

The Journal of Pediatrics

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Volume 128(4)

April 1996

pp 518-523

Pharmacokinetics and effectiveness of recombinant erythropoietin administered to preterm infants by continuous infusion in total parenteral nutrition solution

[Original Article]

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Supported by grants No. HD-00988 and No. HL-44951 from the National Institutes of Health, and an award from The Children's Miracle Network Telethon.

Submitted for publication Sept. 8, 1995; accepted Jan. 1, 1996.

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Abstract

Objectives: To compare the pharmacokinetics and effectiveness of continuously administered recombinant erythropoietin (Epo) in total parenteral nutrition (TPN) solution with daily subcutaneously administered Epo.

Methods: Forty preterm infants in the first 72 hours of life were randomly assigned to receive Epo (200 units/kg per day for 10 consecutive days), either subcutaneously (20 infants, 1051 plus/minus 40 gm, 28.3 plus/minus 0.4 weeks of gestation; mean plus/minus SEM), or added daily to their TPN fluids (20 infants, 1028 plus/minus 36 gm, 27.9 plus/minus 0.4 weeks of gestation). Both groups received iron supplementation (1 mg/kg per day iron dextran in the TPN

solution). Absolute reticulocyte counts and complete blood cell counts with differentials were measured, and transfusions and phlebotomy losses were recorded. Pharmacokinetics were determined in the first 16 infants.

Results: In the infants who received Epo subcutaneously, the elimination half-life was 17.6 plus/minus 4.4 hours on day 3 and 11.2 plus/minus 1.5 hours on day 10; the volume of distribution was 802 plus/minus 190 ml/kg on day 3 and 1330 plus/minus 243 ml/kg on day 10. Serum Epo concentrations were higher on day 3 than on day 10 for both groups (subcutaneous: 400 plus/minus 64 mU/ml vs 177 plus/minus 29 mU/ml, p less than 0.05; TPN: 395 plus/minus 64 vs 194 plus/minus 41 mU/ml, p less than 0.05). Clearance did not differ between the two groups with regard to route of administration and increased significantly from days 3 to 10 in both groups. Reticulocyte counts were similar in both groups. There were no differences between groups in the number of transfusions given, and the overall decline in hematocrit was similar. No adverse effects of Epo were noted in either group.

Conclusions: Adding Epo to the TPN solution in this population results in similar Epo concentrations, clearance, and effectiveness as subcutaneous dosing. (J Pediatr 1996;128:518-23)

Controlled trials have demonstrated that administration of recombinant erythropoietin to preterm infants, beginning in Table IV the first days of life, significantly diminishes the transfusion requirements in a cost-effective manner. [1-4] However, only single-dose pharmacokinetics of Epo administration to preterm infants have been published, [5] and the optimal dose and dosing schedule remains to be determined.

Epo	Recombinant erythropoietin
TPN	Total parenteral nutrition
k_e	Elimination rate constant

Table IV. No caption available

Subcutaneous injections have been the standard route of administration, but concerns have been raised regarding discomfort, repeated breaks of the skin, and the observation that the medication sometimes leaks from the injection site. We proposed avoiding these problems by adding Epo as a constituent of the patient's total parenteral nutrition solution. In a previous report we observed that Epo remained stable during a 24-hour period in commonly used intravenous fluids containing albumin, or in TPN solution containing amino acids. [6] We hypothesized that adding Epo to the TPN solution of preterm infants and administering it as a constant infusion would result in an erythropoietic effect similar to that seen with subcutaneous administration. Our aims were two-fold: to compare the pharmacokinetics of a continuous Epo infusion with those for standard subcutaneous dosing, and to compare the efficacy of continuous Epo versus subcutaneously administered Epo on increasing reticulocyte counts and diminishing erythrocyte transfusions in a randomized, prospective fashion.

