Clinical Pharmacology and Economics of Recombinant Human Erythropoietin in End-Stage Renal Disease: The Case for Subcutaneous Administration1

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ABSTRACT

The clinical pharmacology of human recombinant erythropoietin (epoetin) was studied in order to compare the effectiveness of various routes and dosing schedules in dialysis patients. Thirty-six patients received epoetin beta three times a week i.v. for at least 12 wk. The mean dose needed to achieve target hemoglobin was 225 ± 36 U/kg per week (median dose, 180 U/kg per week). Twenty-eight of 36 patients who were converted to a once-a-week i.v. schedule increased their requirements to 429 ± 50 U/kg per week in order to maintain a target hematocrit of 33 to 40 vol%. Twelve of 28 patients could maintain their target hematocrit when dosed once a week s.c. at 84 ± 10 U/kg. The other 16 patients required 137 ± 15 U/kg per week divided into two doses. In the entire group of 28 patients, the weekly requirement for epoetin was reduced by 50% when the s.c. route was used two or three times a week.

Pharmacokinetic studies performed during chronic therapy indicated rapid clearance of erythropoietin (t1/2 of 6.8 ± 0.3 h). Single i.v. doses >150 U/kg were required to increase basal erythropoietin by 30 mU/ml at 44 h postdosing. With s.c. dosing, such increments in erythropoietin levels frequently persisted beyond 60 h because of prolonged and slow absorption. Pharmacokinetic simulations in conjunction with clinical correlation of the erythropoietic response suggest that the duration that the erythropoietin levels are maintained, and not the absolute peaks, is the primary determinant of efficacy. This may result from nonlinearity in the dose response. Pharmacokinetic simulation also indicated that i.v. dosing could not maintain adequate interdialytic erythropoietin levels, whereas s.c. dosing could. Cost analysis indicated that the use of s.c. dosing two or three times a week at an average total weekly dose of 110 to 120 U/kg is effective treatment of anemia in most dialysis patients.

Key Words: Erythropoietin, ESRD, pharmacology, cost economics

The anemia regularly observed in patients with renal failure is caused primarily by a relative deficiency of erythropoietin production (1–4). A shortened red cell life span (5) and a suppression of red cell production (6) are secondary but potentially significant pathogenetic factors (3,6–8). More than 5 yr ago, the erythropoietin gene was cloned and transfected into mammalian cell lines (9–11), providing large amounts of human recombinant erythropoietin (epoetin) for clinical use. Since then, several studies have shown that dialysis patients treated with recombinant erythropoietin can obtain and maintain an adequate hemoglobin level (12–14).

Because of the easy venous access and the thrice-weekly dialysis schedule of most hemodialysis patients, epoetin in most of these clinical trials has been administered i.v. three times a week. Various therapeutic schedules for correction of the anemia of dialysis patients have been recommended (15). Clinical trials and modeling studies have shown that an adequate response can be achieved (hematocrit 30 to 40 vol%) in 80% of patients with between 25 and 125 U/kg three times a week administered i.v. with a median of 60 to 70 U/kg (13,14,16–20). A minority of "resistant' patients will require more than 150 U/kg three times a week.
With the expansion of indications for epoetin use to nonhemodialysis patients, attempts have been made to determine the comparative pharmacokinetics of s.c. and i.v. administration (21-26). Some of these studies have shown that s.c. administered epoetin is more effective and that considerably smaller doses can maintain an adequate hemoglobin level (25,26). Such a reduction in dose would help make the treatment more cost effective. However, previous pharmacokinetic studies have not attempted to correlate pharmacokinetic data with pharmacodynamic effects to determine the mechanism for the reduction in dose requirements by the s.c. route.

This article compares the effectiveness of various routes and dosing schedules and relates these pharmacodynamic data with the pharmacokinetic data obtained during chronic epoetin therapy. Both frequency and route of administration were evaluated during the course of therapy. The relationship between pharmacokinetics and the pharmacodynamics of different dosing strategies of epoetin beta was examined for their possible economic impact. Our results show that a significant reduction in dose and therefore cost of therapy can be achieved in the majority of patients by switching from i.v. to s.c. dosing.

