Switching from subcutaneous to intravenous erythropoietin α in haemodialysis patients requires a major dose increase

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Abstract

Background. A change in the licensing arrangements for the use of erythropoietin α in haemodialysis patients has required a switch in the route of administration from subcutaneous (SC) to intravenous (IV). Previous work suggested that the IV route was less efficacious but studies since the enforced switch have not confirmed this.

Methods. We studied haemoglobin levels and the mean weekly dose of erythropoietin α in 86 haemodialysis patients at monthly intervals over the 6 month period before and after a change in the route of administration of erythropoietin α from SC to IV. Changes in other parameters known to be associated with erythropoietin response were also monitored.

Results. Mean haemoglobin level fell following the switch from 11.9 g/dl ± 1.4 at baseline to 11.3 g/dl ± 1.4 at 1 month (P = 0.001) and to a trough of 11.0 g/dl ± 1.3 at 2 months (P < 0.001) before partial recovery to 11.4 g/dl ± 1.2 (P = 0.007) at 6 months. Mean weekly dose of erythropoietin after 2 months was significantly higher than baseline (8791 IU ± 5314 vs 8035 IU ± 4893). The dose continued to increase and by 6 months was 10605 IU (P < 0.001), 32% higher than baseline. There was a small reduction in residual renal function, which was an independent predictor of change in dose requirement. There was a small increase in parathyroid hormone levels, but no change in serum ferritin, dosing frequency, total Kt/V, serum albumin, normalised protein catabolic rate, C-reactive protein, hospitalization rate and dialysate reuse rate.

Conclusions. Switching from SC to IV erythropoietin α caused a significant fall in haemoglobin levels in the first 2 months. This was partially reversed by 6 months at the expense of a 32% dose increase in the dose of erythropoietin α by 6 months. The economic impact may be considerable.

Keywords: administration route; epoietin; erythropoietin; haemodialysis; intravenous; subcutaneous

Introduction

Recombinant human erythropoietin has been used for more than 15 years to treat anaemia associated with renal failure, to improve quality of life, outcomes and problems associated with repeated blood transfusions. Although IV erythropoietin has 100% bioavailability, most of the dose is biologically ineffective once the relatively small numbers of erythropoietin receptors are saturated on erythroid progenitor cells. Subcutaneous (SC) administration results in slower increase in serum erythropoietin levels and longer maintenance at this level. Thus, in the United Kingdom, as well as many other European countries, the preferred route of administration has been SC. This has been largely for the financial advantage associated with a perceived substantial dose reduction and an equally low side effect profile. National and international guidelines have supported this decision [1–3].

In the late 1990s, nephrologists became aware of a new and very serious side effect related to the development of neutralising anti-erythropoietin antibodies in chronic dialysis patients. The condition was termed pure red cell aplasia [4], since the patients had a complete inhibition of red blood cell production in the bone marrow. It seems to be a phenomenon related to the immunogenic route of administration and, although rare, it has caused such concern that the licence for SC administration of erythropoietin α has been removed for patients with chronic renal disease. Erythropoietin α remains licensed for SC usage in the treatment of anaemia in adults receiving chemotherapy for specific types of malignancy [5].

Evidence would suggest that switching from the SC to the intravenous (IV) route would increase the average dose (and hence cost) of erythropoietin [6–11].
But the studies performed were not adequate to accurately predict the magnitude of this change [6]. Since the recent enforced systematic change, both reported and unreported studies would suggest that the extent of this change might not be as significant as expected.

We report the effects on haemoglobin levels, and erythropoietin dose and other relevant parameters when 86 of our haemodialysis patients receiving SC erythropoietin \( \alpha \) had the route of administration of the drug switched to IV.

Subjects and methods

The Lister Hospital, Stevenage is a district general hospital with a total haemodialysis population of 350 patients at its main haemodialysis and two satellite units.