METHODS²¹

Infants were eligible for study if they weighed between 750 and 1250 gm, were less than 72 hours of age, and had hematocrits between 0.37 and 0.60. Infants were ineligible for study if hemolytic or hemorrhagic disease was documented, or if significant respiratory disease was present (defined as illness requiring mechanical ventilation with an oxygen requirement of more than 80 percent for 4 or more hours). Infants with significant respiratory distress were ineligible to more closely ensure compliance with the transfusion criteria. Infants were also ineligible if congenital heart disease or disease requiring immediate surgical intervention was present, if seizures were present, or if the infant's mean blood pressures during the first 24 hours of life exceeded the 95th percentile for gestational age. [7]

Infants were randomly assigned to receive 200 units/kg per day of Epo for 10 consecutive days, either subcutaneously or added to their TPN solution. All infants received standard TPN solution containing amino acids (Travasol, Baxter Healthcare Corporation), lipids (Intralipid, KabiVitrum), pediatric multivitamins (M.V.I. Pediatric, Astra), and trace elements (P.T.E.-5, Lymphomed). All infants received 1 mg/kg per day of elemental iron, in the form of iron dextran (InFeD, Schein Pharmaceutical) added to their TPN fluids. [8]

Changes in TPN composition, volume, and decisions to initiate feedings were made by the primary caregiver. Feedings were advanced according to the clinical status of the infant. Heart rate, respiratory rate, and blood pressure were monitored by the bedside nurses during the study period, and infants were observed for specific adverse reactions. A complete blood cell count with differential and absolute reticulocyte count were obtained on days 1, 5, 10, and 15. Serum ferritin concentrations were measured on day 10 in nine infants.

For the first 16 patients enrolled in the study, serum Epo concentrations were measured by enzyme-linked immunoassay (Quantikine kit, R&D Systems, Minneapolis, Minn.) on day 3 and day 10 at 2, 6, 10, and 24 hours after the dose for the subcutaneous group, and once each on days 3 and 10 (12 hours after the start of the new TPN) for the TPN group. The 24-hour point was used as the time zero sample. The elimination rate constant was determined with the 6-, 10-, and 24-hour samples. If the peak concentration occurred at the 10-hour point (which occurred with two infants on day 3, and two infants on day 10), the 10- and 24-hour samples were used to determine the k_e . The area under the curve was calculated with the trapezoidal rule. Both groups used a one-compartment, first-order absorption and elimination model for pharmacokinetic calculations. Elimination rate, clearance (dose per area under the curve), volume of distribution (clearance per k_e), and half-life ($0.693/k_e$) were calculated for the subcutaneous administration group, and clearance was calculated for the TPN group. Clearance and volume of distribution were standardized per kilogram body weight.

The number and volume of transfusions were recorded, as was the total volume of blood withdrawn. Transfusions were administered during the 15-day study period if the hematocrit was less or equal to 0.30 (or hemoglobin less or equal to 10 gm/dl), and the infant had one or more symptoms thought to be attributable to anemia. Symptoms were defined as tachycardia (heart rate greater than 160 beats/min, calculated as the average of all heart rates recorded by the bedside nurse during the preceding 24-hour period), an increasing oxygen requirement (an increase in the inspired fraction of oxygen greater than 0.20 during a 24-hour period), or an increase in the number of episodes of bradycardia requiring stimulation to increase the heart rate from less than 60 beats/min (an increase of such episodes by three or more per day). Infants in both groups whose hematocrits were greater than 0.30 and yet whose phlebotomy losses exceeded 10 ml/kg body weight were eligible to receive an infusion of 0.9 percent sodium chloride, administered in a volume of not less than 10 ml/kg. The intent of this treatment was to

aid in the prevention of hypovolemia [9] when the phlebotomy losses were considerable, but the hematocrit was above the criterion for transfusion. Infants were not given transfusions if they had no symptoms, even if the hematocrit decreased below 0.30.