**METHODS**

**Patients**

Forty-two patients on maintenance hemodialysis were enrolled in two clinical trials of recombinant human erythropoietin (Marogen® sterile powder [epoetin-beta]; Chugai-Upjohn Inc., Rosemont, IL). All protocols were approved by the appropriate Institutional Review Boards. All patients were on maintenance hemodialysis for at least 3 months (40 of 42 for longer than 1 yr), none had clinical or biochemical evidence of aluminum overload at entry, and all received 4 h of dialysis with the surface area of the dialyzer (0.9 to 1.1 m²) determined by body size and diet. None were clinically malnourished by review of serum albumin levels, anthropomorphic measurements, or BUN concentrations. Twenty of the patients were male and 22 were female; their ages ranged from 18 to 71 yr with a median age of 49. The mean hemoglobin was 7.2 ± 0.2 g/dL, and 26 of the patients were transfusion dependent. Enrollment criteria included hemoglobin of less than 8.5 g/dL and withdrawal from androgens for at least 1 month before study.

**Intravenous Administration**

The flow of the 42 patients enrolled is shown in Figure 1. Thirty-one were enrolled into an open-label, randomized, dose-ranging study of three doses of epoetin beta (25, 100, and 200 U/kg) three times a week (Group A). During the initial period of 20 wk, dose titration upward was not permitted, but doses could be decreased if hemoglobin exceeded 13.5 g/dL. After this 20-wk period, when the hemoglobin was maintained in the target range of 10.5 to 13.5 g/dL on three times a week dosing, 29 of these patients were converted to once-weekly i.v. dosing at the same total weekly dose. Further adjustments were made at intervals of 4 wk or more. The duration of once-weekly i.v. dosing lasted from 3 to 6 months depending on individual clinical response. All 29 patients were reestablished back to thrice-weekly i.v. dosing for at least 30 wk before being converted to s.c. dosing (see below). Before conversion to s.c. dosing, a stable hemoglobin in the target had to be maintained on the same dose of epoetin beta during the last 16 wk of administration.

Eleven other individuals (Group B) were enrolled in...
a randomized, double-blind, placebo-controlled study with six patients receiving 100 U/kg of epoetin beta in the active arm three times a week for the first 12 wk. If the target hemoglobin of 9.5 to 12.5 g/dL was reached, the dose was reduced to ≤50 U/kg three times a week. Five placebo patients received the vehicle for the first 12 wk and then, starting in wk 13, four of these received active drug at a lower dose of 50 U/kg. Dose modifications were made no more frequently than every 4 wk to obtain or maintain hemoglobin in the target range of 9.5 to 12.5 g/dL. Seven of the 11 patients enrolled in Group B received active drug for a minimum of 7 months, sufficient time to determine epoetin requirements. They were maintained on a fixed i.v. dose of epoetin thrice weekly for at least 30 wk thereafter. These seven patients subsequently entered the s.c. dosing study. Before conversion, a stable hemoglobin level for >16 wk was maintained on the same dose.

From the pool of 36 patients available after more than 1 yr of epoetin therapy, 29 were converted to once-weekly s.c. dosing. Before this conversion, 16 of 36 participated in pharmacokinetic studies (vide infra) employing i.v. erythropoetin. Two other patients were evaluated only during three-times-a-week s.c. dosing.

Subcutaneous Administration

Twenty-nine patients on i.v. epoetin beta were converted to once-weekly s.c. regimen, starting with a dose 25 to 50% of their previous weekly dose (dose range, 25 to 220 U/kg). The purpose of the initial dose reduction upon conversion was to permit a reduction in hematocrit levels so that retitration of the dose would be necessary in the majority of patients to obtain or maintain the desired target hematocrit. This would allow a separation of the effect of time on epoetin therapy from the effects of route and frequency. The initial once-weekly s.c. dose was maintained for 1 month, with upward dose adjustments thereafter limited to a maximum dose of 9,000 to 12,000 U per injection. This limit was imposed by the volume of 1.5 mL, which could be comfortably and repeatedly injected (maximal strength of epoetin beta, 6,000 to 8,000 U/mL when reconstituted) without changing the concentration of the formulation (mannitol and human serum albumin), which could alter absorption characteristics. Decisions about dose adjustments were based on the slope of the hemoglobin with time during the preceding 4 to 6 wk. A steady state at a given dose or frequency was considered to have been achieved when the hemoglobin-time curve showed no change over a 6-wk period. Subjects who maintained their target hemoglobin during once-weekly s.c. dosing for at least 10 wk were subsequently switched to twice-weekly dosing and then to thrice-weekly dosing, but with progressive reduction of the total weekly dose. Patients who did not maintain their hemoglobin with once-weekly s.c. dosing during the first month were first advanced to twice-weekly administration at the same weekly dosage before upward dose modifications were made. Whenever possible, an attempt was made to keep total weekly dosage constant by changing the frequency of administration. This was followed by an increase in total weekly dose. All patients were on twice-weekly or thrice-weekly dosing for the last 15 wk of the study.

