Safety and Efficacy of Low-Dose Subcutaneous Erythropoietin in Hemodialysis Patients

KATHY P. PARKER,* WILLIAM E. MITCH,†‡ JOHN C. STIVELMAN,‡ EDWIN J. MACON,‡ JAMES L. BAILEY,‡ and JEFF M. SANDS‡

**Nell Hodgson Woodruff School of Nursing, †George M. O'Brien Kidney Research Center, and ‡Renal Division, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia.*

Abstract. Anemia in hemodialysis patients is effectively treated by intravenous (IV) injections of recombinant human erythropoietin (rHuEPO) at each dialysis session. Because the hormone is effective by subcutaneous (SC) administration, it was decided that this study would evaluate low-dose weekly SC rHuEPO therapy. To determine the safety and efficacy of weekly SC rHuEPO administration to hemodialysis patients, only one third the weekly IV dose was given and the effects were compared with those from an age-, gender-, and nephrologic disease–matched control group treated in the standard fashion. Forty-four patients entered the trial and 27 completed the protocol along with 27 control subjects. During Phase 1, experimental and control subjects received standard IV rHuEPO at dialysis for 6 months. During Phase 2, experimental patients received weekly SC rHuEPO at one third the weekly IV dose for 10 months; control subjects continued to receive IV therapy. In Phase 3, both groups were treated for 6 more months with IV rHuEPO. In Phase 2, there was no significant reduction in hematocrit value, reticulocyte count, transferrin saturation, or ferritin level in the experimental group, even with only one third the weekly rHuEPO IV dose over the 10-month period. There were no significant differences between IV and SC rHuEPO administration or between experimental and control subjects in blood pressure, serum chemistries, or parameters of "dialysis adequacy." It was concluded that low-dose weekly SC rHuEPO administration is a safe and effective method for maintaining the hematocrit level of stable hemodialysis patients. This therapy could enhance the efficacy of rHuEPO and substantially reduce costs while preserving patient care outcomes. (J Am Soc Nephrol 8: 288–293, 1997)

Anemia is present in over 90% of dialysis patients in the United States and contributes to the fatigue, reduced exercise tolerance, and poor quality of life reported by these patients (1). Although many factors contribute to the anemia of chronic renal failure (CRF), erythropoietin deficiency is the primary cause (2,3).

Treatment with recombinant human erythropoietin (rHuEPO) increases the hematocrit level of dialysis patients within 8 to 14 wk. Standard maintenance therapy requires 50 to 150 U/kg of rHuEPO intravenously (IV) after each hemodialysis treatment (Epogen, package insert; Amgen, Thousand Oaks, CA). Based on a 1993 cost analysis, it was estimated that in the following 5 yr (1994 to 1999), administration of rHuEPO would cost almost $590 million for each 50,000 patients treated (4). These economic considerations and the increasing number of ESRD patients make it important to explore ways of maximizing response to rHuEPO therapy while containing cost and preserving high-quality patient care.

In a preliminary study, we explored the effectiveness of low-dose, weekly subcutaneous (SC) rHuEPO administration to four chronic, stable hemodialysis patients with a pretreatment hematocrit value averaging 30% while they were treated with IV rHuEPO three times a week (5). After 6 months of SC therapy with one third the weekly IV dose (30 U/kg), there was no significant reduction in hematocrit value. These results suggested that weekly, low-dose SC rHuEPO therapy might be safe and effective in hemodialysis patients and could result in a substantial decrease in rHuEPO usage and cost.

Questions have been raised about the efficacy of SC therapy because of the short duration of therapy and/or the higher rHuEPO doses used in the studies (6–8). The duration of therapy is an important consideration because of the long life-span of erythrocytes even in patients with renal failure (9). In other studies of SC rHuEPO therapy, a reduced dose was reported to be effective when administered two to three times per week (10–13).

The purpose of our study was to evaluate the safety and efficacy of once-weekly SC rHuEPO administration to hemodialysis patients over an extended period. Our goal was to determine if once-weekly SC rHuEPO would maintain hematocrit levels as well as standard therapy with IV rHuEPO, but with a substantial reduction in the amount (and cost) of rHuEPO. We evaluated the safety and efficacy of smaller doses of rHuEPO given SC, compared with standard therapy with IV rHuEPO administered with each dialysis.