Haemodialysis programme

All patients were treated exclusively using high-flux synthetic membranes, predominantly polysulphone. Haemodiafiltration was used as routine treatment for most patients, especially those with residual urea clearance (KRU) <1 ml/min and those of average size. Dialysers were reused using peracetic acid. Bicarbonate was used exclusively as the buffer. Ultra-pure water was used for all dialysis procedures. Dialysis was prescribed and monitored using a two-pool kinetic model to ensure a \( K_t/V \) (renal plus dialysis) of 1.1–1.2 (per dialysis) for thrice weekly dialysis. Urea kinetic modelling parameters were monitored monthly.

Routine anaemia management

Predialysis haemoglobin levels were monitored monthly, serum ferritin levels 3 monthly. Transferrin saturation was not measured routinely but according to clinical need should a lack of response to normal anaemia management protocol occur. Intravenous iron saccharate was administered (100 mg each dialysis for 10 doses) if ferritin levels were below 200 µg/l, and in a maintenance dose of 100 µg every 14 days to ensure a ferritin level in the range 200–700 µg/l. No IV iron was administered if the ferritin level was >700 µg/l. Vitamin \( B_{12} \) (1 mg 6 monthly intramuscularly) and folic acid (5 mg orally daily) were routinely supplemented. Erythropoietin was administered to all patients with haemoglobin levels below 11 g/dl after repletion of haematinics. The dose was adjusted monthly as required to maintain haemoglobin above this level. Preparations used were Epoetin \( \alpha \) (Eprex, Janssen-Cilag), Epoetin \( \beta \) (Neorecormon, Roche) and Darbepoetin \( \alpha \) (Aranesp, Amgen) in approximately equal proportions. Up to November 2002 the route of administration was determined mainly on the grounds of convenience and personal preference.

Study methodology

In November 2002 all patients receiving SC erythropoietin \( \alpha \) were transferred to an IV erythropoietin, which in the majority of cases was to erythropoietin \( \alpha \). Eighty-six patients switched from SC erythropoietin \( \alpha \) to IV erythropoietin \( \alpha \), and completed 6 months of treatment. Patients who entered or left the dialysis programme during this time were excluded, as were those who had been on the dialysis programme for <6 months. All patients underwent thrice-weekly haemodialysis throughout the study period. No change of dose was made at the time of the switch. Dialysis nursing staff administered IV erythropoietin during routine dialysis sessions. Nursing staff had previously administered SC erythropoietin to 83 of the 86 patients in the study group. The other three patients had previously self-administered. Routine haemodialysis and anaemia management continued along with the monitoring schedule described above.

Data collection and analysis

Data were collected on all patients for the 6 months both before (−6 months) and after (+6 months) the administration switch. Data included: monthly haemoglobin level and erythropoietin dose; total \( K_t/V \), urea clearance (KRU), serum ferritin and serum parathyroid hormone (PTH) levels (all factors known to affect response to erythropoietin), at −6, baseline and +6 months; monthly serum albumin and normalised protein catabolic rate (nPCR). Routine blood samples were normally collected immediately prior to the first dialysis session of the week. C-reactive protein (CRP) levels were measured as clinically indicated and not routinely. Serum albumin was measured by the bromocresol purple method and CRP by a low sensitivity method. The Erythropoietin Resistance Index was calculated by dividing the total weekly erythropoietin dose first by the patient’s weight (in kilograms) and then by the patient’s haemoglobin level (in g/dl) and was expressed as units/week per kg per g/dl. Data were analysed using Student’s paired \( t \)-test and \( \chi^2 \) test with Yates’ correction.

Results

The values of continuous variables are usually expressed as mean ± standard deviation. The mean patient age was 66.6 ± 11.5 years with a mean duration of dialysis dependence of 36.8 ± 27.3 months. There were 53 males and 33 females.