Laboratory Monitoring and Maintenance of Iron Stores

Hemoglobin concentration and hematocrit were measured weekly or biweekly during the course of 2 or more years. All determinations were performed on an automatic Coulter Counter (Coulter Electronics, Hialeah, FL). Iron stores were monitored frequently, and patients were supplemented with oral or parenteral iron to maintain serum ferritin >150 ng/mL and serum iron saturation ≥20%.

Pharmacokinetics

Study Design. Pharmacokinetics of i.v. and s.c. administered epoetin beta were studied in 16 patients after they had been receiving i.v. epoetin for 16 to 20 months and had been on three-times-a-week i.v. dosing for at least 30 wk. Patients participated after a 5-day washout period. All subjects received i.v. doses identical to their maintenance dose, ranging from 25 to 225 U/kg. The doses were delivered as an i.v. bolus over 1 min into the venous return line 3 min before the end of dialysis to permit wash in by the patient’s own blood, followed by a saline rinse. Blood samples were taken at 0, 0.25, 0.5, 1, 2, 4, 8, 12, 16, 20, 24, and 44 h postdose. Patients then received their maintenance dose thrice weekly for the next 3 wk. The same 16 patients crossed over to s.c. dosing after another 5-day washout period. They received epoetin beta into the anterior thigh (range, 17 to 150 U/kg). Blood was taken at 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 60, 64, 68, 72, 76, 84, 88, and 92 h postdose to measure serum erythropoetin levels. This frequent sampling was deemed necessary in order to get accurate areas under the concentration-time curve.

All subsequent s.c. doses were rotated between the lower and nonfistula upper extremities. The greater majority were given in the deltoid for reasons of modesty/convenience.

Analysis

Erythropoetin Levels. Serum erythropoetin concentrations for pharmacokinetic analysis were determined by RIA as previously described (27).
Pharmacokinetic. All pharmacokinetic parameters are described as apparent values because of the inability of the RIA to distinguish endogenous erythropoietin from exogenous epoetin beta. Serum concentrations of epoetin beta after i.v. and s.c. administration were plotted versus sampling times on a semilogarithmic scale with two compartments detected in only a few of the patients. The majority of subjects exhibited a monoexponential decline. The baseline erythropoietin concentration for each patient at the zero time point was subtracted from the value at subsequent time points for the pharmacokinetic determinations. All parameters were generated by noncompartmental pharmacokinetic analysis. The area under the serum concentration versus time curve (AUC) from zero time to infinity (i.v. dosing) and from zero time to time t by visual inspection (s.c. dosing) was calculated by using Lagran polynomal interpolation (28). Apparent half-life was calculated by linear regression of the terminal phase of the serum-concentration versus time curves. Total clearance (CL) was estimated by dividing the dose by the total AUC. Volume of distribution at steady state (Vdss) was calculated as dose × AUMC/(AUC)², where AUMC is the area under the first moment curve. 

Comparison among the various dosing regimens and schedules was performed by analysis of variance and paired or unpaired t tests for normally distributed variables. Dosages were log transformed before analysis. Steady-state hemoglobin response (increase from baseline in grams per deciliter) was normalized by the epoetin dose (units per kilogram per week). Either simple linear or multivariate regression was used to evaluate relationships between variables. A P value <0.05 was accepted as significant.

RESULTS

Intravenous Dosing

Three-Times-Per-Week Dosing. Thirty-nine of the 42 patients received active drug, with 36 of these participating in the trials long enough to find an optimal maintenance dose for the three-times-a-week i.v. regimen. The initial doses varied from 25 to 200 U/kg and were titrated to maintain a hemoglobin of 10.5 g/dL or greater. The median weekly dose needed was 180 U/kg per week (60 U/kg per dose); the mean dose was 224 ± 28 U/kg per week (range, 75 to 990 U/kg per week). The mean normalized response was 2.75 ± 0.26 g/dL of hemoglobin per 100 U/kg per week.

The mean weekly increase in hemoglobin during dose initiation was dose dependent. Multivariate regression, however, showed no relationship between the steady-state normalized response and either the prestudy hemoglobin level (r = 0.058; Figure 2) or the prior degree of transfusion dependency.