Materials and Methods

This study was conducted at a large, inner-city dialysis unit, using a protocol approved by the Emory University Human Investigations

Received April 5, 1996. Accepted August 30, 1996.
Portions of this work have been published in abstract form (*J Am Soc Nephrol* 6: 556, 1995) and presented at the 28th Annual Meeting of the American Society of Nephrology, November 5–8, 1995, San Diego, CA.
Correspondence to Dr. Jeff M. Sands, Emory University, Renal Division, 1639 Pierce Drive, Room WMRB338, Atlanta, GA 30322.
1046-6673/0802-0288$03.00/0
Journal of the American Society of Nephrology

Committee. Each subject gave informed consent to participate in the study and the dialysis unit staff were informed of the purpose of the study, the protocol, and the proper technique for SC rHuEPO administration. Epogen was used throughout the study. All subjects were treated by high-flux hemodialysis (14).

All patients over the age of 18 yr who had been treated by hemodialysis three times a week for at least 6 months were screened to determine if they had a stable hematocrit value, were clinically stable as determined by their attending physician, and were willing to change to SC rHuEPO therapy. Other criteria included a predialysis serum urea nitrogen (SUN) level below 100 mg/dL and a diastolic blood pressure < 95 mm Hg (measured at their dry weight). Patients with disorders known to affect the physiologic response to rHuEPO were excluded (*e.g.*, active lupus erythematosus, malignancy, persistent infection, sickle cell disease, hyperparathyroidism [intact parathyroid hormone > 1500 pg/mL], or aluminum toxicity requiring deferoxamine therapy). One hundred seventy-nine subjects were screened according to these criteria. Forty-four were entered into the trial, and 27 completed the 22-month protocol.

The study was divided into three phases:

Phase 1 (6 months): subjects received standard IV rHuEPO at each dialysis;
Phase 2 (10 months): subjects received weekly SC rHuEPO at one third the weekly IV dose determined during Phase 1;
Phase 3 (6 months): subjects received standard IV rHuEPO at each dialysis.

The duration of each phase was chosen to permit an adequate washout period that would eliminate a "carryover effect" of the prior route of administration (15).

Because of the length of our study (22 months), we also followed-up a second group of subjects (drawn from the 135 subjects who refused to receive SC rHuEPO) to assess the impact of changes occurring in the dialysis unit that were independent of the route of administration of rHuEPO. These "control" subjects received standard IV rHuEPO therapy at each dialysis throughout the study. They were matched during Phase 2 of the study for age, gender, and primary nephrologic diagnosis, but not for hematologic values (Table 1). No control subjects died or were lost to follow-up.

The following variables were measured in all subjects:

a. weekly dose of rHuEPO;
b. monthly hematocrit value, reticulocyte count, serum iron saturation, ferritin level, and the amount of IV iron dextran given;
c. systolic, diastolic, and mean arterial blood pressure at the first dialysis of each month when the patient was closest to the dry weight (± 2 dialyses);
d. monthly serum albumin, sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, calcium, and phosphorus levels;
e. monthly PCR and KT/V using a single-pool urea-kinetic model (14); and
f. quarterly intact PTH and aluminum.

Table 1. Demographic data for experimental and control groups

Parameter	Experimental	Control
Age (mean ± SE)	55.0 ± 2.5	56.3 ± 2.5
Gender		
male	18	18
female	9	9
Nephrologic diagnosis		
hypertension	12	15
diabetes mellitus	12	11
other diagnoses (14)	3	1

In Phase 1, the standard dose of rHuEPO for both experimental and control subjects was calculated using a sliding scale based on the hematocrit level with increased doses given at hematocrit levels <34%. During Phase 2, any increase or decrease in rHuEPO dosage (based on the hematocrit level) was given SC but only once a week, beginning with a dose that was roughly one third the weekly IV dose. Regardless of whether rHuEPO administered IV or SC, no rHuEPO was given if the hematocrit was ≥35%. The average number of rHuEPO doses administered per month are shown in Tables 2 and 3. Intravenous iron dextran was given to maintain the transferrin saturation at ≥20%. Oral iron supplements were prescribed by the patient's physician. Patient safety was monitored by the investigators and the patient's nephrologist.

Statistical analysis was performed using repeated measures analysis of variance to determine if there were statistically significant differences between the groups or changes with time ($P < 0.05$ was considered significant). *Post hoc* analysis was performed using paired sample *t* tests with the Bonferroni correction for multiple comparisons (16).