A power analysis (with a one-sided significance level of 0.05 and a power of 80 percent) determined that a sample size of approximately 40 infants was needed to show similar efficacy between the two routes of administration. Demographic data were compared with an unpaired t test. Laboratory data were compared with two-tailed, paired, or unpaired t tests. When data were not parametrically distributed, the Wilcoxon signed rank test was performed. A one-tailed Fisher Exact Test was used to assess differences in the number of transfusions between groups.

Informed consent was obtained from parents of the study infants, and the study was approved by the institutional review board of the University of Florida.

RESULTS¹

There were no differences between groups in birth weight, gestational age, birth hematocrit, or absolute reticulocyte count at the start of the study [Table 1](#). There were no differences between groups in the number of infants treated with surfactant for respiratory distress syndrome, in the incidence of grade 3 or 4 intraventricular hemorrhage, or in the incidence of necrotizing enterocolitis. Equal numbers of patients in each group were treated prophylactically with indomethacin to prevent intraventricular hemorrhage [10] (data not shown).

	Route of Epo administration	
	Subcutaneous (n = 20)	TPN (n = 20)
Birth weight (gm)	1051 ± 40	1028 ± 36
Gestation (wk)	28.3 ± 0.4	27.9 ± 0.4
Age at entry (hr)	42 ± 5	53 ± 3*
Hematocrit at birth (L/L)	0.44 ± 0.01	0.42 ± 0.01
Absolute reticulocyte count (×10 ³ /μL)	448 ± 46	446 ± 58

Values represent mean ± SEM.
*p = 0.054.

Table 1. Characteristics of the study infants

Patients randomly assigned to the subcutaneous administration group first received Epo at 42 plus/minus 5 hours of age; infants assigned to TPN dosing first received Epo at 53 plus/minus 3 hours of age (p = 0.054). One infant in the TPN Epo group had the TPN discontinued on day 5 of

the study (it was judged to no longer be needed; all other infants were receiving at least half of their total fluids parenterally at the end of the study), but was included in the analysis. Another infant in the TPN Epo group died on study day 14 of respiratory failure, but was also included in the analysis. One infant originally assigned to receive Epo subcutaneously died with a grade IV intraventricular hemorrhage (before receiving any Epo), and was not included in the analysis. Therefore 41 patients were enrolled, and 40 were evaluated.

The Epo pharmacokinetics for both groups were similar [Table II](#). Serum Epo concentrations decreased from day 3 to day 10 in both the subcutaneous administration group [Figure 1](#) and the TPN group [Table II](#). In the subcutaneous administration group the elimination half-life was 17.6 plus/minus 4.4 hours on day 3, and 11.2 plus/minus 1.5 hours on day 10; the volume of distribution was 802 plus/minus 190 ml/kg on day 3 and 1330 plus/minus 243 ml/kg on day 10. Clearance increased from day 3 to day 10, and was similar for both routes of administration [Table II](#).

Route and study day	k_e (hr ⁻¹)	Half-life (hr)	Volume of distribution (ml/kg)	Clearance (ml/kg/hr)	Epo (mIU/ml)
SC day 3	0.06 ± 0.01	17.6 ± 4.4	802 ± 190	35 ± 5	400 ± 64
SC day 10	0.07 ± 0.01	11.2 ± 1.5	1330 ± 243	87 ± 16*	177 ± 29*
TPN day 3	—	—	—	26 ± 4	395 ± 64
TPN day 10	—	—	—	65 ± 20*	194 ± 41*

SC, Subcutaneous.
Values represent mean ± SEM
**p* < 0.05 versus day 3.