Once-a-Week Dosing. Twenty-six of 29 eligible patients were able to maintain their hemoglobin levels at 8.5 g/dL or greater during once-weekly i.v. dosing. The total weekly dose in these 26 patients increased significantly, from 260 ± 40 U/kg per week during thrice-weekly i.v. dosing to 461 ± 52 U/kg during once-a-week dosing (P < 0.01 by paired t test). Normalized response, however, decreased from 2.41 ± 0.23 to 1.47 ± 0.28 g/dL per unit per kilogram per week (P < 0.05). The individual normalized responses are shown in Figure 2. The positive correlation of normalized response with baseline hemoglobin during once-weekly dosing did not reach significance (r = 0.312; P > 0.1). Twenty patients were able to maintain their hemoglobin in the target range of 10.5 g/dL or greater, with their weekly dose increasing from 207 ± 29 to 389 ± 50 U/kg per week (P < 0.01 by paired t test). Six patients were unable to do so (mean hemoglobin, 9.7 ± 0.2); however, their hemoglobin level remained above the entry criteria of 8.5 g/dL. Their dose increased significantly from 385 ± 122 to 700 ± 65 U/kg per week (P < 0.05 by paired t test). There was no relationship between the total weekly dose ratio (once a week/three times a week)
and the initial thrice-weekly total dose ($r = 0.22; p = \text{not significant}$). The mean normalized response of patients maintaining hemoglobin $>10.5$ g/dL during once-weekly dosing was $1.75 \pm 0.34$ (range, 0.38 to 5.73) compared with $0.51 \pm 0.03$ (range, 0.23 to 0.72) ($P < 0.05$) in those with hemoglobins between 8.5 and 10.5 g/dL.

**Subcutaneous Dosing**

Of the 29 patients converted to once-weekly s.c. dosing, 28 completed at least two of the three phases of s.c. dosing (Figure 1). Figure 3 shows that the mean thrice-weekly dose of epoetin required by these 28 patients ($225 \pm 32$ U/kg per week) to maintain a mean hemoglobin of 11.7 g/dL as well as the normalized hemoglobin response ($2.78 \pm 0.31$) determined during the second period of three-times-a-week i.v. therapy (more than 12 months post-initial epoetin therapy) did not differ from that required by the initial cohort of 36 patients determined during the first 3 to 6 months. These 28 patients received epoetin beta, administered s.c. once a week, at an initial mean dose of one third ($78 \pm 8$ U/kg per week) their previous total weekly dose (Figure 4). By the end of the once-a-week dosing period, the average weekly dose had increased to $115 \pm 8$ U/kg (Figure 3). Figure 4 shows that during the first 4 wk, when no dose or frequency modifications were made, mean hemoglobin decreased by 1.1 g/dL. Over the next 28 wk, mean doses increased from 78 to about 110 U/kg per week. There was no apparent benefit from dosing three times a week compared with two times per week at the same total weekly dose (wk 12 to 30). However, when response was normalized, frequency did make
a difference. As shown in Figure 3, average effective doses during once-, twice-, and three-times-a-week s.c. administration decreased only slightly (115 ± 8, 111 ± 9, and 105 ± 9 U/kg per wk, respectively). Corresponding hemoglobin levels during once-a-week, twice-a-week, and three-times-a-week dosing were 10.4 ± 0.2, 11.0 ± 0.2, and 112 ± 0.2 g/dL, respectively. As a result, the normalized response increased progressively. Figure 5 shows the normalized hemoglobin responses to both i.v. and s.c. dosing of all individuals, including those who did not participate in at least two of the s.c. phases. The negative correlation with patient number is artifactual (data for subjects sorted by ascending i.v. dose requirement). Except for four subjects (Patients 1, 2, 13, and 20), the normalized hemoglobin response was greater with either twice- or thrice-weekly s.c. dosing than with thrice-weekly i.v. dosing. Patients 1, 3, and 13 had very high normalized responses to i.v. epoetin; Patient 20 was not studied during twice- or thrice-weekly dosing.

The decrease in hemoglobin that occurred during the first 4 wk after initiating once-weekly s.c. epoetin (Figure 4) was noted primarily in a subset of 16 patients, whereas 12 patients were able to maintain their hemoglobin within the target range during once-weekly dosing for up to 10 wk. This less-responsive group was clinically indistinguishable from the more-responsive group. Table 1 presents the differences noted between the two groups. The responsive group had higher normalized responses to prior epoetin

![Figure 5. Individual normalized hemoglobin (HgB) responses. The subjects were initially sorted in ascending dose requirements during three-times-a-week i.v. dosing. The negative correlation is artifactual and reflects autocorrelation with epoetin (EPO) dose. Twice-a-week i.v. and once-a-week, twice-a-week, and thrice-a-week s.c. dosings are depicted by closed circles, inverted open triangles, open triangles, and closed triangles, respectively. Note that during two- or three-times-a-week s.c. dosing, the normalized responses exceed the i.v. three-times-a-week response in all patients except 1, 2, and 13.](image)

