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Efficacy of Bolus Intravenous Iron Dextran Treatment in Peritoneal Dialysis Patients Receiving Recombinant Human Erythropoietin

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The efficient use of recombinant human erythropoietin (rHuEPO) requires adequate body stores of iron. In peritoneal dialysis (PD) patients, iron replacement is most commonly administered orally. In this study, we prospectively followed 7 stable PD patients following bolus intravenous infusion of 1 g iron dextran in an outpatient setting. At 12 weeks, significant ($p < 0.05$) increments in mean hematocrit from 29.13% to 34.85%, transferrin saturation from 10.15% to 29.33%, serum iron from 27.38 to 67.00 µg/dL, and serum ferritin from 150.30 to 331.40 ng/mL were observed. Post-treatment, there was less requirement of rHuEPO, and at six months there was a 26% reduction in the mean weekly subcutaneous rHuEPO dose. At 12 weeks, serum albumin increased significantly from 3.50 to 3.76 g/dL ($p < 0.05$). There was no abnormality in any of the measured liver function tests. No patient developed an adverse or allergic reaction. We concluded that bolus intravenous infusion of iron dextran is an effective and well-tolerated method of repleting iron stores, and will allow a more efficient and economic use of rHuEPO in PD patients.

Key words
Iron dextran, intravenous infusion, anemia, end-stage renal disease

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Introduction

The use of recombinant human erythropoietin (rHuEPO) to treat anemia in patients with end-stage renal disease (ESRD) is a major therapeutic advance (1,2). However, rHuEPO therapy frequently causes iron deficiency due to transfer of bone marrow iron stores to erythroid progenitor cells. Therefore, efficient use of rHuEPO requires long-term maintenance therapy with iron and frequent monitoring for adequacy of iron stores (3). Iron therapy in dialysis patients is most commonly administered orally. However, patient noncompliance, gastrointestinal side effects, and poor gastrointestinal absorption due to drug interaction are the limiting factors in the efficacy of oral iron therapy. To eliminate these factors, the intravenous route has become the preferred method of iron supplementation in chronic hemodialysis patients. Alternatively, in some situations, for example in peritoneal dialysis (PD) patients, the intramuscular route has been successfully used. In both of these parenteral methods, several small doses (usually 100 mg) of iron dextran are administered on successive days or weeks. Neither of these methods, however, is an attractive alternative in outpatient PD patients. The purpose of this study, therefore, was to evaluate prospectively the efficacy of bolus infusion of intravenous iron dextran in PD patients with iron deficiency anemia during rHuEPO treatment.

Patients and methods

Seven adult, stable ESRD patients (6 Caucasian and 1 Hispanic) were prospectively followed for a period of six months. There were 5 females and 2 males. Mean age was 33.4 years (range 21 – 54

years). Five patients were on continuous ambulatory peritoneal dialysis, and 2 were on continuous cycling peritoneal dialysis. The average duration on PD was ten months (range 1 – 37 months). All patients received oral iron supplementation (average 3.5 tablets of ferrous sulfate per patient per day) and self-administered rHuEPO subcutaneously. None of the patients had recent bleeding episodes, hematologic disease other than anemia, hyperparathyroidism, aluminum toxicity, and/or recent blood transfusion. Patients were admitted to the outpatient infusion room of the Milton S. Hershey Medical Center, Hershey, Pennsylvania, and received brief physical examinations. They were informed about the treatment procedure and anticipated side effects. After premedication with intravenous hydrocortisone (100 mg) and diphenhydramine (25 mg), and oral acetaminophen (1000 mg), all patients received a test dose of intravenous iron dextran (25 mg) given slowly over ten minutes by a nephrologist. The patients were closely observed for 15 minutes for possible adverse or anaphylactic reactions. Then, 975 mg of iron dextran mixed in 500 mL of 0.45% sodium chloride solution were infused at a rate of 100 mL per hour for five hours (delivering 3.25 mg of iron dextran per minute). During the infusion, pulse rate and blood pressure were recorded at 30-minute intervals. Postinfusion and prior to discharge, patients were observed an additional 30 minutes. Patients were then followed in the outpatient PD clinic at monthly intervals. Complete blood count, serum iron, ferritin, total iron binding capacity (TIBC), transferrin saturation (TSAT) (serum iron divided by TIBC multiplied by 100), electrolytes, blood urea nitrogen, and serum creatinine were measured monthly. Liver function tests (alkaline phosphatase, total bilirubin, and aspartate aminotransferase) and serum albumin were measured every three months.

Statistical methods

Analysis of variance of repeated measures was used for analysis of hematocrit and rHuEPO dose data. Two-tailed Student's t-tests were used for comparing the baseline and subsequent data. All results are expressed as mean ± standard error of mean. A probability value of <0.05 was considered significant.

