Intravenous Infusion of Total Dose Iron Is Superior to Oral Iron in Treatment of Anemia in Peritoneal Dialysis Patients: A Single Center Comparative Study

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Abstract. In the treatment of anemia of chronic renal failure, the most common cause of recombinant human erythropoietin (rhEPO) resistance is iron deficiency. In peritoneal dialysis (PD) patients, oral iron therapy is an accepted and convenient method of iron supplementation. The effectiveness of oral iron, however, is limited by many factors, including gastrointestinal side effects and poor gastric absorption. This study prospectively compared the efficacy of single intravenous infusion of total dose iron (ITDI) group given in an outpatient setting with oral iron (oral group) for the treatment of anemia in PD patients. Twenty-five adult stable PD patients with baseline hematocrit 25 to 35% were entered into the study. Thirteen patients with serum transferrin saturation (TSAT) <25% received ITDI, and 12 patients with TSAT between 25 and 35% received oral iron. One patient in the oral group received emergent blood transfusion and was excluded from analysis. Hematocrit and iron indices were measured at monthly intervals. Doses of rhEPO were adjusted monthly to maintain target hematocrit at 35%. At the end of the study (6 mo), despite similar baseline mean hematocrit (31.0 ± 0.9 versus 33.0 ± 1.0%), comparable mean baseline weekly rhEPO dose (7886 ± 1449 versus 6370 ± 1553 U/wk), and significantly lower level of mean TSAT (11.3 ± 3.5 versus 30.1 ± 3.5%; P < 0.05), the ITDI group when compared with the oral group had significantly higher mean hematocrit (36.0 ± 1.0 versus 31.4 ± 1.1%; P < 0.05) and TSAT (33.7 ± 3.7 versus 22.6 ± 4.0%; P < 0.05) values. In addition, the final mean dose of weekly rhEPO was significantly lower in the ITDI group (4799 ± 981 versus 9998 ± 1027 U/wk; P < 0.05). No patient in the ITDI group developed an adverse reaction to intravenous iron. It is concluded that ITDI represents a more efficacious method of iron supplementation in PD patients receiving rhEPO. Moreover, ITDI is safe and well tolerated and can be administered in an outpatient setting. (J Am Soc Nephrol 9: 664–668, 1998)

The introduction of recombinant human erythropoietin (rhEPO) in the mid-1980s to treat anemia in patients with end-stage renal diseases (ESRD) was a major therapeutic advance (1,2). Because rhEPO therapy is frequently associated with functional iron deficiency due to transfer of bone marrow iron to newly formed erythrocytes, efficient use of rhEPO requires adequate replenishment of body stores of iron (3–10).

Iron therapy in ESRD patients on dialytic treatment is most commonly administered orally. Many factors, including patient compliance, gastrointestinal side effects, and poor gastrointestinal absorption due to drug interaction, limit the clinical efficacy of oral iron therapy (11–13). In hemodialysis (HD) patients, small doses of frequently administered intravenous iron have been found to be effective in maintaining iron stores (7,8,10,14–16). Alternatively, in peritoneal dialysis (PD) patients, the intramuscular route has been successfully used (17). However, in addition to the discomfort to patients, the requirements of repeated venous access and frequency of iron administration for the above parenteral methods preclude their widespread acceptance in PD patients. Thus, for PD patients, oral iron (despite its potential difficulties and suboptimal clinical efficacy) remains the most common method of iron supplementation. As a result, many of the PD patients are persistently anemic despite concomitantly receiving large doses of rhEPO and maximal therapeutic dose of oral iron. Previously, we have reported the safe and effective use of intravenous infusion of total dose iron (ITDI) in the treatment of anemia in PD patients (18). The purpose of this current study was to compare prospectively the efficacy of ITDI with oral iron for maintenance iron therapy in PD patients receiving rhEPO.

Materials and Methods

Patients

Over a period of 18 mo, after screening 40 patients, 25 stable adult (age, >18 yr) ESRD patients with hematocrit levels between 25 and 35% receiving PD at the Milton S. Hershey Medical Center, Hershey, PA, were entered into the study. Patients (n = 13) with serum transferrin saturation of <25% and who failed to achieve a target hematocrit of 35% while on oral iron sulfate (325 mg three times a day [195 mg elemental iron] for 3 mo) received ITDI. Other patients (n = 12) with serum transferrin saturation (TSAT) between 25 and 35% and considered to have adequate iron stores (9) received oral

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ferrous sulfate (325 mg three times a day for 6 mo). Because it is the better marker of iron available for erythropoiesis, in this study TSAT (serum iron divided by total iron binding capacity multiplied by 100), but not serum iron or serum ferritin, was selected to evaluate the response to iron therapy. Patients with age <18 yr (n = 4), TSAT >35% (n = 3), and TSAT <35% plus serum ferritin >500 ng/ml (n = 0) were not entered into the study. Other patients with identifiable causes of anemia other than ESRD, such as occult gastrointestinal bleeding (n = 2), hyperparathyroidism (intact parathyroid hormone [iPTH] >400 pg/ml) (n = 2), and aluminum toxicity (>50 μg/L) (n = 1); abnormalities in liver function tests (alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase 1.5 times the upper limit of normal) (n = 2); and inadequate dialysis (combined peritoneal and residual renal clearance: weekly Kt/V <1.8) (n = 1) were excluded.