Results

In the experimental group, seven of the 44 subjects who entered the trial withdrew because of dissatisfaction with the treatment, primarily related to stinging at the injection site. Four other subjects died or underwent transplantation, and three were transferred to another unit. Because of a clerical error, two subjects were withdrawn from the study by their physician. During the following 10 months, the average hematocrit value of both experimental and control patients increased 1% over their average baseline values during Phase 1 (Tables 2 and 3). One additional subject was withdrawn because of treatment failure; within the first 3 months, her hematocrit level dropped from 30% to 22% in spite of increasing the dosage of SC rHuEPO. After 6 wk of IV rHuEPO at each dialysis, there was a return to baseline hematocrit level. No specific reason for treatment failure was identified.

Doses of rHuEPO and IV iron dextran given to the two groups pre-treatment (Phase 1), during treatment (Phase 2), and post-treatment (Phase 3) are presented in Tables 2 and 3. As planned, in Phase 2, the SC dose of rHuEPO given to the experimental group was significantly less (approximately one third the weekly IV rHuEPO dose) than in Phases 1 or 3 or than that given to the control group in all phases of the study. For unknown reasons, the doses of iron dextran were lower in both groups during Phase 2 but there were no significant differences in the amount of IV iron dextran given to the two groups over the entire study period.

Hematologic indices and blood pressure data (mean ± SE) for the 6 months of IV therapy, the 10 months of SC therapy (experimental group only), and the final 6 months of IV therapy are presented in Tables 2 and 3. No significant differences between the groups were detected in hematocrit level, reticulocyte count, transferrin saturation, or ferritin level. There was

Table 2. Experimental group[a]

Parameter	Phase 1 (6 months)	Phase 2 (10 months)	Phase 3 (6 months)
Hematocrit/EPO			
hematocrit (%)	30.5 ± 0.6	31.0 ± 0.9	33.4 ± 0.9[b]
rHuEPO dose (U/kg per wk)	103 ± 4	33 ± 5[b]	115 ± 5
rHuEPO doses/month	7.2 ± 0.8	2.4 ± 0.3[b]	9.3 ± 0.8
mean EPO dose/month (U/kg)	246	79[b]	356
reticulocytes (%)	0.73 ± 0.04	1.20 ± 0.07[b]	1.39 ± 0.08[b]
Iron			
iv iron dose (mg/month)	135 ± 23	85 ± 14	113 ± 24
transferrin saturation (%)	22.2 ± 1.1	24.3 ± 1.1	23.5 ± 1.0
ferritin (ng/mL)	359 ± 68	328 ± 82	236 ± 48
Blood pressure			
systolic	154 ± 4	156 ± 4	158 ± 4
diastolic	83 ± 2	82 ± 2	84 ± 3
MAP	106 ± 3	107 ± 3	108 ± 3

[a] Data: mean value over the entire phase ± SE. EPO, erythropoietin; rHuEPO, recombinant human erythropoietin; MAP, mean arterial pressure.
[b] $P < 0.05$ *versus* Phase 1.

Table 3. Control group[a]

Parameter	Phase 1 (6 months)	Phase 2 (10 months)	Phase 3 (6 months)
Hematocrit/EPO			
hematocrit (%)	28.8 ± 0.7	28.9 ± 0.9	30.5 ± 1.1
rHuEPO dose (U/kg per wk)	132 ± 4	132 ± 5[b]	163 ± 7
rHuEPO doses/month	8.4 ± 0.8	8.1 ± 0.9[b]	9.9 ± 0.7
mean EPO dose/month (U/kg)	370	354[b]	536
reticulocytes (%)	0.69 ± 0.04	1.06 ± 0.06[c]	1.14 ± 0.07[c]
Iron			
iv iron dose (mg/month)	107 ± 23	93 ± 14	135 ± 25
transferrin saturation (%)	22.1 ± 1.1	24.8 ± 1.2[c]	24.7 ± 1.4
ferritin (ng/mL)	341 ± 79	283 ± 64	272 ± 52
Blood pressure			
systolic	152 ± 4	155 ± 3	158 ± 3
diastolic	84 ± 2	83 ± 2	85 ± 3
MAP	106 ± 3	107 ± 2	109 ± 3

[a] Data: mean value over the entire phase ± SE. Abbreviations are defined in the footnote to Table 2.
[b] $P < 0.05$ *versus* Experimental Group.
[c] $P < 0.05$ *versus* Phase 1.

a small but significant increase in hematocrit ($P < 0.001$) and reticulocyte count ($P < 0.001$) in both groups during the last two phases of the study (Figure 1). No significant difference was detected in systolic, diastolic, or mean arterial blood pressure (MAP) between the experimental and control groups throughout the study. Likewise, no significant difference between the groups was detected in serum chemistries or dialysis "adequacy" measures (Table 4).