### Table 1. Comparison of two subsets of patients

<table>
<thead>
<tr>
<th></th>
<th>Responsive</th>
<th>Less Sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three Times per Week i.v.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoetin dose (U/kg)</td>
<td>128 ± 15</td>
<td>251 ± 30</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.2 ± 0.2</td>
<td>11.4 ± 0.2</td>
</tr>
<tr>
<td>Normalized response</td>
<td>4.23 ± 0.44</td>
<td>1.88 ± 0.22</td>
</tr>
<tr>
<td>(g/dL)/(100 U/kg/wk))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once a Week s.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoetin dose</td>
<td>84 ± 10</td>
<td>137 ± 15</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11.7 ± 0.3</td>
<td>9.6 ± 0.1</td>
</tr>
<tr>
<td>Normalized response</td>
<td>5.84 ± 0.74</td>
<td>1.65 ± 0.14</td>
</tr>
<tr>
<td>Twice a Week s.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoetin dose</td>
<td>72 ± 7</td>
<td>137 ± 10</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11.3 ± 0.1</td>
<td>11.0 ± 0.2</td>
</tr>
<tr>
<td>Normalized response</td>
<td>6.00 ± 0.73</td>
<td>2.88 ± 0.31</td>
</tr>
</tbody>
</table>

a All parameters were significantly different.
b Responsiveness was determined by the response during once weekly subcutaneous dosing.

### Pharmacokinetic Measurements

After i.v. administration, both the 15-min and 1-h plasma erythropoietin levels were linearly correlated with dose (25 observations). The regression of 1-h postdose erythropoietin level with dose is: \( y = -0.04 + 19.08 \times (r = 0.989) \). Figure 6 shows representative data from two patients requiring different doses of epoetin i.v. three times a week (190 compared with 50 U/kg per dose) to obtain the same hemoglobin response. The half-life of epoetin was the same, as can be seen in the upper panel. The less-sensitive patient had to be maintained at higher epoetin levels. The lower panel shows the erythropoietin levels from the same two patients after single s.c. doses of 37 and 137 U/kg, respectively. There is an absence of high peaks in both patients (100 and 160 mU/mL), but levels of erythropoietin above baseline persisted for 90 h. The curves indicate that absorption from the s.c. dose is slow and may have occurred during the entire 4-day observation period.

Table 2 summarizes the pharmacokinetic data in
Figure 6. Comparison of two patients (EMB 712 and DDW 724) with differing requirements for epoetin during i.v. dosing. The upper panel shows that the half-life (t1/2) was the same. The nearly fourfold-greater dosage in the less-responsive patient maintained plasma levels above 30 mU/ml for only an additional 20 h. The bottom panel shows the wide variability in absorption after s.c. dosing. Despite a nearly fourfold difference in dosage (133 versus 37 U/kg), the AUC were nearly the same. Both patients maintained levels above their baseline for 90 h.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Mean ± SE</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>6.8 ± 0.3</td>
<td>4.3–11.3</td>
</tr>
<tr>
<td>CL (mL/h/kg)</td>
<td>8.0 ± 0.4</td>
<td>2.9–11.3</td>
</tr>
<tr>
<td>Vss (mL/kg)</td>
<td>70.0 ± 5.2</td>
<td>53–103</td>
</tr>
<tr>
<td>Cmax/dose</td>
<td>19.1 ± 1.3</td>
<td>11.2–25.2</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioavailability (F)</td>
<td>48.8 ± 5.2%</td>
<td>14.5–96.5</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>22.6 ± 3.4</td>
<td>6–52</td>
</tr>
<tr>
<td>Cmax/dose</td>
<td>1.9 ± 0.3</td>
<td>0.31–4.42</td>
</tr>
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</table>

a t1/2, half-life measured from terminal elimination phase (4 to 44 h); Cmax/dose, maximum concentration adjusted for dose; Bioavailability (F), AUC for s.c. dose as a percentage of i.v. dose.

The 16 patients studied rigorously. The apparent i.v. half-life averaged 6.83 ± 0.31 h and was unrelated to dose over the range of doses studied (25 to 225 U/kg). The total clearance averaged 8.0 ± 0.4 mL/kg per hour. The volume of distribution averaged 70 mL/kg, compatible with a distribution primarily in the plasma compartment. The bioavailability after s.c. administration was 48.8 ± 5.7% of the i.v. dose (range, 14.5 to 96.5), and the time to maximum concentration averaged 22.6 ± 3.4 hours. Cmax/dose after s.c. administration, however, was only 10% of that seen after i.v. dosing.