Table II. Pharmacokinetics of the first eight patients in each group

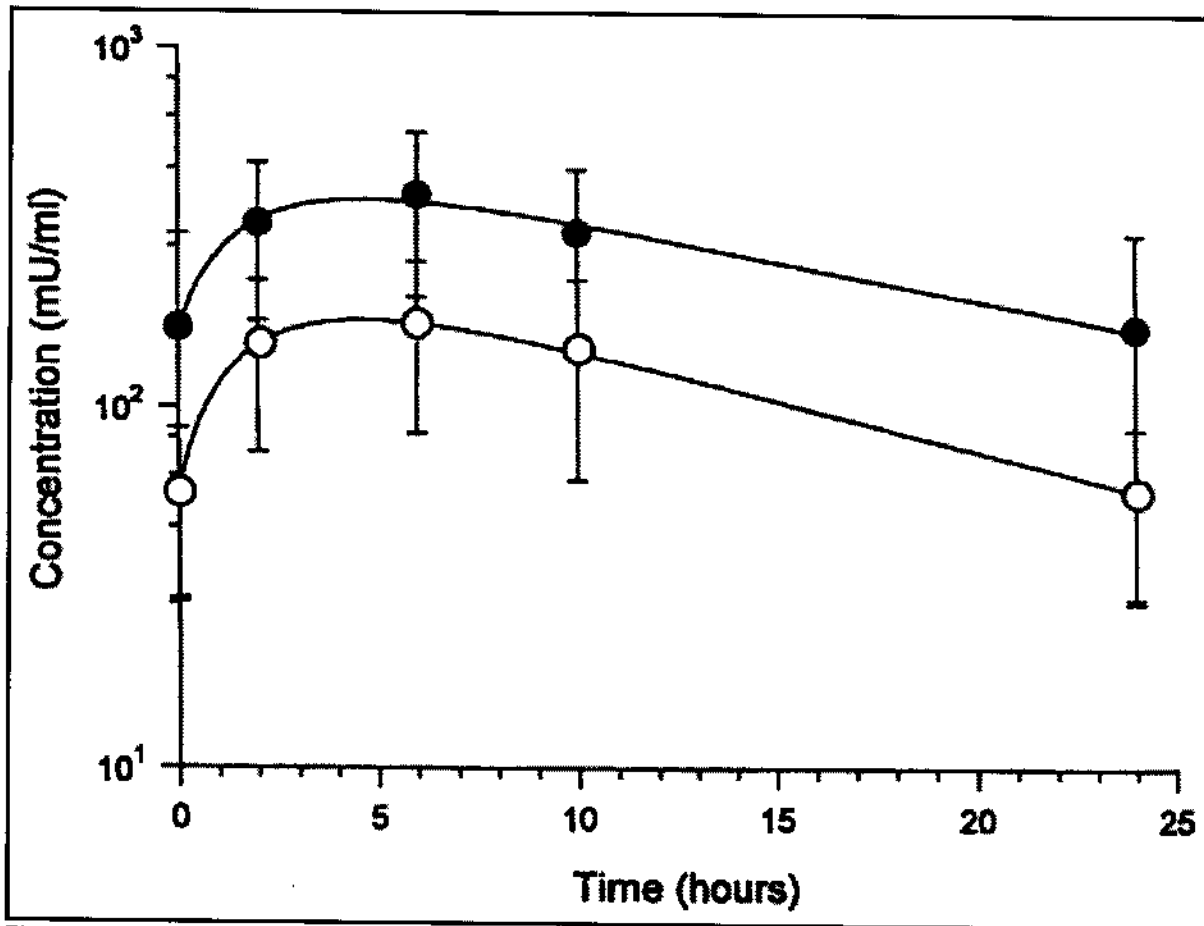


Figure 1. Erythropoietin concentrations at 2, 6, 10, and 24 hours after a subcutaneous dose of 200 units/kg recombinant Epo. Day 3 concentrations are represented by the closed circles, and day 10 concentrations by open circles. Values represent mean plus/minus SEM.