**Study Protocol**

ITDI was administered as described previously (18). Briefly, after premedication with hydrocortisone (100 mg, intravenously), oral acetaminophen (1000 mg), and oral diphenhydramine (25 mg), patients received a 25-mg intravenous test dose of INFeD® (iron dextran, Schein Pharmaceuticals, Steris Laboratories, Phoenix, AZ). If there was no adverse reaction within 15 min, 975 mg of INFeD® mixed in 500 ml of normal saline was infused intravenously over 4 h. Patients were monitored closely during and 30 min after infusion. During the follow-up period, oral iron therapy was not resumed in the ITDI group. One patient in the oral group required emergent blood transfusion and was excluded from the final analysis. All patients were followed monthly in the outpatient PD clinic for 6 mo. Complete blood counts, electrolytes, blood urea nitrogen, serum creatinine, liver function tests, and iron indices (serum iron, ferritin, and total iron binding capacity) were measured monthly. rhEPO was administered weekly by subcutaneous route. Because we had recently increased the target hematocrit for our PD program from 31 to 35%, the doses of rhEPO were adjusted monthly to maintain a hematocrit level of 35%. At the end of the study, plasma iPTH and Kt/V were repeated.

**Statistical Analyses**

All results are reported as mean ± SEM. The analysis of differences in hematocrit, serum iron, serum ferritin, TSAT, and rhEPO doses between the ITDI and oral groups at each follow-up time was performed with repeated-measures analysis of covariance models. All P values were adjusted for age, sex, and number of months on dialysis in the repeated-measures analysis of covariance models. For each response variable (e.g., hematocrit), two models were fitted to the data. The first model was not adjusted for baseline differences in the response variable (e.g., baseline hematocrit), whereas the second model was adjusted for baseline differences. Differences in baseline variables between the ITDI and oral groups were assessed with ANOVA, t tests, or Fisher's exact test when appropriate. Analysis was performed using the Statistical Analysis System statistical software package. Differences were considered significant when P was <0.05.

**Results**

Patient demographics are listed in Table 1. The mean age (38.1 ± 3.5 versus 51.9 ± 4.1 yr; P < 0.05) and duration of peritoneal dialysis (12.1 ± 3.6 versus 27.1 ± 6.1 mo; P < 0.05) were significantly lower in the ITDI group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ITDI</th>
<th>Oral</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>M/F</td>
<td>7/6</td>
<td>8/3</td>
</tr>
<tr>
<td>Age (mean ± SEM)</td>
<td>38.1 ± 4.7</td>
<td>51.9 ± 4.1b</td>
</tr>
<tr>
<td>Caucasian</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>CAPD/CCPD</td>
<td>11/2</td>
<td>9/2</td>
</tr>
<tr>
<td>Months on dialysis</td>
<td>12.1 ± 3.6</td>
<td>27.1 ± 6.1b</td>
</tr>
<tr>
<td>Causes of ESRD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diabetes mellitus</td>
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<td>5</td>
</tr>
<tr>
<td>glomerulonephritis</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>others</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Aluminum (baseline (μg/L)</td>
<td>11.2 ± 2.6</td>
<td>7.5 ± 1.7</td>
</tr>
<tr>
<td>Kt/V (weekly)</td>
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<td></td>
</tr>
<tr>
<td>baseline</td>
<td>2.3 ± 0.2</td>
<td>2.2 ± 0.1</td>
</tr>
<tr>
<td>6 mo</td>
<td>2.3 ± 0.1</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
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<td></td>
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<tr>
<td>baseline</td>
<td>213 ± 49</td>
<td>303 ± 33</td>
</tr>
<tr>
<td>6 mo</td>
<td>245 ± 42</td>
<td>285 ± 28</td>
</tr>
</tbody>
</table>

* ITDI, intravenous infusion of total dose iron; CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cyclic peritoneal dialysis; ESRD, end-stage renal disease; iPTH, intact parathyroid hormone.  
  b P < 0.05.

