Wk) had satisfactory levels of haemoglobin (12.4 g/dL). Two patients in this group had polycystic kidneys which have been shown to enhance erythropoiesis production (Eckardt et al., 1989). In this small group one could argue as to the need for Eprex and most dialysis units will have HD patients who do not require erythropoietin. Studies have shown that lower haemoglobin levels are achieved with once-weekly IV Eprex in the HD population (Geddes & Woo, 2003; Messa et al., 2005). Messa et al. suggested a role for neocytolysis which may destroy newly formed erythrocytes when erythropoietin levels decrease below critical thresholds. Smaller repeat doses may ensure a better effect on red cell production than one large dose given IV (Besarab et al., 1999).

Conclusion

In conclusion, we have shown that the majority of patients on thrice-weekly IV Eprex can be effectively managed with twice-weekly dosing, achieving better haemoglobins with smaller weekly Eprex doses.

Acknowledgements

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References


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