Absolute reticulocyte counts in both groups declined by day 5, but increased to levels seen at birth by day 10 [Figure 2](#). There were no differences between groups in absolute reticulocyte counts during the 15-day study period. Hematocrits declined in both groups [Figure 2](#). Although at birth the hematocrits of the two groups were similar, by the start of the study those who received Epo subcutaneously had a slightly higher hematocrit than did the TPN Epo recipients (0.40 plus/minus 0.01 vs 0.36 plus/minus 0.01, $p = 0.06$). During the next 15 days, hematocrits declined by 0.05 plus/minus 0.01 in the TPN group, and by 0.06 plus/minus 0.02 in the subcutaneous group.

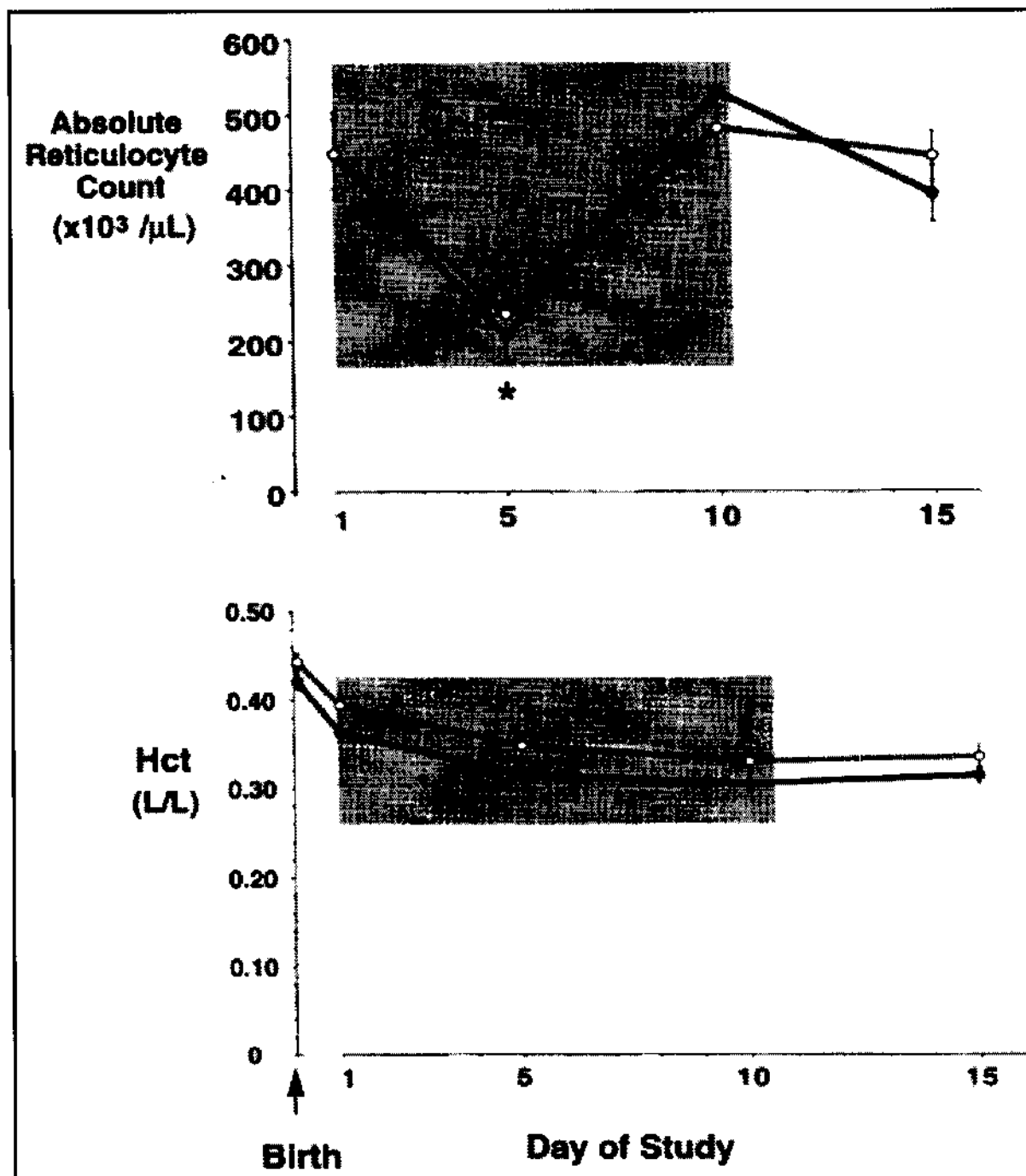


Figure 2. Absolute reticulocyte counts (upper panel) and hematocrits (lower panel) during the study period for recipients of subcutaneously administered Epo (dashed line, open circles) and recipients of Epo in their TPN solutions (solid line, solid circles). The shaded area represents the 10-day treatment period. Absolute reticulocyte counts were lower in both groups on day 5, then increased to day 1 levels by day 10. Values represent mean plus/minus SEM.

Phlebotomy losses were similar in the two groups Table III. Eight infants in each group did not receive a transfusion during the study. There were no significant differences in number or volume of transfusions between groups during the study Table III.

	Route of Epo administration	
	Subcutaneous (n = 20)	TPN (n = 20)
Phlebotomy losses (ml/kg) (range)	34 ± 5 (15-86)	40 ± 6 (11-121)
Percent of patients who received transfusions	60%	60%
Transfusions per patient	1.2 ± 0.3	1.4 ± 0.3
Volume transfused (ml/kg)	16 ± 4	18 ± 5
Number of transfusions per transfused patient (range)	1.9 ± 0.4 (1-5)	2.3 ± 0.4 (1-5)
Blood transfused per transfused patient (ml/kg)	26 ± 5	30 ± 6

Values (except percentage of patients who received transfusions) represent mean \pm SEM.

Table III. Phlebotomy losses and transfusions given from birth to day 15 of the study

There were no significant changes in platelet count or absolute neutrophil count in either group throughout the study. Moreover, no adverse effects of Epo administration were noted, and there were no differences in mineral or electrolyte requirements between groups during the study. Serum ferritin concentrations in the two groups after 10 days of intravenous administration of iron dextran were 225 plus/minus 42 ng/ml (range 77 to 493 ng/ml), and did not differ between treatment groups.