To identify factors associated with the response to SC *versus* IV rHuEPO therapy, correlational analyses were conducted between the hematocrit level and each of the above variables. No significant relationships were detected across the study period in the experimental group, control group, or both groups considered together.

Discussion

To our knowledge, this is the first evaluation of the safety and efficacy of low-dose, weekly SC rHuEPO therapy in hemodialysis patients during long-term therapy. The results demonstrate that SC rHuEPO at one third the total weekly IV dose can successfully maintain a stable hematocrit level in most chronic, stable hemodialysis patients. Evidence of safety and efficacy includes our finding that there were no significant differences in hematocrit level, reticulocyte count, transferrin

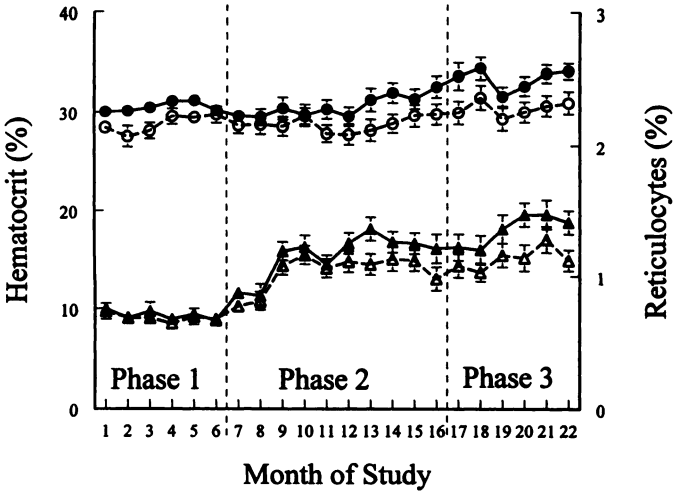

Figure 1. Hematocrit (circles) and reticulocyte count (triangles) for experimental (solid symbols) and control (open symbols) patients during each month of the study. During Phase 1 (Months 1 through 6), all patients received IV rHuEPO. During Phase 2 (Months 7 through 16), experimental patients received SC rHuEPO while control patients received IV rHuEPO. During Phase 3 (Months 17 through 22), all patients received IV rHuEPO. Data: mean ± SE.

saturation, or serum ferritin values in the experimental subjects during the three study phases or between the experimental and control groups.

Recombinant human erythropoietin is approved by the FDA for IV or SC administration. However, it is currently recommended that rHuEPO be administered IV three times a week to chronic hemodialysis patients (Epogen, package insert). Pharmacokinetic studies have demonstrated that the half-life for an IV dose of rHuEPO is approximately 6 to 9 h but after SC administration there is continuous absorption for at least 60 to 70 h (2, 17). This pharmacologic difference may influence the efficacy of the hormone.

It has been suggested that hemodialysis patients might not respond to low-dose, low frequency SC rHuEPO because of increased erythrocyte destruction plus blood losses during hemodialysis (18). Several reports suggest this is incorrect, but generally these reports are based on small numbers of patients receiving multiple doses of rHuEPO each week or are based on short observation periods (6–8,10,12,13,19). Failure to include an appropriate "washout period" can confound interpretation of the results (9). Because there is a lag time of 3 to 6 wk before a change in rHuEPO dose is reflected in the hematocrit value, an evaluation of a change in dose or route of administration should last at least 6 months to avoid the influence of the previous rHuEPO dose. We extended the treatment period to 10 months or more than three lifespans because the lifespan of the erythrocyte is estimated to be approximately 60 days in uremic patients (20).

One subject failed SC therapy; the hematocrit value decreased from 30% to 22% and returned to 30% with IV therapy. We could not find any clinical differences between this subject and others in the experimental group. Because we did not administer SC rHuEPO two to three times a week, we cannot comment on whether this patient would have responded to more frequent administration of SC rHuEPO (10–13). We did not measure plasma erythropoietin levels and cannot comment on the possibility that this patient absorbed rHuEPO poorly. We also cannot explain why both the experimental and control groups had a small, but significant, increase in hematocrit value and reticulocyte count during Phases 2 and 3 of the study, nor can we explain why the IV iron dextran use decreased during Phase 2 in both control and experimental subjects. Because the goal of our study was to show that SC rHuEPO administration would maintain hematocrit value as well as standard therapy with IV rHuEPO, the unexplained changes in reticulocyte count and hematocrit value in both groups suggest they are independent of the route of administration of rHuEPO. We suspect that the increase in hematocrit and reticulocyte count may be related to an increased awareness of the importance of iron replacement by the dialysis staff because we notified them if a patient's transferrin saturation was decreasing towards 20%. The routine policy at this dialysis center is to obtain monthly measurement of serum iron saturation and ferritin level, and to give IV iron dextran when the transferrin saturation is ≤20%. In fact, iron saturation levels were also slightly higher than baseline values in both groups during Phases 2 and 3. These results underscore the importance of iron supplements during rHuEPO therapy to obtain maximum benefit.