Results

When compared with pre-infusion, at 12 weeks there were significant increases in hematocrit from 29.13 ± 1.14% to 34.85 ± 0.77% ($p < 0.005$), TSAT from 10.15 ± 1.62% to 29.33 ± 3.79% ($p < 0.005$), serum iron from 27.38 ± 4.59 to 67.00 ± 9.24 μg/dL ($p < 0.005$), and serum ferritin from 150.30 ± 47.86 to 331.40 ± 110.69 ng/mL ($p < 0.05$). Serum albumin also increased significantly from 3.50 ± 0.11 to 3.76 ± 0.13 g/dL ($p < 0.05$). There was no significant abnormality in liver function tests (Table I, Figure 1). At six months, the mean weekly dose of subcutaneous rHuEPO was reduced from 8000 ± 2070 to 5875 ± 1171 units; statistical significance was not achieved due to the small number of our patient population (Figure 2). None of the patients developed immediate or delayed hypersensitivity and/or anaphylactoid reaction. Clinical evidence of volume

TABLE I Laboratory variables (mean ± SEM)

	Baseline	*6 weeks*	*12 weeks*	*6 months*
HCT (%)	29.13±1.14	32.43±0.97[b]	34.85±0.77[a]	32.85±0.91[b]
TSAT (%)	10.15±1.62	28.31±5.70[b]	29.33±3.79[a]	20.93±2.52[b]
Iron (μg/dL)	27.38±4.59	59.13±10.29[a]	67.00±9.24[a]	41.33±4.71[b]
Ferritin (ng/mL)	150.30±47.86	430.90±81.32[b]	331.40±110.69[b]	131.60± 53.73
Albumin (g/dL)	3.50±0.11	–	3.76±0.13[b]	–
AST (U/L)	38.00±8.47	–	25.00±4.19	–
ALP (U/L)	121.43±12.05	–	112.43±17.97	–
T. bili (mg/dL)	0.50±0.05	–	0.48±0.02	–

[a] $p < 0.005$.
[b] $p < 0.05$ (compared with baseline).
HCT = hematocrit; TSAT = transferrin saturation; AST = aspartate aminotransferase; ALP = alkaline phosphatase; T. bili = total bilirubin.

overload during and/or following infusion was not observed.

Discussion

This study in patients clearly demonstrates that bolus intravenous iron dextran infusion can be used effectively in the treatment of iron deficiency anemia in PD patients during rHuEPO therapy. When compared with the baseline, at 12 weeks there were significant increments in mean hematocrit, TSAT, serum iron, and serum ferritin. Also, the therapy with rHuEPO became more effective due to better iron stores, demonstrated by the mean rHuEPO dose at six months, which was 26% less