Relationship of Pharmacokinetic and Pharmacodynamics Data

During i.v. therapy, there was no relationship between the maintenance dosage needed to maintain the target hematocrit and the half-life. Increases in dosage during once-weekly i.v. dosing were independent of the thrice-weekly maintenance dose. After conversion to s.c. dosing, there was no relationship between the percent reduction in dosage and the bioavailability (r = 0.2; P > 0.05). There was a correlation between the percent reduction in dosage during two-times-a-week s.c. dosing and the previous i.v. maintenance dose (r = 0.57; P < 0.05), that is, the degree of dose reduction was greatest in those needing the largest doses.

These aspects are illustrated by the two subjects whose pharmacokinetic data are shown in Figure 6. Despite the similarity in the AUC after a s.c. dose in the two subjects, there was marked biological variability in the biological response on repeated s.c. dosing. The more-responsive patient subsequently responded to long-term once-a-week dosing of 70 U/kg or twice-weekly dosing of 30 U/kg, a significant reduction from the patient’s previous i.v. maintenance dose of 150 U/kg per week. By contrast, the less-responsive patient, originally requiring 570 U/kg per week, could not be maintained during once-weekly dosing of 200 U/kg but responded to 100 U/kg twice weekly and to 60 U/kg thrice weekly s.c.

To evaluate the possible mechanisms for the changes in dosing needs during the various dosing schedules, we performed pharmacokinetic stimulation as shown in Figure 7. The weekly dose of 120 U/kg per week chosen was based on the average dose administered to 844 patients from 25 centers (29). The target range for increases in erythropoietin levels (30 to 100 mU/mL) above baseline is based on previous studies in anemic patients by Caro et al. (2). Thrice-weekly dosing at an average dose of 120 U/kg per week produces periods within each cycle, particularly in the 3-day interdiabetic period, during which erythropoietin levels fall below the target range. Simulation for once-weekly dosing is not shown, but levels decrease below target within 2 days. By contrast, at a constant weekly dose of 120 U/kg administered s.c., peak levels decrease from 500 to 300 mU/mL as the frequency of administration per week increases from once to thrice weekly. Trough values are critically dependent on the dosing interval. Both twice-a-week and thrice-a-week s.c. dosings result in
persistent increases in erythropoietin levels within the target range, whereas during once-a-week dosing, they fall below the target by the fourth day.

DISCUSSION

Initial clinical trials of epoetin focused on the thrice-weekly i.v. administration in ESRD patients on dialysis. Efficacy in these patients is established, and erythropoietin use has expanded to predialysis patients with progressive renal failure (30). During the past 4 yr, we have administered epoetin to 60% of our patients on dialysis. The studies reported here are on a subset of patients who participated in two multicenter trials conducted to demonstrate the efficacy and safety of epoetin beta in dialysis patients. We focused on examining the relationship between pharmacokinetics and pharmacodynamics of different dosing strategies and the possible economic implications of such findings. We tested the hypothesis that erythropoietic response, and therefore cost benefit, was more dependent on sustained maintenance of erythropoietin levels than on very high transient unsustainable levels.

The efficacy of the three-times-a-week i.v. administered epoetin reported here is similar to that reported by others (12,13,31) who aimed for the same target hematocrit. A lower target has been associated with a lower dose requirement (19,20). Similarly, the pharmacokinetic parameters of t₁/₂, Vdss, and CL after i.v. administration are similar to previous results in humans reported by Egrie et al. (21), Salmonson (32), and Hughes et al. (33). Comparison of these results with the published results of others indicates no consistent differences. Some investigators have noted a decrease in the half-life of erythropoietin after repeated administration (21,31), but this has not been a consistent finding (32,33).
pharmacokinetic measurements performed here after chronic administration of epoetin do not address this issue. The mean bioavailability after s.c. administration was approximately 50%, with a large individual variation from 15 to 96%. The factors determining the bioavailability are unknown but were not related to age, sex, or diabetes. All injections were done in the thigh, excluding site as a potential variable.

In order to compare the dose requirements needed to achieve the target hematocrit by the differing routes and frequencies of administration, several precautions were taken to avoid bias. First, comparisons were not attempted until all patients had been on therapy for more than 1 yr and all patients were reestablished on an i.v. three-times-a-week dosing schedule for a minimum of 30 wk. Thus, the effects of long-term epoetin therapy on expansion of the bone marrow and on red cell survival should have been minimal, if any. The equivalence of dosing needs and hematological response during initial and final three-times-a-week i.v. therapy phases attests to the stability and reproducibility of the hematological response in our subjects. Second, all patients were maintained in an iron-replete state through continued oral iron or intermittent parenteral iron-dextran therapy to maintain iron saturation above 20% and ferritin levels above 150 ng/mL.