Expected from the study design at baseline, compared with the oral group, the ITDI group had significantly (P < 0.05) lower mean TSAT (11.3 ± 3.5 versus 30.1 ± 3.5%), serum ferritin (89.9 ± 46.5 versus 174.1 ± 56.2 ng/ml), and serum iron (30.3 ± 8.7 versus 71.3 ± 9.5 mg/dl) values. At study completion when P values were adjusted for age, sex, months on dialysis, and baseline differences, both mean hematocrit (36.0 ± 1.0 versus 31.4 ± 1.1%; P < 0.05) and TSAT (33.7 ± 3.7 versus 22.6 ± 4.0%; P < 0.05) were significantly higher in the ITDI group (Figures 1 and 2). There was no significant difference in final mean ferritin (ITDI versus oral, 278.9 ± 56.5 versus 214.9 ± 66.9 ng/ml) and serum iron (ITDI versus oral, 68.7 ± 11.9 versus 62.3 ± 12.1 mg/dl) between the two groups (Table 2).

There were no differences between the groups with respect to mean baseline weekly doses of rhEPO (ITDI versus oral, 7886 ± 1449 versus 6370 ± 1553 U/wk). At the end of 6 mo, however, the mean weekly dose of rhEPO was significantly lower in the ITDI group (4779 ± 981 versus 9998 ± 1027 U/wk; P < 0.05) (Figure 3).

There also was no significant difference between baseline and final serum iPTH, and weekly Kt/V (Table 1). In the ITDI group, no patient developed an adverse or allergic reaction to intravenous iron. There were no abnormalities in any of the measured liver function tests (data not shown), and clinical evidence of volume overload was not encountered in any of the ITDI-treated patients.
Table 2. Changes in serum iron and serum ferritin levels*

<table>
<thead>
<tr>
<th>Category</th>
<th>Baseline</th>
<th>3 Months</th>
<th>6 Months</th>
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<tr>
<td>Iron (mg/dl)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ITDI</td>
<td>30.3 ± 8.7(^b)</td>
<td>77.8 ± 13.0</td>
<td>68.7 ± 11.9</td>
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<tr>
<td>oral</td>
<td>71.3 ± 9.6</td>
<td>63.6 ± 11.6</td>
<td>62.3 ± 12.1</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITDI</td>
<td>89.9 ± 46.5(^b)</td>
<td>312.4 ± 53.3</td>
<td>278.9 ± 56.5</td>
</tr>
<tr>
<td>oral</td>
<td>174.1 ± 56.2</td>
<td>175.0 ± 66.9</td>
<td>214.9 ± 66.9</td>
</tr>
</tbody>
</table>

* In spite of significantly lower baseline values in the ITDI group, at the end of the study there were no significant differences between the groups with respect to serum iron and serum ferritin. Abbreviations as in Table 1.
\(^b\) \(P < 0.05\) refers to comparisons between groups and not among different time points.

Discussion

We found that outpatient intravenous ITDI effectively treated iron deficiency anemia in ambulatory PD patients receiving rhEPO therapy. At the end of the 6 mo of study, when compared with conventional oral iron prescribed with a maximal recommended dose of ferrous sulfate of 325 mg three times a day, there were significant increments in mean hemoglobin and iron saturation in patients treated with ITDI. In addition, rhEPO therapy became more effective as demonstrated by the requirement of significantly lower doses of rhEPO to maintain similar target hematocrit in patients treated with ITDI. At the same time, this study demonstrated that at the end of the study, higher doses of rhEPO failed to achieve a similar target hematocrit in the oral group, mainly due to their inability to maintain an adequate TSAT. Although some patients with borderline low TSAT and normal or high serum ferritin fail to respond to iron therapy, in our study, TSAT again was found to be a better marker of iron available for erythropoiesis in patients with ESRD. As reported by others (4), both serum iron and serum ferritin, unless very low, were again found to be poor markers because these were affected by many factors including diurnal variation and inflammatory reactions, respectively.

Known factors associated with erythropoietic resistance include hyperparathyroidism (19), aluminum toxicity (20), inad-
equate dialysis (21), and endogenous inhibitors of rhEPO (22). However, the most common cause of rhEPO failure is iron deficiency resulting from increased iron utilization during stimulated erythropoiesis (3–10,23). Among the U.S. ESRD patients treated with rhEPO, more than 40% are anemic, defined as having hematocrit <30%. More than 50% of the anemic ESRD patients have TSAT <20%, suggesting that iron deficiency contributed to the low hematocrit levels (24). In HD patients, blood loss during dialysis, phlebotomy, and by means of the gastrointestinal route may result in a total loss of 400 mg of iron over 3 mo. In these patients (average weight of 70 kg and with blood volume of 5 to 6 L), to increase hematocrit from 25 to 35% the estimated iron requirement is approximately 600 mg. Therefore, an ESRD patient must be provided with a total of 1000 mg of iron over a 3-mo period to achieve a target hematocrit of 35% (25). It is well recognized that predialysis patients and those undergoing PD have less severe iron deficiency anemia than those receiving HD, mainly due to relatively smaller blood loss and/or low rhEPO requirement than HD patients (17,18,26). Therefore, iron needs are more modest in PD patients, and many PD patients are able to maintain adequate iron status using minimal iron supplementation (17,18).