There was no significant difference in haemoglobin levels in the 4 months prior to administration switch, although for the 2 months prior to that the mean haemoglobin was significantly lower at 11.3 g/dl ± 1.4 \( (P = 0.005) \) and 11.2 g/dl ± 1.4 \( (P = 0.001) \), respectively (Figure 1). After the switch, a significant fall in the mean haemoglobin was noted in the first month \([11.9 \text{ g/dl ± 1.4–11.3 g/dl ± 1.4 } (P = 0.001)]\). The mean haemoglobin continued to significantly fall to a trough of 11.0 g/dl ± 1.3 after 2 months before recovering over the rest of the study period. Recovery was not complete. The final mean level of haemoglobin was 11.3 g/dl ± 1.2, and remained significantly lower than at baseline \( (P = 0.007) \). The proportion of patients achieving the haemoglobin target of 11 g/dl or greater was stable at 74.4–79.9% in the 2 months prior to the switch but fell significantly to a nadir of 51.8% 2 months after switching \( (P = 0.0036) \), recovering to 70.5% by the end of the 6 month follow-up (Figure 2).
There was no significant change in the mean weekly erythropoietin dose throughout the 6 months prior to administration switch. The mean weekly dose of erythropoietin was significantly higher 2 months after switching than at baseline [8012 IU±4966 at time of switch rising to 8790 IU±5313 (P=0.03)]. The dose continued to increase thereafter in a highly significant fashion (Figure 3). By the end of the study the mean weekly dose was 10605 IU per patient. This represents a weekly increase in dose of 2593 IU per patient (P<0.001), a mean rise of 32.4% from baseline doses.

The Erythropoietin Resistance Index was greater 6 months after the switch than at the time of the switch (14.07±10.40 vs 10.02±7.43 U/week per kg per g/dl: P<0.001) or 6 months before it (10.46±7.28 U/week per kg per g/dl: P<0.001). There was no significant difference between the Erythropoietin Resistance Index at the time of the switch or 6 months before it.

Mean KRU deteriorated slightly over the 12 months of the study. There was a non-significant fall during the 6 months prior to switching whilst that during the 6 months following was significant [1.4 ml/min±1.7 to 1.2 ml/min±1.6 (P=0.012)]. The delivered Kt/V increased slightly in the 6 months prior to the switch but did not significantly change in the following 6 months. Change in KRU was weakly correlated to change...
in erythropoietin requirement \( (R = 0.354, \ P = 0.001; \text{ Figure 4}) \), but not with change in haemoglobin.

PTH levels rose from 318 pg/ml ± 281 to 449 ± 395 pg/ml \( (P < 0.001) \) after administration switch, an observation not seen in the previous 6 months. There was a weak negative correlation between the mean PTH level during the 6 months following the switch and change in erythropoietin requirement \( (R = -0.208; \ P = 0.077) \). There was no correlation with change in PTH level after the switch and change in dose. Eighteen patients had mean PTH levels >500 pg/ml during the 6 months following the switch. However the change in

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**Fig. 3.** Mean weekly dose of erythropoietin \( \alpha \) at monthly intervals for 6 months before and after the switch from SC to IV administration of erythropoietin \( \alpha \). Error bars denote 95% confidence intervals. Figures shown above error bars denote degree of significance of differences from baseline values by Student’s paired \( t \)-test.

**Fig. 4.** Scatterplot showing correlation of change in mean dose of erythropoietin \( \alpha \) and reduction in residual renal function (KRU) over the observation period following switching from subcutaneous to intravenous erythropoietin \( \alpha \). Negative numbers on \( x \)-axis indicate improvement in renal function and on \( y \)-axis indicate reduction in dose of erythropoietin \( \alpha \).
erythropoietin requirement was less in these patients than in those with lower mean PTH levels (1500 vs 2891 IU; \( P = \text{NS} \)).

Serum ferritin levels did not significantly change following the switch although had significantly increased from 408\( \mu \)g/l to 491\( \mu \)g/l in the 6 months prior to this. (Table 1). This corresponded to a reduction in the proportion of patients with serum ferritin levels less than 200\( \mu \)g/l over the whole 12 month observation period (from 22.9 to 7%; \( P = 0.038 \)). In the 6 months following switching, the proportion with low ferritin levels reduced from 12.8 to 7%. There was no correlation between ferritin level at any time-point or change in ferritin level after the switch and change in erythropoietin requirement.