DISCUSSION ²¹

Numerous clinical trials testing the administration of Epo in preterm infants have evaluated a wide range of doses and dosing schedules. [1-4,11-13] Early trials were performed before neonatal pharmacokinetic data became available to aid in choosing the dose or dosing schedule, and the dosing schedules of many trials were based on Epo pharmacokinetics from adults. Recently

Brown et al. [5] reported peak concentrations and half-lives for single doses of Epo administered either subcutaneously or intravenously to preterm infants. However, information regarding steady-state Epo pharmacokinetics in preterm infants is lacking.

Our study differs from that reported by Brown et al. [5] in that multiple-dose pharmacokinetics were performed. We determined that serum Epo concentrations and clearance were similar for the two routes of administration. Serum Epo concentrations declined significantly, and clearance increased from day 3 to day 10 in both populations. This phenomenon has been noted in neonates treated with other medications [14-16] and is thought to be related in part to maturation of renal and hepatic function. Changes in the pharmacokinetics of Epo, however, appear to be unique to preterm infants. Although there is not complete agreement on the change occurring in pharmacokinetics with multiple dosing, adult animals and human beings receiving long-term Epo therapy do not appear to experience altered pharmacokinetics of the drug. [17-19]

Most neonates have a decrease in total body water from birth to day 10 of life. On this basis, the volume of distribution of Epo would be expected to be lower (assuming that the distribution of Epo is in part dependent on total body water), and the serum Epo concentrations higher, at the end of our study. We found the opposite. The increase in apparent volume of distribution supports the theory that Epo is being cleared more rapidly, perhaps through increased specific receptor binding. Because the concentration of progenitor cells is higher in the circulation in neonates, [20] we speculate that there might be more cells with Epo receptors on their surface, and therefore more binding of Epo. As erythroid progenitor cells are stimulated by Epo to expand clonally, an even greater number of erythroid progenitors may become available to bind Epo, and thus to increase the clearance and expand the volume of distribution of Epo.