Numerous studies have also clearly demonstrated that efficient use of rhEPO requires adequate body stores of iron (4–10,15,18,24,26). The most convenient and easiest means of iron supplementation is oral iron. However, the clinical efficacy of oral iron in ESRD patients is affected by cost, patient noncompliance due to side effects and/or the effect of polypharmacy, gastrointestinal side effects, downregulation of gastrointestinal absorption, and decreased bioavailability due to drug interaction (4,11–13). A number of studies have documented the failure of oral iron supplementation to maintain adequate iron stores in rhEPO-treated ESRD patients (9,10,14,16–18,27–29). Consequently, in many cases, maximally recommended doses of oral iron (195 mg of elemental iron) ingested daily will not meet the demands of rhEPO-induced erythropoiesis and concurrent iron losses (9,15,16,27–31). In HD patients, frequent administration of small doses of intravenous iron allowed effective use of rhEPO in the management of anemia (6,7,10,14,16). Compliance is guaranteed, and the number of pills the patient must take is reduced. Due to the absence of convenient vascular accesses and the frequent need for intravenous iron administration, the above method is not an acceptable option for ambulatory PD patients. Also, for logistical reasons, weekly or biweekly intramuscular injections of iron dextran, although effective, are an unacceptable alternative in these patients (17). To this end, in an uncontrolled study, we previously reported the safe and effective use of ITDI in PD patients (18). The current comparative study demonstrated the superiority of ITDI when compared with oral iron in the treatment of anemia in PD patients receiving rhEPO.

In this study, we excluded patients with other possibilities of rhEPO resistance, e.g., hyperparathyroidism, aluminum toxicity, and inadequate dialysis. We recognize that there are possible biases inherent to any open-label study. By study design, the ITDI group was placed at the disadvantage of having significantly lower mean baseline iron indices. Also, due to the nonrandomized nature of this protocol, the two study groups were not completely matched with regard to age and duration of dialysis. It was therefore possible that younger patients in the ITDI group had higher baseline iron requirements due to the inclusion of menstruating female patients. It was also possible that the ITDI group, which was relatively newer to dialysis, had the greater iron requirements associated with initiation of rhEPO therapy and therefore had a steeper hematocrit rise. Despite these differences, when P values were adjusted for age, sex, months on dialysis, and baseline differences, the mean hematocrit value in the ITDI group improved significantly after ITDI therapy and thus resulted in significantly lowering weekly rhEPO doses in these patients. Although we cannot categorically exclude the possibility of noncompliance to oral iron as one of the reasons for the progressive fall in TSAT in the oral group, we made every effort to encourage compliance. In our opinion, the progressive decrease in TSAT in this group can be explained by rapid utilization of iron stores secondary to rhEPO-enhanced erythropoiesis.

A major concern with the use of intravenous iron is the risk of anaphylaxis, with reported incidence ranging from 0.6 to 10% (32). In a retrospective study involving 573 hemodialysis patients, serious reactions were found to be 0.7%, with no fatality reported (33). In this study, a high percentage (17%) of patients with a history of multiple drug allergies reportedly developed anaphylactoid reaction. In 481 nonuremic patients, using larger doses (500 mg of iron dextran), Haamastra et al. (34) found a 0.6% rate of immediate serious reaction. In the current study, no adverse reaction due to ITDI was encountered. This finding is probably due to our small sample size, but our precautionary measures, including premedication, slow infusion rate, and infusion of diluted preparation, may also contribute to the safety of intravenous administration of relatively large doses of iron. In addition to the potential risk of iron overload, abnormalities of liver function tests (35) and significant volume overload are two other potential risks of ITDI not encountered in any of the patients treated with ITDI (data not shown).

In summary, this study found that ITDI is a safe, effective, and superior method to oral iron in treating iron deficiency anemia in rhEPO-treated patients with PD. However, we recommend that before ITDI, all patients should be carefully examined by a physician, and in those with a prior history of multiple drug allergy, physicians should be prepared to care for the rare episodes of anaphylactoid reaction associated with ITDI. A large multicenter clinical trial involving more patients should be considered to confirm the safety of this method of iron repletion.

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References