There was no difference between the pre- and post-switch periods in mean frequency of administration of erythropoietin (2.19 ± 0.65 vs 2.24 ± 0.64). In the 67 patients in whom the drug was administered twice or more times weekly, the mean increment in erythropoietin dose was 3194 ± 5028 (39.9%) whilst in the remainder whose dosing frequency was less than twice weekly the mean increment was only 474 ± 3204 (5.9%; \( P = \text{ns} \)). Mean erythropoietin dose was significantly higher, in those with high dosing frequency, at all stages throughout the pre- and post-switch periods than in those with lower dosing frequency. Likewise the Erythropoietin Resistance Index was significantly higher in those with higher dosing frequency in \( \text{Kt/V} \) and in most patients, haemodiafiltration, employing high convection rates. These factors increase the clearance of middle molecules but erythropoietin \( \alpha \), which has a molecular weight of \(~30000\) kDa, is unlikely to be cleared significantly. Likewise we do not think there were compliance issues. 83 of 86 patients had their SC erythropoietin administered at baseline by nursing staff during the dialysis session compared with all 86 after the switch. In this setting any effect of compliance is likely to have reduced the dose requirement after the switch.

Loss of residual renal function might decrease the sensitivity to erythropoietin and require a dose increase. The observed reduction was small and total \( \text{Kt/V} \) did not change. Furthermore there is little literature on the effect of residual renal function on erythropoietin requirement. In this setting any effect of compliance is likely to have reduced the dose requirement after the switch.

Change in \( \text{KRU} \), mean PTH levels and frequency of administration (twice or more times weekly vs less than twice weekly) were modelled in multiple regression analysis as potential determinants of the post-switch change in erythropoietin dose. Only change in \( \text{KRU} \) emerged as an independent predictor of change in erythropoietin dose (\( \beta = 0.325, P = 0.005 \)).

**Discussion**

At the time of enforced erythropoietin \( \alpha \) administration change, the majority of available evidence suggested that higher doses of erythropoietin \( \alpha \) were needed to produce the same effect on haemoglobin levels when administration was by the IV route rather than SC [6–11]. Although the quality of some of these studies can be criticised, as can meta-analyses in general, our results confirm those previous studies that a significant dose increase is required amounting to about 33% of baseline values or approximately 3000 IU per patient per week.

This was an observational study so there may be confounding factors. We used high-flux membranes and in most patients, haemodiafiltration, employing high convection rates. These factors increase the clearance of middle molecules but erythropoietin \( \alpha \), which has a molecular weight of \(~30000\) kDa, is unlikely to be cleared significantly. Likewise we do not think there were compliance issues. 83 of 86 patients had their SC erythropoietin administered at baseline by nursing staff during the dialysis session compared with all 86 after the switch. In this setting any effect of compliance is likely to have reduced the dose requirement after the switch.

It is possible that the small increase in PTH level, which occurred after the switch, may have had an effect on the sensitivity to erythropoietin, and thus increased the dose requirement. However we found no evidence of a positive correlation between PTH and erythropoietin dose: in fact there was a weak negative relationship, high PTH levels tending to be associated with lower dose increments. The effect of PTH on resistance to erythropoietin is thought to be minor in comparison to other factors [12] and we think it unlikely that the change in PTH was a significant factor in the changing erythropoietin requirements we have observed. Likewise we think that changes in iron stores were unlikely to have affected erythropoietin \( \alpha \) dose requirement since there were no significant changes in

### Table 1. Comparison of parameters 6 months prior to switching from subcutaneous to intravenous erythropoietin, at the time of the switch and 6 months after the switch