Finally, we deliberately reduced the initial s.c. dose by 50% or more in all subjects to induce, if possible, a decrease in erythropoiesis and a resulting need to titrate the dose. Retitration from the original dose was necessary in all patients and could usually be detected within 4 wk from the slope of the hemoglobin curve. By the end of the once-weekly s.c. dosing period, both patients who could and could not maintain their hemoglobin above 10.5 g/dL underwent the same degree of dose reduction (43 ± 7 versus 47 ± 6%) from their prior three-times-a-week i.v. dose. Neither subgroup showed a change in normalized hemoglobin response during once-weekly dosing. The less-responsive group had required much higher weekly doses during three-times-a-week i.v. dosing. Thus, it is not surprising that these subjects were unable to maintain their hemoglobin concentrations during once-weekly s.c. dosing. It was not the intent of this study to determine the ultimate dosing requirement of once-weekly s.c. dosing of this subgroup but rather to assess the effect of changing dosing frequency. During two- or three-times-a-week s.c. dosing with slightly lower weekly doses, hemoglobin in this subgroup increased. In the entire population, we were able to show a significant 50% lowering of the total weekly dosage by the end of 32 wk of s.c. therapy. With progressive increases in the frequency of s.c. administration at average lower doses, the normalized hemoglobin response increased. Those patients with the greatest three-times-a-week i.v. dosing requirements showed the greatest degree of dose reduction during two- or three-times-a-week s.c. dosing.

Our pharmacodynamic studies and pharmacokinetic simulations provide some insight on the factors determining erythropoietic responsiveness. There is no doubt that the dose response to epoetin is nonlinear after either i.v. or s.c. administration. This non-linearity may result from a combination of receptor-mediated events (binding may differ at differing stages of erythropoiesis) as well as the non-steady-state characteristics of erythropoietin levels after dosing. However, it was demonstrated more than two decades ago that a fixed dose of erythropoietin, when administered by repeated injections of small fractions, had a greater effect on red cell production than when administered in a single injection (34,35). It appeared that the response was not dependent on the peak concentration of erythropoietin but on the duration that erythropoietin levels were maintained above a "critical concentration." This concentration could undoubtedly vary from patient to patient and could determine the difference between very responsive, average responsive, and relatively resistant patients.

The pharmacokinetic simulations (Figure 7) illustrate these aspects. The dose modeled was 120 U/kg per week, the average dose used by 25 dialysis centers (29). If sustained levels of 30 to 100 mU/mL above a patient's baseline are needed to sustain effective erythropoiesis to achieve a hematocrit of 30 to 36 vol%, then three-times-a-week dosing will be insufficient, particularly during the 3-day "weekend" interdialytic period. Some committed but still erythropoietin-dependent cells may perish in the bone marrow during the periods of relative erythropoietin deficiency just before the next dose. Increasing the trough levels i.v. requires either more frequent dosing or larger single doses. The importance of sustaining an optimal erythropoietin level over time is demonstrated by the once-a-week i.v. dosing results. Single doses were increased sixfold, yet one fourth of the patients failed to maintain their hemoglobin above the lower target limit. When converted back to thrice-weekly dosing, patients then obtained the target at the same lower dosage administered previously.

Simulation of the s.c. injection of epoetin beta shows a prolonged bioavailability of the drug. At a constant weekly dose of 120 U/kg, peak levels decrease from 500 to 300 mU/mL as the frequency increases from once to thrice weekly. Trough values are critically dependent on the dosing interval. Both twice-a-week and thrice-a-week s.c. dosings result in persistent increases in erythropoietin levels within or above the target zone. Once-a-week dosing does not.
Our simulations are similar but not identical to those of Salmonson (32), and Macdougall et al. (36) and indicate that repetitive s.c. dosing causes a more moderate and constant elevation of erythropoietin levels. The actual levels attained depend critically on the absorption (bioavailability) and terminal elimination rate constants and may account for some of the differences in steady-state trough levels calculated by various investigators. By using a constant dose of 120 U/kg but variable dosing intervals of 48, 72, and 96 h, Macdougall and coworkers calculated steady-state minimum levels of 224, 119, and 70 mU/mL, respectively. They concluded that s.c. dosing with 60 U/kg two times weekly would be sufficient in most patients.