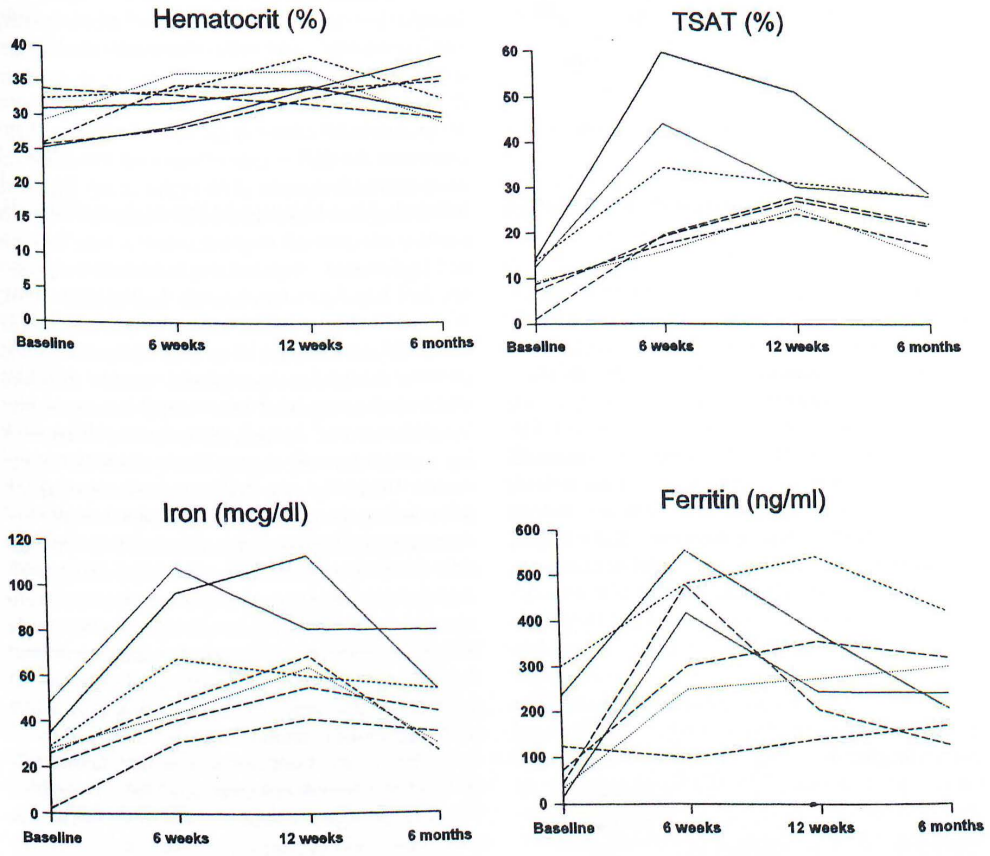

FIGURE 1 Changes in individual patients' hematocrit, transferrin saturation (TSAT), serum iron, and ferritin levels before and after intravenous iron dextran infusion.

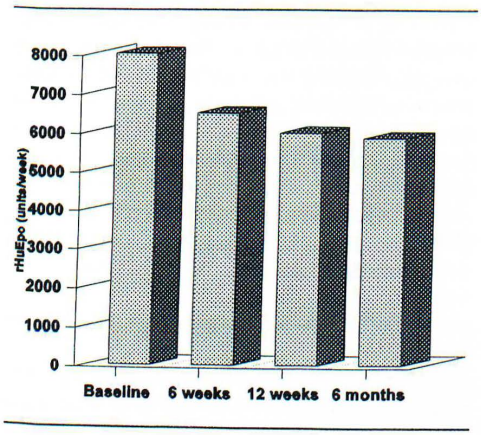

FIGURE 2 Mean changes in weekly subcutaneous rHuEPO doses before and after intravenous iron dextran infusion.

than that of the baseline. Overall, the bolus iron dextran infusion appeared to be safe and was well tolerated.

With the advent of rHuEPO therapy, nonspecific therapies for managing the anemia of renal failure are of historic interest. Since its release for use in dialysis patients in July, 1989, rHuEPO therapy has resulted in an improved quality of life for the majority of patients with ESRD (1–3). The economic cost of rHuEPO therapy is substantial when the expense of treatment of almost 90% of patients with end-stage renal disease is a federal obligation. With continued pressure to reduce costs, judicious use of rHuEPO is imperative. Although use of the subcutaneous route has helped in decreasing the dosage requirement of rHuEPO by 25% – 50%, undertreatment remains a common problem (4,5).

The most common cause of rHuEPO resistance is iron deficiency anemia resulting from enhanced iron utilization due to erythropoietin-enhanced red blood cell formation, and almost all patients on rHuEPO therapy are treated with oral iron supplementation. Although the most convenient and easiest means of iron supplementation, there are many disadvantages inherent in the use of oral iron therapy. Many patients are noncompliant due to side effects such as nausea, stomach irritation, and constipation, especially when subjected to the maximum therapeutic dose (6). In addition, poor gastrointestinal absorption and decreased bioavailability — due to drug interaction with antacids, phosphate binders, and gastric acid reduction drugs, for example, histamine 2 antagonist and proton pump inhibitors — further reduce the efficacy of oral iron (7). Finally, side effects and efficacy profiles also depend on the type of preparation ingested. Wingard *et al.* (8) reported that patients treated with a fumarate-containing oral iron preparation (Tabron) had the highest iron indices when compared with other preparations.

In hemodialysis patients with iron deficiency anemia, iron dextran given in small doses weekly or biweekly has practically eliminated most of the problems associated with oral iron preparation. Compliance is guaranteed, and the number of pills the patient must take is reduced. Fishbane *et al.* (9) compared the safety and efficacy of biweekly intravenous iron dextran (100 mg/session) with oral iron therapy in chronic hemodialysis patients. In this study, patients receiving intravenous iron dextran had significantly higher hematocrit and iron indices and required significantly less rHuEPO (9). While the intravenous route is preferred for hemodialysis patients, it is less desirable in PD patients due to poor peripheral access. Suh and Wadhwa (10) reported that weekly intramuscular injections of iron dextran are effective in correcting anemia and restoring all iron indices in PD patients. However, for logistical reasons, both parenteral methods of iron replacement in PD patients are unacceptable alternatives. Moreover, besides the pain and trauma associated with both intravenous and intramuscular methods, the inconvenience and economic loss involving repeated clinic visits can be substantial. Our study has demonstrated the efficacy of bolus infusion of iron dextran in PD patients who developed iron deficiency anemia while receiving rHuEPO therapy.

In this study, improvement in hematocrit following bolus iron dextran persisted for six months. This change in erythropoiesis was most likely due to improvement in iron stores. The maximum increment in mean hematocrit was observed at 12 weeks; mean serum iron and TSAT were also maximally increased at 12 weeks. Beyond this point, along with the fall in serum iron and TSAT, hematocrit began to decrease. Nonetheless, at six months all these parameters, except for serum fer-

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