Significant differences in Epo pharmacokinetics exist among adults, children, and neonates. The clearance and volume of distribution of Epo are significantly greater in preterm neonates than in children or adults. It is unknown when Epo pharmacokinetics change from neonatal values to pediatric and adult values. A previous study by Kling et al. [21] evaluating Epo (750 U/kg per week) administered to a term neonate with renal failure reported a volume of distribution of 82.8 ml/kg at the start of therapy (1 month of age), and a volume of distribution of 57.8 ml/kg at 3 months. The clearance was 12.6 ml/kg per hour at 1 month, and 14.8 ml/kg per hour at 3 months of age. These values are similar to those published for the pediatric population, [22,23] in which clearance ranges from 10 to 14 ml/kg per hour, and volume of distribution averages 60 to 80 ml/kg. Pharmacokinetic values calculated in healthy adults are similar to those calculated in pediatric patients, in that clearance of Epo ranges from 4 to 15 ml/kg per hour, and volume of distribution ranges from 40 to 90 ml/kg. [24]

It is unknown whether constantly elevated serum Epo concentrations are more effective in stimulating erythropoiesis than high concentrations interspersed with low concentrations. In this study, we demonstrated that addition of Epo to the TPN solution of very low birth weight infants resulted in increases in reticulocyte counts and hematocrits similar to those after subcutaneous Epo dosing.

Previous studies in adults and pediatric patients have reported limitations of erythropoiesis when iron supplementation is not adequate. [25,26] Neonatal studies have evaluated the use of both parenteral and enteral iron, in doses ranging from 2 to 20 mg/kg per day, [1,4,9-11,27,28] and have noted a variety of erythropoietic responses. One concern about iron administration has been the reported increased risk of infection. [29,30] However, past studies reporting increased incidence of infection in infants who received parenteral iron were based on studies with intramuscular doses that far exceeded (greater than 100 mg/day) the dose used in this study. Friel

et al. [8] recently evaluated the use of iron dextran added to the TPN of 14 very low birth weight infants, and noted that at doses of 200 to 250 microgram/kg per day (with a parenteral plus enteral iron intake of 400 microgram/kg per day), infants remained in negative iron balance during the course of study. They noted no adverse effects of this treatment, and recommended an iron intake of 1000 microgram/kg per day supplemented in TPN.

On the basis of conservative estimates of iron requirements, we hypothesized that 1 mg/kg per day given parenterally would provide an adequate supply of iron for preterm infants receiving Epo. Infants in both study groups had active erythropoiesis, without obvious adverse effects. Although ferritin levels are an incomplete measure of iron deficiency or iron overload, of the patients in whom ferritin levels were measured, none had concentrations above the normal range for newborn infants. [31] Further studies are required to determine the optimal iron dose for preterm infants, especially those infants undergoing active erythropoiesis in the face of ongoing blood loss. [32] In addition, compatibility issues may arise when other medications are administered simultaneously in TPN solution and will have to be addressed in further studies.

We conclude that, in this population, adding Epo to the TPN solution was as effective as subcutaneous dosing and resulted in similar Epo concentrations and clearance. We speculate that adding Epo to the TPN solution will avoid the problems inherent in treating very low birth weight infants by the subcutaneous route. Further studies (including more conclusive evaluation of iron requirements) are needed to determine the pharmacokinetics of long-term administration of Epo in preterm infants.

We thank Lisa Mandell, RN, JD, and Jenny Harcum, RN, for their assistance in monitoring enrolled patients and collecting data; Hartmut Derendorf, PhD, for assistance in pharmacokinetics; and John C. Adair, MD, for statistical assistance.

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