The mechanism causing hypertension with rHuEPO is unknown but has been linked to changes in endothelin levels (21). It has been suggested that hypertension may be less severe with SC administration. We found no significant decrease in systolic and diastolic blood pressures or MAP during SC administration.

A major complaint with SC rHuEPO administration was stinging at the injection site. Seven subjects dropped out of the study because of this stinging sensation. They returned to IV rHuEPO therapy at each dialysis and their hematocrit values and serum chemistries were within the range of the treated group. The diluent for the rHuEPO preparation we used contained citrate, a known irritant. Newer preparations contain benzol alcohol, a mild local anesthetic and this preparation could improve patient acceptance of SC administration. If this occurs, then the number of potential long-term patients could increase sharply.

Besides a new diluent, the problems with SC dosing may be mitigated by several advantages over IV injection, including the longer duration of hormone action with continuous stimulation of bone marrow and, importantly, substantial financial savings. A conservative calculation based on our data indicates that simply decreasing the total weekly rHuEPO dose for a 70-kg patient by 50% from 10,500 units (50 U/kg delivered IV three times a week) to 5250 units (once weekly SC) will reduce costs by $3276 per year per patient (rHuEPO = 1.2 cents/U) (22). If 50,000 patients (4) were changed from IV to SC rHuEPO therapy, $164 million could be saved annually without compromise in patient care.

Costs other than for rHuEPO are unlikely to be affected by changing from IV to SC administration. We found no differences in the amount of IV iron dextran administered between groups in any phase of our study. Nursing time was roughly

Table 4. Serum biochemistries and urea kinetic indices of the adequacy of dialysis[a]

Variable	Phase 1		Phase 2		Phase 3		Significance (*P*)
	Exp.	Cont	Exp.	Cont	Exp.	Cont	
Electrolyte							
Na^+ (mEq/L)	136	137	138	139	138	138	0.48
K^+ (mEq/L)	4.8	4.7	4.8	4.7	4.7	4.7	0.48
Cl^- (mEq/L)	97	97	97	97	95	95	0.75
CO_2 (mEq/L)	20	20	22	21	23	22	0.45
Dialysis adequacy							
BUN (mg%)	69	71	66	71	65	71	0.33
creat (mg%)	14.6	14.4	14.6	14.5	14.1	13.9	0.99
Kt/V	1.27	1.35	1.27	1.31	1.27	1.31	0.12
PTH (intact) (pg/mL)	497	469	524	691	433	557	0.51
aluminum (μg/L)	16	21	15	17	24	18	0.87
calcium (mg%)	9.0	9.2	9.3	9.0	9.2	8.8	0.11
phosphate (mg%)	5.5	5.3	5.1	5.8	5.0	5.4	0.32
Ca × P (mg^2/dL^2)	48	47	47	51	44	47	0.33
Nutritional							
albumin (mg/dL)	3.9	3.9	3.7	3.8	3.8	3.8	0.77
PCR (g/kg per day)	0.94	0.98	0.94	0.99	0.99	1.10	0.44

[a] Data: mean value over the entire phase. Exp, experimental group; Cont, control; KT/V, index of removal of urea; PCR, index of dietary protein calculated from urea kinetics (14).

equivalent for IV and SC administration: the extra time of administering SC rHuEPO once a week is offset by the need to administer IV therapy three times a week.

In conclusion, low-dose weekly SC rHuEPO administration was a safe and effective method for maintaining the hematocrit value of the stable hemodialysis patients who volunteered for this study. Weekly SC rHuEPO maintained hematocrit value as well as conventional IV therapy, but with a substantial reduction in the amount and cost of rHuEPO. Additional research is needed to identify those factors associated with treatment failure and to determine whether SC therapy will be efficacious in other hemodialysis patients.

Acknowledgments

The authors thank the nursing staff at REN/Gambro Healthcare-Atlanta for their help throughout the performance of this study. This study was funded by a grant from the Nell Hodgson Woodruff School of Nursing, Emory University (KPP), and by DK45215 (WEM). JMS performed portions of this work during the tenure of an Established Investigatorship from the American Heart Association.

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