<table>
<thead>
<tr>
<th>Parameter</th>
<th>–6 months At switch</th>
<th>6 months At switch</th>
<th>( P )-value</th>
<th>+6 months At switch</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin (( \mu )g/l)</td>
<td>408 ± 250</td>
<td>491 ± 237</td>
<td>0.001</td>
<td>497 ± 231</td>
<td>\text{NS}</td>
</tr>
<tr>
<td>( \text{KRU} ) (ml/min)</td>
<td>1.5 ± 1.7</td>
<td>1.4 ± 1.7</td>
<td>\text{NS}</td>
<td>1.2 ± 1.6</td>
<td>0.012</td>
</tr>
<tr>
<td>( \text{Kt/V} )</td>
<td>1.30 ± 0.23</td>
<td>1.35 ± 0.30</td>
<td>0.043</td>
<td>1.35 ± 0.21</td>
<td>\text{NS}</td>
</tr>
<tr>
<td>Serum PTH (pg/ml)</td>
<td>341 ± 319</td>
<td>318 ± 281</td>
<td>\text{NS}</td>
<td>449 ± 395</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\( \text{KRU} \), residual urea clearance (ml/min); PTH, parathyroid hormone (pg/ml); \text{NS}, non-significant.
ferritin levels after the switch. Furthermore, our analysis indicates that low ferritin levels (<200 mg/l) were less frequent following the switch, making iron deficiency an unlikely cause of increasing erythropoietin requirement during this period. This conclusion would have been firmer if corroborated by transferrin saturation levels but these data were not routinely available.

Mean CRP decreased significantly following the switch suggesting that inflammation was not a factor in the observed increase in mean erythropoietin dose. It is unlikely that intercurrent illness was a factor since there was a non-significant reduction in hospitalization. It is recognized that low protein catabolic rate and low serum albumin correlates with relative erythropoietin resistance [13], but we found no major difference in serum albumin and nPCR, suggesting that there were no significant changes in nutritional status. Re-use statistics were identical before and after the switch.

We acknowledge that a higher dosing frequency may be more important when erythropoietin α is administered IV rather than SC. However, we found that frequency of administration did not change before and after the switch and we were unable to detect a convincing effect of frequency on the change in dose requirement. That mean erythropoietin dose and mean Erythropoietin Resistance Index were lower in those dosed less frequently both before and after the switch may be best explained by a tendency for lower doses of erythropoietin to be administered less frequently for pragmatic reasons, rather than by a direct effect of increased dosing frequency on erythropoietin resistance. Our data also suggest that lower doses tend to be less affected by the switch from SC to IV.

Comparative studies using erythropoietin β show a similar administration and dosing effect as for erythropoietin α [14–19], though the route of administration of darbopoietin α does not seem to affect haemoglobin levels [20]. This may be due to the longer circulating half-life of the molecule (25.3 h after IV and 48.8 h after SC administration) relative to that of erythropoietin α and erythropoietin β (8.5 h after IV and 16–24 h after SC administration). A minimal threshold concentration of these agents needs to be maintained throughout most of the dosing interval to ensure effective erythropoiesis.

Other factors may have been involved. The needle of a pre-filled syringe broke during the IV administration of erythropoietin α to one patient, prompting a general change in practice, the drug being aspirated into another syringe prior to administration through a more robust needle. This began 3 months after the switch, by which time the most dramatic reduction in

![Fig. 5. Mean serum albumin (upper panel) and nPCR (upper panel) at monthly intervals for 6 months before and after the switch from SC to IV administration of erythropoietin α. Error bars denote 95% confidence intervals. Figures shown above error bars denote degree of significance of differences from baseline values by Student’s paired t-test.](image-url)
haemoglobin level had already occurred. We cannot exclude an effect of this practice on the results during the final 3 months of the study, though again we think the effect, if any, is likely to have been minimal.

To conclude, switching from SC to IV erythropoietin α in haemodialysis patients requires a dose increase of approximately one-third. The financial implications of this are significant and in this study approximate to an annual increase in cost of £1500 per patient. Because of the nature of this study the dose increment cannot be categorically attributed solely to the change in route of administration. Other changes occurred during the study with changes in KRU being the most likely to have contributed to the change in dose requirement. We found little evidence to incriminate other potential factors including frequency of administration, PTH levels, iron status, dialysis adequacy, nutritional status, inflammation, intercurrent illness and dialyser reuse.

Conflict of interest statement. None declared.

References

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