Because levels are inadequately maintained during a once-a-week s.c. dosing, this finding may account for the failure of once-a-week dosing to sustain effective rates of erythropoiesis in 57% of our patients, a group whose initial dose requirements were higher. We believe that the s.c. dosing frequency is affected by the relative sensitivity of the patient to epoetin. In a recently completed evaluation of hemodialysis and peritoneal dialysis patients, we noted that frequency and single-dose amounts during s.c. dosing were influenced by pretreatment determinants of response such as hematocrit and degree of prior blood transfusion dependency (37).

Other investigators have found similar results—a lower total weekly dose by the s.c. route (23,25,26); others have not (32). The reasons for the discordance are unknown. In pre-ESRD patients, Eschbach et al. (30) have shown that the dosage needed was one third less by the s.c. compared with the i.v. route. Similarly, we have recently shown that, when controlled for other factors, s.c. epoetin alfa produces a 38% greater increase in the normalized hematocrit response than does i.v. epoetin (29). This effect was independent of the type of hemodialysis modality used. Granolleras and coworkers (26) have shown that the degree of dose reduction after s.c. administration varies directly with the frequency of s.c. administration. In individual subjects, the degree of dose reduction is variable, and our results suggest that the least-sensitive patients may benefit most. Patients with poor absorption or those whose endogenous erythropoietin levels for adequate erythropoiesis are relatively high might not benefit and might be more effectively treated i.v.

The above considerations are important factors in evaluating the effect of reimbursement regulations. The total drug cost alone approaches many hundreds of millions of dollars in the United States. Because a fixed rate per treatment policy previously in effect mandated that facilities control operating costs, the net result had been a decrease in dose and therefore response from those seen during the early clinical trials. Both we (29) and Sisk et al. (38) have reported that less than 49 and 45%, respectively, of patients treated for 6 months or more attained the target hematocrit of 29%. The average dose was 2,670 and 2,700 U/kg, respectively. Down-shifting of the target hematocrit has occurred. Mean hematocrit has decreased from 35% in the clinical trials to less than 30% in clinical practice. Although low-dose therapy (i.e., 45 to 50 U/kg) i.v. three-times-a-week can increase hematocrit by six points, lower doses are not able to maintain the hematocrit levels (39). The optimal range of hematocrit, however, is controversial, with many advocating maintenance hematocrits of less than 30 vol% in some patients.

The "payment per unit epoetin administered" reimbursement policy in effect since January 1991 may remove the incentive to start with a low dosage. In fact, the spread between recombinant human erythropoietin revenue and cost widens at higher dosage amounts. Sisk et al. (38) have estimated that the "break-even" dose ranges from 3,000 to 11,000 U/dose, depending on the true cost of administration and coinsurance factors. They also warn of incentives that encourage the use of unnecessarily high doses. This type of reimbursement policy may be inappropriate if the goal of therapy is to induce a safe and smooth correction of the anemia. Increased dosage may increase the number of patients reaching the target range, but some patients may do so precipitously because the responsive patients can not be identified in advance. Teehan et al. (40) have warned about the dangers of too rapid a correction of anemia.

The major questions related to the most effective dose and route of administration should be more global. In this article, we present the pharmacokinetic and pharmacodynamic bases for the cost-economic advantage of s.c. over i.v. administration for the health care system. For a given target response, less epoetin is needed when administered s.c. There is also the potential to reduce costs further by teaching patients to self-administer the drug. This is particularly important in predialysis patients and in patients receiving peritoneal dialysis. However, patient preference must be considered as well. Because twice-weekly s.c. dosing is equally efficacious and more comfortable to patients and also reduces costs, it could be the preferred schedule and route in some patients under current reimbursement policies. In the subgroup of more-responsive patients, which may be 40% or more of the dialysis population, once-a-week s.c. dosing is both therapeutically and cost economically effective, whereas i.v. dosing is not.

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The authors thank Drs. S. Bray, E. Jones, J.F. Burke, and G.F. Francois for their care of the patients, Ms. R. Atkinson, N. Picarillo, and indicate that repetitive s.c. dosing causes a more moderate and constant elevation of erythropoietin levels. The actual levels attained depend critically on the absorption (bioavailability) and terminal elimination rate constants and may account for some of the differences in steady-state trough levels calculated by various investigators. By using a constant dose of 120 U/kg but variable dosing intervals of 48, 72, and 96 h, Macdougall and coworkers calculated steady-state minimum levels of 224, 119, and 70 mU/mL, respectively. They concluded that s.c. dosing with 60 U/kg two times weekly would be sufficient in most patients.

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REFERENCES


Subcutaneous Delivery of EPO


